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HEART CARE TEAM/MULTIDISCIPLINARY TEAM LIVE

Newborn With Severely Depressed Left Ventricular Function
Acute Myocardial Infarction in a Newborn

Neha Ahluwalia, MD, Robert H. Pass, MD, Scott I. Aydin, MD

ABSTRACT

We describe a rare case of spontaneous coronary artery thrombosis in a newborn leading to rapid severe ventricular dysfunction. Early diagnosis is critical and management strategies are varied including hemodynamic support with extracorporeal membrane oxygenation, systemic/local thrombolytic therapy with tissue plasminogen activator, or surgical thrombectomy. (Level of Difficulty: Advanced.) (J Am Coll Cardiol Case Rep 2020;2:1837–40)

HISTORY OF PRESENTATION

The patient was born via elective Cesarean section at 36 weeks gestation for maternal indication of placenta previa. The prenatal maternal history was significant for bleeding at 35 weeks of gestation and she was admitted to the hospital for monitoring and therapy with intravenous iron and vitamin B12. During admission, the fetal non-stress test was reassuring. Fetal echocardiogram demonstrated normal cardiac anatomy and function. Delivery was uncomplicated with Apgar scores of 9 and 9. At 2 h of life, the patient developed tachypnea, grunting, and cyanosis. Initial oxygen saturation of 78% on the right foot and a noxygen saturation differential was observed with upper extremity saturation of 92%. Blood pressure was 58/31 mm Hg, heart rate was 147 beats/min, temperature was 36.6°C (97.9°F), and respiratory rate 85 breaths/min. Blood gas showed metabolic acidosis (pH 7.23, bicarbonate 17 mmol/l, base excess –10.0 mmol/l, lactate 7.3 mmol/l). Chest radiograph was notable for pulmonary plethora and bilateral hazy opacities concerning for pulmonary edema. In the setting of respiratory distress with differential cyanosis, the patient was transferred from newborn nursery to the neonatal intensive care unit with a subsequent screening bedside echocardiogram showing severely depressed left ventricular (LV) function.

LEARNING OBJECTIVES

- To evaluate cardiogenic shock in a neonate with elevated cardiac enzymes and electrocardiogram changes concerning for myocardial ischemia should prompt evaluation of coronary arteries when no other etiology is immediately apparent.
- To recommend management of coronary thrombosis in a tertiary care center with availability of extracorporeal membrane oxygenation and a multidisciplinary team for reducing morbidity and mortality.
QUESTION 1. WHAT IS THE DIFFERENTIAL DIAGNOSIS OF DEPRESSED FUNCTION WITH DIFFERENTIAL CYANOSIS IN A NEONATE?

Answer 1. Differential cyanosis refers to cyanosis in both lower extremities with a pink right upper extremity. This can be seen in newborns with patent ductus arteriosus and persistence of elevated pulmonary arterial hypertension leading to shunting of deoxygenated blood to lower half of the body. However, persistent pulmonary hypertension in a neonate is not typically associated with depressed LV function. Other differential diagnoses include left-sided obstructive lesions (aortic arch hypoplasia, interrupted aortic arch, critical coarctation, and critical aortic stenosis) which can present with depressed function and the cardiac output to the lower half of the body being supplied by the patent ductus arteriosus. Other possible causes included cardiomyopathy, myocarditis, and rare diagnoses of coronary artery abnormalities such as ostial stenosis/atresia, thrombosis, and dissection. Anomalous left coronary from the pulmonary artery can also present with depressed LV function usually within first few months of life as the pulmonary vascular resistance falls with associated coronary steal causing myocardial ischemia.

In the neonatal intensive care unit, cardiac markers were elevated with troponin (12 ng/ml) and creatine kinase myocardial band (135.6 ng/ml). The ECG showed a QS pattern in lead I and AVL concerning for lateral infarct (Figure 1). An echocardiogram showed severely depressed LV function (ejection fraction, 25%), moderate-to-severe mitral regurgitation, and no evidence of critical aortic stenosis or coarctation (Video 1). The clinical status, lactic acidosis, and troponin levels continued to worsen.

QUESTION 2. HOW WOULD YOU ACUTE MANAGE THIS PATIENT?

Answer 2. Prompt recognition of cardiogenic shock is crucial and initial management included improving oxygen delivery to peripheral tissue with optimizing ventilation and gas exchange (oxygen therapy and intubation), optimizing pre-load and afterload with fluid resuscitation, diuretics, and inotropes (milrinone or dobutamine). It is also important to decrease oxygen consumption by treating for curable causes such as sepsis with broad spectrum antibiotics.

However, because of continued clinical deterioration with rising lactate levels and unclear etiology of...
depressed LV function, the patient was cannulated on ventriculoarterial extracorporeal membrane oxygenator (ECMO) at 6 h of life. After being placed on ECMO, the patient underwent systemic heparinization.

**QUESTION 3. WHAT ADDITIONAL INVESTIGATIONS DO YOU PROPOSE TO COMPLETE YOUR DIAGNOSIS AND WORKUP?**

Answer 3. Detailed review of the echocardiogram revealed the normal origin of coronary arteries; however, a mobile echogenic focus in the aortic root close to the origin of the left coronary artery (Video 2) and antegrade flow in the proximal left main coronary were observed. Further assessment of the echocardiogram with focused imaging of the coronary artery suggested a membranous structure within the aortic root extending from the ostia of the left main coronary artery.

Based on these echocardiographic findings concerning for coronary thrombus versus aortic dissection, a cardiac catheterization was performed for better delineation of coronary anatomy. While the patient was on ECMO, an ascending aortic injection showed a non-occlusive thrombus in the left main coronary artery with a small degree of contrast passing above and below the thrombus with filling of the distal left anterior descending and circumflex (Video 3). The hematology department was consulted and a thrombophilia workup including prothrombin, partial thromboplastin, thrombin time, fibrinogen, as well as levels of antithrombin III, protein S and C were all within normal limits. Genetic screening for protein C, S, and factor V Leiden was negative. Because of clinical instability, evaluation of any other systemic thrombosis (renal/hepatic/ductus venosus) was not performed. No evidence of hemorrhage or ischemia was seen on head ultrasound.

These findings in conjunction with the continued elevated troponin levels despite full cardiac output support via ECMO suggested ongoing myocardial ischemia.

**QUESTION 4. WHAT ARE THE RISK FACTORS FOR DEVELOPING CORONARY THROMBOSIS IN A NEONATE AND HOW WOULD YOU MANAGE IT?**

Answer 4. Neonatal coronary thrombosis is a rare diagnosis and associated with significant morbidity and mortality from myocardial infarction and ischemia resulting in severe ventricular dysfunction. Prior suggested etiologies for coronary thrombosis in the structurally normal heart include hypercoagulability, prematurity, neonatal asphyxia, myocarditis, delayed cord clamping, paradoxical systemic emboli off the renal or placental vasculature through a patent foramen ovale into the left side of the heart, and placement of an umbilical venous catheter (1-3). In many cases, similar to this patient, no identifiable cause is detected. A common feature of all of these patients at presentation has been global ventricular dysfunction causing “myocardial stun,” a physiologically reversible process, especially in the neonatal myocardium (4). Earlier studies have reviewed the important role of hemodynamic stabilization with ECMO and association with long-term survival (5,6). In recent years, successful use of selective intra-coronary injection of recombinant tissue plasminogen activator has been described (7-9).

Others have reported surgical thrombectomy (10). In this case, because of rapid clinical deterioration and the use of ECMO for hemodynamic support and stabilization, the risk of life-threatening bleeding with recombinant tissue plasminogen activator in a fully heparinized patient outweighed the benefits, and the decision was made to proceed with surgical thrombectomy. The patient was taken to the operating room on day of life 1 where the aorta was transected distal to the sinotubular junction. A thrombus was identified in the left coronary cusp, extending into the left main coronary artery.
thrombus was removed and the left coronary artery was subsequently probed without difficulty. The specimen was sent for pathology and was confirmed as dark red tissue resembling a blood clot and measuring 0.9 × 0.1 × 0.05 cm (Figure 2). Post-surgical thrombectomy the patient remained on ECMO and returned to the cardiac intensive care unit in stable condition.

**QUESTION 5. HOW WAS THE PATIENT MANAGED POST-OPERATIVELY?**

Answer 5. Over the course of the next 24 post-operative hours, both troponin and lactic acid levels improved. Additionally, elevated liver enzymes were noted, which were thought to be due to ischemic liver injury from severe cardiac dysfunction. Renal function was unaffected. ECMO course was uncomplicated and standard anticoagulation strategy with heparin was used with close titration to maintain activated clotting time of 180 to 200 ms. The patient underwent daily head ultrasounds while on ECMO as per protocol, and on day 6 of ECMO was noted to have very small area of hyperechogenicity in the right caudate nucleus measuring 0.5 × 0.8 × 0.7 cm, likely an area of hemorrhage and/or ischemia. Video electroencephalograph showed generalized background slowing with no electrographic or clinical seizures. On post-operative day 7, the patient was successfully decannulated from ECMO. Follow-up brain magnetic resonance imaging/magnetic resonance angiography/magnetic resonance venography showed right parietal subacute ischemic stroke, multifocal hemorrhage supra- and infra-tentorial, and no cerebral venous thrombosis. There was discussion to start anticoagulation with low-molecular-weight heparin for an unprovoked coronary thrombosis; however, given the concern for intra-cranial hemorrhage, the decision was made to hold off. Follow-up head ultrasound showed no change in findings.

The patient was discharged home on post-operative day 30 with mildly depressed LV systolic function (ejection fraction 48%). LV function has improved gradually 3 months post event with a normal ejection fraction of 56% (Video 4).

**AUTHOR RELATIONSHIP WITH INDUSTRY**

All authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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**KEY WORDS** coronary artery thrombosis, myocardial ischemia, neonate

**APPENDIX** For supplemental videos, please see the online version of this paper.
Right and Left-Sided Carcinoid Heart Disease in the Setting of Selective Serotonin Reuptake Inhibitor Use

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ABSTRACT

Carcinoid heart disease is a complication of carcinoid syndrome. The role of selective serotonin reuptake inhibitors in carcinoid heart disease is unclear. We present a case of refractory heart failure due to right- and left-sided carcinoid heart disease in the setting of selective serotonin reuptake inhibitor use despite remission of carcinoid syndrome. (Level of Difficulty: Beginner.) (J Am Coll Cardiol Case Rep 2020;2:1841–4) © 2020 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

HISTORY OF PRESENTATION

A 73-year-old female presented to the emergency department with acute heart failure. She presented afebrile with a blood pressure of 92/60 mm Hg, a heart rate of 103 beats/min, and oxygen saturation of 94% on room air. Her physical exam findings were suggestive of volume overload, including jugular venous distension, bilateral lung crackles, hepatomegaly, and lower-extremity edema.

PAST MEDICAL HISTORY

Her past medical history was notable for a malignant carcinoid tumor with mesenteric metastasis in 2009, which was resected and treated with monthly octreotide injections. In June 2017, she was deemed to be in remission based on laboratory and imaging studies; therefore, octreotide was discontinued. In early 2018, she suffered multiple major depressive episodes with psychosis and was started on the selective serotonin reuptake inhibitor (SSRI) citalopram with gradual dose up-titration over the course of several months. Six months later, she developed flushing, diarrhea, and progressively worsening dyspnea on exertion requiring multiple hospitalizations.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis for heart failure exacerbation included coronary ischemia, valvular heart
disease, or underlying atrial or ventricular arrhythmias.

**INVESTIGATIONS**

Labs were remarkable for an elevated N terminal pro-B-type natriuretic peptide of 1,657 pg/ml. Chromogranin A level was markedly elevated to 1,677 ng/ml. Urine 5-hydroxyindoleacetic acid was elevated to 28.6 mg/24 h. An echocardiogram revealed a dilated left ventricle with an ejection fraction of 50%, severe tricuspid regurgitation attributed to thickened leaflets in a fixed open position (Figure 1), severe pulmonary regurgitation (Figure 2), and severe aortic regurgitation (Figure 3). The right ventricle was moderately dilated with moderate dysfunction. This was a marked difference from prior echocardiograms in 2015 and 2016, with an ejection fraction of 60%, trace mitral regurgitation, trace pulmonary regurgitation, no aortic insufficiency, and a structurally normal tricuspid valve. The atrial septum was intact without evidence of right-to-left shunt. Coronary angiography showed no significant coronary artery disease. An octreotide scan did not show any evidence of metastatic or recurrence of carcinoid disease. Computed tomography angiogram of the chest and abdomen did not have findings suggestive of tumor burden.

**MANAGEMENT**

She was treated with intravenous diuresis then transitioned to oral torsemide before discharge. Octreotide therapy was reinitiated. No additional medications were started. She was discharged home to await surgical replacement of the tricuspid and aortic valve.

**DISCUSSION**

Neuroendocrine tumors (NETs) mainly arise from exocrine cells throughout the gastrointestinal tract and to a lesser extent, the bronchopulmonary system, releasing vasoactive amines, such as prostaglandins, bradykinin, histamine, and most prominently, serotonin (5-hydroxytryptamine receptor [5-HT]) (1). These tumor products are usually inactivated by the liver. However, with metastases to the liver, hormonal activity may exceed the hepatic capacity for degradation leading to carcinoid syndrome (CS) (1). Symptoms are characterized by cutaneous flushing, gastrointestinal hyper-motility, and bronchospasm (2). The cardiac manifestations of an NET are referred to as carcinoid heart disease (CHD), also called Hedinger syndrome. Carcinoid tumors are rare with 27 per 1,000,000 diagnosed in the United States per year according to the National Organization of Rare Diseases. Only 10% of NETs develop CS (1). Once CS is established, more than half of these patients will go on to have carcinoid tumors specifically involving the heart (2,3). The tricuspid valve is most commonly affected, whereas the pulmonic valve is involved 60% of the time. Left-sided valves are rarely impacted and account for <10% of cases due to the pulmonary metabolism and deactivation of the hormonal substances (4,5). Left-sided involvement usually occurs in either the presence of right-to-left shunt, carcinoid of the lung, or very high levels of vasoactive substances (2). The development of cardiac pathology in a patient with CS has a 3-year survival rate of 31%, whereas patients without cardiac involvement have approximately twice the survival rate (2,3). The burden of illness can be significant for patients living with NET, and they often experience depression and anxiety requiring treatment with SSRIs. Whether SSRIs are safe to use in combination with treatment for NET remains controversial.

The exact mechanism for development of CHD in the setting of CS is poorly understood. A strong body of evidence implying that 5-HT is linked to cardiac...
valve disease exists (3,5–7). The popular diet pill fenfluramine-phentermine, which has 5-HT-releasing activity from the 5-HT transporter, brought to light the relationship between 5-HT and valvular heart disease (8). Remarkably, the valve pathology seen with the use of fenfluramine-phentermine is similar to findings in CHD. 5-HT_{2B}, a subtype of the 5-HT receptor, is most prevalent on cardiac valves (4–6,9). Activation of 5-HT_{2B} causes upregulation of fibroblast proliferative properties, such as tissue growth factor B1, which leads to deposition of plaques on the endocardial surfaces of the valve leaflets and the subvalvular apparatus (3–5,7); thus, resulting in valve regurgitation. Urinary 5-hydroxyindoleacetic acid, the serotonin metabolite which reflects the amount of serotonin production, is significantly higher in patients with CHD compared with those without cardiac involvement (2,10), implicating 5-HT as the mechanism for valvular heart disease. SSRIs increase the availability of 5-HT by inhibiting the 5-HT transporter that transports 5-HT from synaptic spaces into presynaptic neurons (9). Somatostatin receptors are expressed in approximately 80% to 90% of NETs, which makes them a therapeutic target (8). The mechanisms by which somatostatin and its analogues exert their effects on the NET cells are complex and not well described (8). The mechanisms by which somatostatin and its analogues exert their effects on the NET cells are complex and not well described (8). We know from various studies that use of somatostatin analogues can modify the 3-dimensional configuration of somatostatin receptors. This alteration affects receptor regulation and density at the cell surface (8), which may explain why somatostatin analogue resistance is encountered in patients with CS after long-term octreotide therapy. We theorize a similar modification may occur with 5-HT receptors after long-term use of octreotide. Although no evidence establishes the role of SSRIs in CHD, multiple case reports regard SSRIs as responsible for unmasking CS in patients with an occult carcinoid tumor (9).

**FOLLOW-UP**

Her surgery was initially postponed due a continuing rise in chromogranin A level despite octreotide therapy. She was transitioned to lanreotide as this has been shown to have similar efficacy and is better tolerated than octreotide. Telotristat ethyl, a tryptophan hydroxylase inhibitor that reduces peripheral 5-HT levels, was also initiated. Because of the coronavirus disease 2019 pandemic, her surgery has been postponed.

**CONCLUSIONS**

Guidance on the safety of antidepressants in NETs, CS, and CHD is lacking. To our knowledge this is the first case report where SSRIs may cause rapid progression of CS to CHD in the setting of previous treatment with a somatostatin analogue. We hypothesize that the exposure to long-term octreotide changes the density and/or sensitivity of 5-HT receptors on carcinoid tumors, laying the foundation for a predisposition to CHD. Coupled with the additional insult of increased 5-HT availability from SSRIs, a reactivation of CS occurred with subsequent CHD. Unmasking of undetectable micro-disease by the use of SSRIs cannot be excluded. This case highlights the
potential provocative role SSRIs play in the rapid progression of right- and left-sided CHD. CHD portends a worse prognosis and represents a major cause of morbidity and mortality. Death as a result of cardiac decompensation in this patient population is as high as 43% in untreated patients (3). Therefore, this possible association between SSRIs and CHD is important to consider when managing patients with depression and a history of CS.

REFERENCES
1. Aluri V, Dillon JS. Biochemical testing in neuroendocrine tumors. Endocrinol Metab Clin North Am 2017;46:669–77.
2. Fox DJ, Khattar RS. Carcinoid heart disease: presentation, diagnosis, and management. Heart 2004;90:1224–8.
3. Rajamannan NM, Caplice N, Anthikad F, et al. Cell proliferation in carcinoid valve disease: a mechanism for serotonin effects. J Heart Valve Dis 2001;10:827–31.
4. Jian B, Xu J, Connolly J, et al. Serotonin-induced up-regulation of transforming growth factor-β1 via G-protein signal transduction in aortic valve interstitial cells. Am J Pathol 2002;161:2111–21.
5. Simbera Z, Balon R. Carcinoid tumor, selective serotonin reuptake inhibitors, and diarrhea. Psychosomatics 2005;46:88–9.
6. Elango S, Job LE, Zadrozy LM, et al. (2008) 5-Hydroxytryptamine (SHT)-induced valvulopathy: compositional valvular alterations are associated with SHT2B receptor and SHT transporter transcript changes in Sprague-Dawley rats. Exp Toxicol Pathol 2008;60:253–62.
7. Connolly JM, Bakay MA, Fulmer JT, et al. Fenfluramine disrupts the mitral valve interstitial cell response to serotonin. Am J Pathol 2009;175:988–97.
8. Grozinsky-Glasberg S, Shimon O, Korbonits M, Grossman AB. Somatostatin analogues in the control of neuroendocrine tumours: efficacy and mechanisms. Endocr Relat Cancer 2008;15:701–20.
9. Williams MD, Dolenc TJ. Selective serotonin reuptake inhibitors and patients with carcinoid tumor. Psychosomatics 2005;46:370–2.
10. Zuetenhorst JM, Bonfret JM, Korse CM, Bakker R, van Tinteren H, Taal BG. Carcinoid heart disease: the role of urinary 5-hydroxyindoleacetic acid excretion and plasma levels of atrial natriuretic peptide, transforming growth factor-β1 and fibroblast growth factor. Cancer 2003;97:1609–15.

KEY WORDS carcinoïd heart disease, carcinoïd syndrome, Hedinger syndrome, valvular disease
The Thickened Valve*

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In this issue of JACC: Case Reports, Bell et al. (1) present an interesting case report describing right- and left-sided valvular heart disease in a 73-year-old woman being treated with a selective serotonin reuptake inhibitor (SSRI) (citalopram) for major depressive episodes with psychosis. Intriguingly, the past medical history was notable for a carcinoid tumor with mesenteric metastases. The tumor was surgically resected, and the patient was treated with monthly octreotide injections for 8 years until the patient was considered to be in remission based on laboratory and imaging studies. The patient subsequently developed characteristic triad symptoms of carcinoid syndrome 3 years later including flushing, diarrhea, and worsening dyspnea on exertion with elevated N-terminal pro-hormone BNP, indicating heart failure, and elevated serotonin levels. The echocardiographic imaging during the current admission revealed severe right- and left-sided valvular regurgitation with thickened leaflets, which were not seen in prior echocardiograms 3 years ago. There was no evidence of recurrence of tumor both on octreotide scan and computed tomography angiograms of the chest and abdomen. The clinical picture was considered consistent with carcinoid syndrome-like valvular heart disease in the setting of SSRI use. In particular, the involvement of the left-sided valve supports drug-induced valvular heart disease.

The valve thickening other than calcification could result from myxomatous degeneration, post-inflammatory valvular involvement (e.g., rheumatic heart disease, endocarditis, and autoimmune diseases such as lupus), and less frequently carcinoid heart valve disease. The rare causes of valvular heart disease include storage diseases and drug-related valvular pathology such as seen in the present case with SSRI use; other drugs include ergotamine and anorectic agents (2,3). Distinct pathologic alterations seen in valves in carcinoid heart disease, rheumatic heart disease, and myxomatous degeneration are discussed subsequently (Figures 1 to 3).

In carcinoid heart disease, the endocardium of the right-sided chambers of the heart, tricuspid and pulmonary valves, the subvalvular apparatus (chordae tendineae and papillary muscles), venae cavae, pulmonary arteries, and coronary sinus are involved (4). The right-sided valves account for 92% of the surgically excised valves (5). Clinically, tricuspid valve is affected in 90% of patients with established carcinoid heart disease (6). The valvular dysfunction in carcinoid heart disease occurs due to the formation of fibrous plaques that lead to thickening of the leaflets and encase the subvalvular apparatus; the fibrotic involvement may result in varying degrees of valve stenosis and regurgitation. These plaques are composed of myofibroblasts and extracellular matrix with neovascularization and mild chronic inflammation; extracellular matrix comprises of collagen and myxoid ground substance. It is important to recognize that these plaques are deposited on the valvular surfaces and do not destroy the underlying valve morphology. In the right heart, these surface plaques could lead to the adherence of the tricuspid valve to the mural endocardium and valve regurgitation. On echocardiography, diffuse thickening, loss of valve curvature, and significant impairment of mobility of the tricuspid valve leaflets are seen. The thickening
typically extends to the subvalvular apparatus, which contributes to the retraction of the tricuspid valve leaflets. In advanced cases, thickened, retracted, echo bright tricuspid leaflets appear fixed in a “semi-open” position resulting in some degree of tricuspid stenosis as well as severe regurgitation with a characteristic triangular spectral Doppler pattern. The pulmonic valve typically shows a similar echocardiographic pattern of leaflet thickening, impaired mobility, and poor coaptation resulting in a combination of valvular stenosis and regurgitation. Left-sided involvement is seen in <10% of cases, especially in patients with liver metastases or pulmonary carcinoid, or in those with patent foramen ovale (7). There is no evidence of commissural fusion as seen in post-inflammatory valvular diseases and hooding of the leaflets as seen in floppy valves. Other accompanying manifestations of carcinoid heart disease include coronary artery vasospasm (8), ventricular tachycardia (9), and metastatic carcinoid spread to the myocardium (5).

The mitral valve is the most commonly affected valve in rheumatic heart disease, followed by the aortic, tricuspid, and pulmonary valves. The valves are fibrotic and demonstrate commissural fusion. The valves are often calcified, and the chordae tendineae thickened and shortened. Histologically, the valves in rheumatic heart disease show fibrosis, neo-vascularization, and chronic inflammation. However, in contrast to the valvular morphology in carcinoid heart disease, wherein the valvular structure is intact and the fibrous plaques are layered on the endocardial surfaces of the valve, the underlying valve architecture is destroyed in valves afflicted by rheumatic heart disease (10). On echocardiography,
FIGURE 2  Gross Images of 3 Explanted Hearts

(A) Normal mitral valve. The cusps are thin and translucent (black arrows) and the chordae tendinae (yellow arrow) are thin and delicate. (B) Mitral valve of the heart shows thickened leaflets with commissural fusion (black arrow). The orifice of the mitral valve viewed from the left atrial aspect has a fish mouth appearance due to the fused commissure. (C) The mitral valve has myxomatous degeneration. Hooding of the posterior cusp (black arrows) is present.

FIGURE 3  Histologic Features of Normal, Rheumatic, Myxomatous, and Carcinoid Mitral Valve

(A) The normal valve is lined by endothelial cells (brown arrow) and is composed of 3 distinct layers: fibrosa, ventricularis, and spongiosa. The fibrosa (black arrow) provides structural support and is composed of compact collagen fibers; the spongiosa (blue arrow) is composed of extracellular matrix, elastic fibers, and valvular interstitial cells; the ventricularis (red arrow) contains large amounts of elastic fibers. (B, C) histological images of post-inflammatory valvular disease, the most common cause of which is rheumatic heart disease. The valves are thickened due to fibrosis, and there is disruption of the normal layers of the valve, as seen at low-power magnification in B. On higher magnification, neovascularization (red arrows) is present. (D) In myxomatous degeneration, thickening of the leaflets is due to accumulation of glycosaminoglycans in the spongiosa layer (black arrow), with attenuation of the fibrosa layer. (E, F) Valvular involvement in carcinoid heart disease. (E) Fibrous plaques (blue arrows) are layered on the valve leaflet (black lines). (F) At higher magnification, the fibrous plaques are composed of collagen (purple arrow), myofibroblasts (black arrow), ground substance (brown arrow), and neovessels (red arrow).
commissural fusion is the most characteristic feature of the rheumatic valve disease. In mitral stenosis, it manifests as characteristic doming of the anterior mitral leaflet in diastole along with restricted mobility of the posterior mitral leaflet. Commissural fusion results in a funnel-like narrowing of the mitral valve with a typical “fish mouth” appearance. In addition, valve thickening, valve and commissural calcification, and subvalvular involvement are seen, all of which are important components for the assessment of percutaneous intervention feasibility.

Myxomatous degeneration can be sporadic or seen in patients with Marfan syndrome, Ehlers-Danlos syndrome, or osteogenesis imperfecta. The valves are thickened, gelatinous, and have elongated and thinned chordae. The thickening of the leaflets is due to accumulation of glycosaminoglycans in the spongiosa layer with attenuation of the fibrosa. The posterior leaflet is most commonly involved. Barlow’s disease is the term used when the entire valve is involved. There is no evidence of commissural fusion, and calcification is usually not seen (11,12). On echocardiography, myxomatous Barlow disease appears as thickening and redundancy of the mitral valve leaflets, which can be associated with valve prolapse, flail segments, and mitral annular disjunction. The tricuspid valve can be similarly affected in some patients. On the other hand, fibroelastic deficiency results in a localized prolapse or flail valve segment without diffuse valve thickening.

In conclusion, although rare, carcinoid heart disease results in a unique pattern of cardiac pathology and valvular dysfunction, distinct from other more common causes of valvular involvement. Understanding the pathologic basis of this condition helps highlight the features commonly seen on in vivo cardiac imaging.

AUTHOR RELATIONSHIP WITH INDUSTRY

The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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REFERENCES

1. Bell J, Alhudairy M, Kazakova V, Johnstone M, Tsao L. Right- and left-sided carcinoid heart disease in the setting of selective serotonin reuptake inhibitor use. J Am Coll Cardiol Case Rep 2020;2:1841–4.
2. Hauck AJ, Edwards WD, Danielson GK, Mullany CJ, Bresnahan DR. Mitral and aortic valve disease associated with ergotamine therapy for migraine. Report of two cases and review of literature. Arch Pathol Lab Med 1990;114:62–4.
3. Steffee CH, Singh HK, Chitwood WR. Histologic changes in three explanted native cardiac valves following use of fenfluramines. Cardiovasc Pathol 1999;8:245–53.
4. Pellikka PA, Tajik AJ, Khandheria BK, et al. Carcinoid heart disease. Clinical and echocardiographic spectrum in 74 patients. Circulation 1993;87:1188–96.
5. Simula DV, Edwards WD, Tazelaar HD, Connolly HM, Schaff HV. Surgical pathology of carcinoid heart disease: a study of 139 valves from 75 patients spanning 20 years. Mayo Clin Proc 2002;77:139–47.
6. Bhattacharyya S, Toumpanakis C, Burke M, Taylor AM, Caplin ME, Davar J. Features of carcinoid heart disease identified by 2- and 3-dimensional echocardiography and cardiac MRI. Circ Cardiovasc Imaging 2010;3:103–11.
7. Fox DJ, Khattar RS. Carcinoid heart disease: presentation, diagnosis, and management. Heart 2004;90:1224–8.
8. Erdem R, Slabbynck H, Van den Branden F. Carcinoid crisis with fatal coronary spasm in a small localized peripheral bronchial carcinoid. Acta Cardiol 2010;65:471–5.
9. Rupp AB, Ahmadjee A, Morshedzadeh JH, Ranjan R. Carcinoid syndrome-induced ventricular tachycardia. Case Rep Cardiol 2016;2016:9142598.
10. Veinot JP. Pathology of inflammatory native valvular heart disease. Cardiovasc Pathol 2006;15:243–51.
11. Edwards JE. Floppy mitral valve syndrome. Cardiovasc Clin 1988;18:249–71.
12. Waller BF, Morrow AG, Maron BJ, et al. Etiology of clinically isolated, severe, chronic, pure mitral regurgitation: analysis of 97 patients over 30 years of age having mitral valve replacement. Am Heart J 1982;104:276–88.

KEY WORDS carcinoid, myxomatous, rheumatic, valve
We report the case of a 30-year-old man who underwent orthotopic heart transplant via biatrial anastomosis technique. His post-operative electrocardiogram showed atrial dissociation, which is infrequently seen with newer surgical techniques in heart transplantation. (Level of Difficulty: Advanced.) (J Am Coll Cardiol Case Rep 2020;2:1849–51) © 2020 Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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The electrocardiogram demonstrates atrial dissociation with 2 distinct P-wave morphologies, from both the donor and native sinus nodes (Figure 3). Native sinus node activity is dissociated from the active rhythm. Distinguishing this from other atrial arrhythmias and, specifically, atrioventricular block is important, because the management is different. The patient underwent a heart transplant using the biatrial anastomosis technique, which involves suturing the donor right atrium to a portion of the native right atrium. This was done to displace the ventricles more laterally to the left and reduce the amount of compression on the right ventricle by his pectus excavatum after chest closure. In the biatrial technique, the native sinus node is frequently preserved but does not conduct to the transplanted donor heart because of disruption of blood supply and denervation. There is also conduction block across the suture line in the right atrium (1). Atrial dissociation after orthotopic heart transplant is not commonly seen these days because the bicaval anastomosis technique is considered a more preferable approach except under unique circumstances (2,3).
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REFERENCES

1. Thajudeen A, Stecker EC, Shehata M, et al. Arrhythmias after heart transplantation: mechanisms and management. J Am Heart Assoc 2012;1:e001461.
2. Davies RR, Russo MJ, Morgan JA, et al. Standard versus bicaval techniques for orthotopic heart transplantation: an analysis of the United Network for Organ Sharing database. J Thorac Cardiovasc Surg 2010;140:700–8.
3. Weiss ES, Nwakanma LU, Russell SB, Conte JV, Shah AS. Outcomes in bicaval versus biatrial techniques in heart transplantation: an analysis of the UNOS database. J Heart Lung Transplant 2008;27:178–83.

KEY WORDS biatrial anastomosis, bicaval anastomosis, heart transplant
Percutaneous Management of a Contained Annular Rupture Occurring With Self-Expanding Transcatheter Aortic Valve Replacement

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ABSTRACT

Annular rupture is a rare catastrophic event during transcatheter aortic valve replacement, often life threatening and requiring emergent surgical repair. We describe herein, a case of contained annular rupture successfully managed percutaneously with coiling and polymer injection. This is a novel technique to manage this complication. (Level of Difficulty: Advanced.) (J Am Coll Cardiol Case Rep 2020;2:1852–8) © 2020 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

HISTORY OF PRESENTATION

We describe a 70-year-old man who presented with gastrointestinal bleeding and was found to have evidence of heart failure and severe aortic stenosis (peak/mean gradients: 125/80 mm Hg, respectively). Coronary angiography was without significant obstruction. Four-dimensional ECG-gated cardiac computed tomography (CT) angiography (Figure 1) showed a moderately calcified aortic annulus (mean diameter area-derived: 22.7 mm, perimeter-derived: 22.3 mm), a Bicuspid Severs-1 aortic valve, and no left ventricular outflow tract (LVOT) calcium. Low-risk isolated surgical aortic valve replacement was recommended; however, the patient indicated a strong preference for transcatheter aortic valve replacement (TAVR).

We performed transfemoral TAVR with a 26-mm Evolut Pro+ valve (Medtronic, Minneapolis, Minnesota) after pre-dilation with 20- and 21-mm TRUE valvuloplasty balloons (Bard Peripheral Vascular, Tempe, Arizona). The residual mean gradient was 17 mm Hg—which was felt to be unacceptably high—and post-dilation with a 22-mm TRUE balloon was performed (Video 1). Thereafter, the mean gradient was 10 mm Hg. No pericardial effusion was present; however, a contained area of contrast extravasation was noted on aortography (Figure 2, Video 1). The patient remained asymptomatic and hemodynamically stable and was admitted to the cardiac care unit.

LEARNING OBJECTIVES

- To review a case of contained annular rupture occurring during post dilation after self-expanding TAVR implantation.
- To recognize the imaging findings of annular rupture.
- To understand the role of surgical and nonsurgical management of annular rupture.
PAST MEDICAL HISTORY

Prior to presentation, there was no prior medical or surgical history.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of contrast extravasation from the aorta or LVOT to the extraluminal space is limited and includes contained or uncontained aortic root and LVOT rupture.

INVESTIGATIONS

On post-operative day (POD) 2, a CT scan showed a $1.1 \times 0.8 \times 0.7$ cm opacified pseudoaneurysm inferior to the right coronary cusp compressing the right coronary artery (Figure 3). Serial CT scan on POD 6 remained unchanged, and the patient was discharged. A repeat CT scan performed empirically on POD 23 to assess for stability showed enlargement of the pseudoaneurysm. He remained asymptomatic. Surgical correction was recommended; however, the patient declined unless necessary. We planned for a percutaneous repair with surgical bailout during the same procedure if unsuccessful.

MANAGEMENT

On POD 45, the patient was placed under general anesthesia in our hybrid operating room. Right coronary artery angiography demonstrated new proximal stenosis from extrinsic compression (Figure 4); however, the patient remained without signs of ischemia. We crossed the aortic valve bioprosthesis in a retrograde fashion and exchanged to a Simmons 1 catheter (Cordis Medial, Santa Clara, California), which was manipulated to look up toward the LVOT, but we were unable to lodge the catheter tip outside of the inferior margin of the valve scaffold in a location under the right coronary cusp. Under transesophageal echocardiography and fluoroscopic guidance, the tip of the Simmons catheter was instead placed behind the valve cage at its inferior margin below the left main coronary artery, and a Choice PT Extra Support 0.014-inch coronary guidewire (Boston Scientific, Marlborough, Massachusetts) was advanced outside of the valve frame and used to direct a Prowler Plus 0.021-inch neurovascular microcatheter (Johnson & Johnson, New Brunswick, New Jersey) into the pseudoaneurysm (Video 2).

The Prowler Plus microcatheter delivered two $5 \times 20$ mm and two $4 \times 12$ nylon-fibered helical detachable Concerto coils (Medtronic) into the outpouching. We then injected 0.3 ml of Onyx LD ethylene-vinyl alcohol copolymer (Medtronic). At the conclusion, there was no extravasation of contrast into pseudoaneurysm (Central Illustration, Video 2). The patient was discharged the following day and remains asymptomatic.

DISCUSSION

Uncontained annular rupture is estimated to occur in 0.4% of TAVR cases (1–4). Risk factors have been described including subannular LVOT calcification,
balloon-expandable valve oversizing, aggressive balloon post-dilation, and bicuspid anatomy, whereas the use of multislice CT has improved rates of TAVR complications including rupture (5,6). Uncontained rupture is managed with emergent surgery; however, there are prior case reports of the use of coil embolization, N-butyl-2-cyanoacrylate-based glue, and an Amplatzer Vascular Plug for management of annular rupture with hemodynamic collapse (7–10).

Contained annular rupture is more common than uncontained rupture, occurring in 1.2% to 4.6% of TAVR cases (11,12) and is associated with more favorable short and long-term outcomes (5,11–14). Notably, all patients in these prior series were implanted with balloon-expandable valves. For contained rupture, a “watchful waiting” approach is recommended (3–5,15).

Percutaneous management of annular rupture with a self-expanding valve presents unique challenges as the valve scaffold is longer, complicating visualization and reaccess. We are aware of 1 other case where a percutaneous strategy was used (9). In that case, the rupture was uncontained and the injury was accessible from the left coronary cusp with an XB-LAD guiding catheter (Cordis, Santa Clara, California) in the standard fashion for coronary reaccess after TAVR.

**FOLLOW-UP**

Follow-up cardiac CTA at 2 months post-coiling showed obliteration of pseudoaneurysm without extravasation of contrast. The right coronary artery showed no progression of extrinsic compression, and the patient remained free of symptoms of ischemia.

**CONCLUSIONS**

Annular rupture may occur with self-expanding valves, typically during pre- or post-dilation. In this case, we describe a case of annular rupture managed with an endovascular strategy.
Computed tomography images of aortic valve showing a contained outpouching (A) at the inferior aspect of the valve cage below the right coronary artery (B). The arrows point to the “contained outpouching.”
(A) Right coronary angiography. (B) Aortic root angiograph did not demonstrate the outpouching. (C) Infra-annular ventriculography of the LVOT from within the Evolut Pro+ valve frame did not demonstrate the expected outpouching below the right coronary artery secondary to the skirt, which surrounds the valve cage below the neoannulus. (D) Left anterior oblique projection demonstrating the tip of the Simmons 1 catheter behind the valve frame at a location under the left main coronary artery, the only place it could be stably positioned behind the valve frame. From the catheter, a Prowler Plus microcatheter (Johnson & Johnson, New Brunswick, New Jersey) guided by Choice PT Extra Support coronary guidewire (Boston Scientific, Marlborough, Massachusetts) is advanced anteriorly around the outside of the valve frame and directed toward the expected location of the outpouching. Contrast injections through the microcatheter were able to fill the outpouching. (E) The first of 4 nylon-fibered helical Concerto coils (Medtronic, Minneapolis, Minnesota) is delivered to the contained rupture. (F) Final result after coiling and injection of Onyx LD ethylene-vinyl alcohol copolymer glue (Medtronic).
AUTHOR RELATIONSHIP WITH INDUSTRY

Dr. Laham has served as a consultant for Medtronic. All other authors have reported that they have no relationships relevant to the content of this paper to disclose.

REFERENCES

1. Pasic M, Unbehau A, Buz S, Drews T, Hetzer R. Annular rupture during transcatheter aortic valve replacement: classification, pathophysiology, diagnostics, treatment approaches, and prevention. J Am Coll Cardiol Intv 2015;8:1-9.

2. Walthor T, Hamm CW, Schuler G, et al. Perioperative results and complications in 15,964 transcatheter aortic valve replacements: prospective data from the GARY Registry. J Am Coll Cardiol 2015;65:2173-80.

3. Masson J-B, Kovac J, Schuler G, et al. Transcatheter aortic valve implantation: review of the nature, management, and avoidance of procedural complications. J Am Coll Cardiol Intv 2009;2:811-20.

4. Langer NB, Hamid NB, Nazif TM, et al. Injuries to the aorta, aortic annulus, and left ventricle during transcatheter aortic valve replacement: management and outcomes. Circ Cardiovasc Interv 2017;10:e004735.

5. Barbanti M, Yang T-H, Rodés CJ, et al. Anatomical and procedural features associated with aortic root rupture during balloon-expandable transcatheter aortic valve replacement. Circulation 2013;128:244-53.

6. Mylotte D, Lefevre T, Sandergaard L, et al. Transcatheter aortic valve replacement in bicuspid aortic valve disease. J Am Coll Cardiol 2014;64:2330-9.

7. Azarrafy R, Albuquerque FN, Carrillo RG, Cohen MG. Coil embolization to successfully treat annular rupture during transcatheter aortic valve replacement. Catheter Cardiovasc Interv 2018;92:1205-8.

8. Pignatelli A, Pestrichella V, Contegiacomo G, Navarese EP. Percutaneous treatment of aortic root rupture after transcatheter aortic valve replacement procedure. J Cardiovasc Med (Hagerstown) 2020;21:158-60.

9. Chakravarty Tarun, Cox Justin, Abramowitz Ygal, et al. Percutaneous management of aortic root rupture during transcatheter aortic valve replacement with coil embolization. Circ Cardiovasc Interv 2018;11:e005590.
10. Piliero N, Thony F, Vanzetto G, Barone-Rochette G. Gluing of an aortic perforation during transcatheter aortic valve replacement: an alternative treatment for annular rupture? J Am Coll Cardiol Intv 2015;8:2037–8.

11. Breitbart P, Minners J, Pache G, et al. Outcomes in patients with contained ruptures of the aortic annulus after transcatheter aortic valve implantation with balloon-expandable devices. EuroIntervention 2017;13:1300–2.

12. Blanke P, Reinöhl J, Schlensak C, et al. Prosthesis oversizing in balloon-expandable transcatheter aortic valve implantation is associated with contained rupture of the aortic root. Circ Cardiovasc Interv 2012;5:540–8.

13. Aminian A, Lalmend J, Dolatabadi D. Late contained aortic root rupture and ventricular septal defect after transcatheter aortic valve implantation. Catheter Cardiovasc Interv 2013;81:E72–5.

14. Subban V, Incani A, Clarke A, et al. Conservative management and resolution of a contained rupture of aortic annulus following transcatheter valve replacement. J Am Coll Cardiol Intv 2013;6:e33–4.

15. Lange R, Bleiziffer S, Piazza N, et al. Incidence and treatment of procedural cardiovascular complications associated with trans-arterial and trans-apical interventional aortic valve implantation in 412 consecutive patients. Eur J Cardiothorac Surg 2011;40:1105–13.

**KEY WORDS** annular rupture, coiling, Evolut, TAVR

**APPENDIX** For supplemental videos, please see the online version of this paper.
Calcium Assessment, Correct Sizing, and Care With Balloons

Three Commandments to Prevent Annular Rupture Post-TAVR*

Gianluca Lucchese, MD, PhD,a Omar A. Jarral, MBBS, PhD,a Simon Redwood, MD,b Bernard Prendergast, MDb

In this issue of JACC: Case Reports, Kellogg et al. (1) from Boston describe the successful percutaneous management of contained annular rupture following transcatheter aortic valve replacement (TAVR). Following deployment of a self-expandable valve in a fit 70-year-old patient with aortic stenosis, an area of contrast extravasation was noted and was managed conservatively. Post-operative surveillance demonstrated enlargement of the pseudoaneurysm with compromise of the right coronary artery. Since the patient declined surgical correction, they proceeded with percutaneous closure using 4 coils and polymer injection. This case is interesting for a number of reasons. First, the operators showed extreme technical skill in dealing with this difficult situation—one of just a few reported cases where treatment completely sealed the origin of the pseudoaneurysm. Second, the patient had limited calcification in the landing zone, and was theoretically at low risk of complications, demonstrating the importance of vigilance in all cases. Last, as the patient preferred a nonsurgical approach throughout, it demonstrates how difficult navigating patient preference and consent can be in the face of rapidly developing technology.

DEFINITION AND INCIDENCE

Annular rupture is a term that refers to a broad and imprecise category of injuries to the TAVR landing zone (2) and can be further categorized based on anatomical location, completeness of injury (contained or uncontained), and subsequent impact (e.g., pericardial effusion, coronary compromise, or fistula). The reported incidence is 0.5% to 1.0%, but is probably higher due to unidentified contained ruptures of little clinical significance. Annular rupture accounts for 15% of patients requiring a bail-out surgical procedure following TAVR, and in-hospital mortality is 50% for contained and >75% when uncontained (3,4).

ANATOMY AND CLASSIFICATION

Anatomically, injuries may be annular, subannular, or supra-annular (5). Detailed knowledge of landing zone anatomy is essential for operators in understanding the mechanism and impact of potential injuries, particularly in the subannular region. Annular injuries are typically localized and may subsequently be sealed by the implanted valve. Supra-annular injuries may traumatize the aortic wall (leading to aortic dissection) or coronary ostia. The consequences of subannular perforation depend on location, since the left ventricular outflow tract (LVOT) has fibrous and muscular parts (6). The fibrous part forms the aorto-mitral continuity, sitting between the right/noncoronary commissure and the mid portion of the left coronary cusp. In the healthy patient, this region is strong and distensible, and damage can typically result in acute mitral regurgitation or a ventricular septal defect, rather than catastrophic bleeding. The muscular part lies under the right coronary sinus and the left...
portion of the left coronary sinus. The portion under the right sinus is formed by the interventricular septum and anatomically supported by the overriding right ventricular outflow tract, and injuries are therefore less likely to be immediately life threatening. The remainder of the muscular LVOT is less protected, and thus is more likely to lead to bleeding (6). Hematoma in neighboring muscle has potential to spread to the subepicardial fat, and subsequently the pericardial space. Typically, this would occur in the proximal atrioventricular groove behind the main pulmonary artery, and close to the base of the left atrial appendage and proximal circumflex (6). The anatomic heterogeneity of annular injuries understandably means that it can present in a wide variety of ways, including totally silent, unexplained circulatory collapse, coronary ischemia, arrhythmias, pericardial effusion, and the presence of periaortic hematoma or abnormal shunts.

**RISK FACTORS**

Conceptual knowledge regarding this topic is in its infancy: there are just a handful of reviews in the published data, there are no basic science studies, and predictors are based on retrospective and registry data, which may be subject to confounding. However, a number of contributory factors have emerged (7). The risk of annular rupture is significantly higher in the presence of moderate or severe LVOT calcification (8). This makes sense from a biomechanical point of view, since these regions of stiffness have lower yield strength. Calcification may also be a marker of overall patient frailty. Not all LVOT calcification is the same: the highest risk is in the anatomically weakest region of the muscular LVOT, as described in the previous text (6).

Rupture is mainly a complication associated with balloon-expandable TAVR devices and seldom encountered with self-expanding devices unless excessive balloon pre- or post-dilatation is performed. Balloon-expandable valves exert greater radial force and circularize the annulus (9). This risk is significantly exacerbated with aggressive over sizing (>20%) or post-dilatation in the presence of calcification.

Other anatomic risk factors include bicuspid valve, small root diameter (<20 mm), annular asymmetry, and asymmetric LVOT hypertrophy. Institutional/operator risk factors include poor patient selection, low procedural volumes, lack of experience, and incorrect aortic measurements.

**TIPS TO AVOID ANNULAR RUPTURE: LESSONS FROM EXPERIENCE**

Aortic annular rupture is among the most devastating life-threatening complications of TAVR. Although uncommon, the high associated mortality requires careful procedural planning and execution. We have identified the following golden rules from our own experience:

1. Always perform a detailed quantitative and descriptive assessment of leaflet, annular, and LVOT calcification.
2. Size the device carefully based on annular and LVOT dimensions. Utilize the latest imaging software to obtain measurements in multiple views and at multiple levels.
3. In a high-risk patient, consider using smaller valves, and use balloon-expandable devices with caution. Consider incomplete inflation if a balloon if used (e.g., 2 to 3 ml underfilled) (2). If balloon dilatation is required, do not exceed the mean diameter of the LVOT or sinotubular junction (whichever is smaller). A balloon-to-artery ratio of 1 can be used for semicompliant balloons and <1 for noncompliant balloons (10). Adopting a slow 2-step deployment is an alternative technique to reduce the risk of annular rupture using balloon expandable valves in the presence of adverse anatomical features.
4. Ensure that the valve is deployed in a plane parallel to the annulus. Modify implantation (e.g., higher valve positioning to avoid protruding deposits) if required.
5. The presence of multiple risk factors for annular rupture in low- or intermediate-risk patients should heighten awareness and may favor conventional surgery at the time of heart team discussions.
6. Uncontained rupture requires emergency surgery and carries a very high mortality. Contained ruptures with no evidence of ongoing bleeding or compromise can be managed conservatively, with appropriate surveillance in-hospital and after discharge. This case is an extraordinary example of effective complete transcatheter occlusion of a “benign” contained rupture.

**CONCLUSIONS**

Annular rupture can be a devastating complication of TAVR. Awareness and avoidance are key, with particular focus on high-risk LVOT calcium, correct
valve sizing, and careful use of balloons. Operators implanting in the high-risk setting need advanced percutaneous skills to deal with potential complications, and the judgement to know when to manage rupture using a conservative, percutaneous, or surgical approach. Patient preferences need to be taken into consideration, but ultimately, the heart team should lead the decision-making process in the patient’s best interest.

**REFERENCES**

1. Kellogg MS, Tuttle MK, Shama R, Mehta SV, Laham RJ. Percutaneous management of a contained annular rupture occurring with self-expanding transcatheter aortic valve replacement. J Am Coll Cardiol Case Rep 2020;2:1852–8.

2. Pasic M, Unbehaun A, Buz S, Drews T, Hetzer R. Annular rupture during transcatheter aortic valve replacement: classification, pathophysiology, diagnostics, treatment approaches, and prevention. J Am Coll Cardiol Intv 2015;8:1–9.

3. Arslan M, Kim WK, Van Linden A, et al. Predictors and outcome of conversion to cardiac surgery during transcatheter aortic valve implantation. Eur J Cardiothorac Surg 2018;54:267–72.

4. Pineda AM, Harrison JK, Kleiman NS, et al. Incidence and outcomes of surgical bailout during TAVR: insights from the STS/ACC TVT registry. J Am Coll Cardiol Intv 2019;12:1751–64.

5. Aksoy O, Paiaoa AR, Marmagkiolis K, Mego D, Rollefson WA, Cilingiroglu M. Aortic annular rupture during TAVR: mini review. Cardiovasc Revasc Med 2016;17:199–201.

6. Girdauskas E, Owais T, Fey B, et al. Subannular perforation of left ventricular outflow tract associated with transcatheter valve implantation: pathophysiological background and clinical implications. Eur J Cardiothorac Surg 2017;51:91–6.

7. Yoon SH, Bleiziffer S, De Backer O, et al. Outcomes in transcatheter aortic valve replacement for bicuspid versus tricuspid aortic valve stenosis. J Am Coll Cardiol 2017;69:2579–89.

8. Okuno T, Asami M, Heg D, et al. Impact of left ventricular outflow tract calcification on procedural outcomes after transcatheter aortic valve replacement. J Am Coll Cardiol Intv 2020;13:1789–99.

9. Das R, Puri R. Transcatheter treatment of bicuspid aortic valve disease: imaging and interventional considerations. Front Cardiovasc Med 2018;5:91.

10. Coughlan JJ, Kiernan T, Mylotte D, Arnous S. Annular rupture during transcatheter aortic valve implantation: predictors, management and outcomes. InterV Cardio 2018;13:140–4.

**KEY WORDS** annular rupture, aortic stenosis, complications, TAVR
Calcified Nodules in the Superficial Femoral Artery Confirmed by Intravascular Ultrasound, Angioscopy, and Histology

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ABSTRACT

An 84-year-old man was admitted to the authors' hospital for the treatment of intermittent claudication. Angiography revealed an exophytic calcified nodules in the distal superficial femoral artery. Angioscopy also revealed abundant exophytic atherosclerotic calcification. Histology confirmed the diagnosis. (Level of Difficulty: Beginner.) (J Am Coll Cardiol Case Rep 2020;2:1862-6) © 2020 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Calcified nodules (CNs) have been previously described by optical coherence tomography (OCT) and intravascular ultrasound (IVUS). Histologically, CNs are defined as heavily involved by calcified plates and a surrounding area of fibrosis in the presence of a necrotic core. These plaques are vulnerable to rupture of calcified lesions and thrombi (1). Furthermore, calcified sheets or plates break and form nodules which can protrude into the lumen where they are associated with platelet-rich thrombi. The IVUS images of CNs can have various characteristics, such as convex shape of the luminal surface and side of the calcium, irregular luminal surface, and leading edge of the calcium. On OCT, CNs are defined as low-intensity, heterogeneous regions that are clear outside of the borderline. OCT has demonstrated a high, backscattering, protruding mass with signal attenuation. Previous angioscopy reports of coronary artery atherosclerotic plaques have described dense polypoid lesions protruding into the vessel lumen (2), but there are no reports of superficial femoral artery (SFA) CN plaques.

This paper describes the case of CNs in the SFA confirmed by angioscopy and removed by biopsy forceps, with histologic confirmation.

PRESENTATION

In June 2019, an 84-year-old man was admitted to our hospital with signs of intermittent claudication. The
symptoms began after approximately 3 to 5 min of walking or while seated for a prolonged period with his knee in a flexed position. Physical examination showed that his bilateral lower extremity pulses were weak. Initial blood pressure was 130/90 mm Hg; heart rate was 64 beats/min; oxygen saturation was 98%; his breathing respiratory rate was 18 breaths/min; and his temperature was 36.3°C. The ankle-brachial index was 0.69 on the right side and 0.79 on the left side. Echography revealed diffuse soft plaque in the right SFA and calcified lesions in the left distal SFA. The authors suspected significant stenosis in both SFAs.

**MEDICAL HISTORY**

The patient had diabetes mellitus, hypertension, and hyperlipidemia as risk factors of atherosclerosis. His right SFA was treated with drug-coated balloon angioplasty (130 cm, 6.0- × 150-mm, Lutonix DCB, Lutonix, New Hope, Minnesota).

**DIFFERENTIAL DIAGNOSIS**

The differential diagnosis included neurogenic claudication and critical limb ischemia. The patient’s orthopedic disease was ruled out by an orthopedic surgeon because the patient did not display any neurological signs.

**INVESTIGATIONS**

When the right SFA was treated, an angiogram revealed an eccentric calcified plaque in the left distal SFA.
Angioscopy cross-sectional images show an exophytic lesion in the distal superficial femoral artery (SFA). See Video 2.

Masson trichrome staining showing a fibrous cap over the nodule and intranodular fibrin.
MANAGEMENT

One month later, after his right SFA was treated, the authors performed endovascular treatment on the left side through a right femoral artery approach using a 6-F Sheathless PV (Asahi Intecc, Nagoya, Japan). A Vassallo Floppy 300-cm guidewire (Cordis, Cardinal Health, Tokyo, Japan) could be advanced into the lesion without any resistance. IVUS (Atlantis, Boston Scientific, Natick, Massachusetts) was performed, and high-resolution angioscopy (Zemporshe, Taisho Biomed Instruments, Osaka, Japan), because characteristics were recognized, including vessel diameter and length of treated lesion. IVUS showed a convex and irregular intimal lesion with acoustic shadowing (Figure 1). Angioscopy revealed a nonmobile, irregular surface, and white cauliflower-like shape accompanied by red thrombus (Figure 2). Because this type of atherosclerotic plaque can be difficult to treat, it was decided to remove the exophytic calcified plaque with biopsy forceps. The protruded calcified plaque was debulked several times using biopsy forceps, which allowed significant restoration of the left SFA.
lumen. Then the lesion was checked using IVUS and angioscopy, which showed removal of a considerable amount of calcified plaque and an increase in luminal area of the stenosis lesion. Balloon angioplasty was then performed using a Vascu Trak 140-cm, 6.0-× 40-mm (Bard Peripheral Vascular, Tempe, Arizona), followed by drug-coated balloon angioplasty (130-cm, 6.0-× 100-mm, Lutonix DCB, Lutonix). Post-treatment angiography of the left SFA showed sufficient dilation. IVUS and angioscopy also revealed no major dissection and good dilation of the treatment site (Video 3).

Plaque histology also was investigated. Exophytic intimal calcification was observed with hematoxylin and eosin staining. Masson trichrome staining indicated a fibrous cap over the nodule as well as fibrin deposition within the nodule (Figure 3).

**DISCUSSION**

CNs were defined as calcified plates surrounded by fibrosis. The luminal surface of the plaque contained fissures in the fibrous cap and calcifications with osteogenesis with overlying thrombus (1). IVUS showed a convex lesion with superficial hyperechoic signal with shadowing. Coronary angioscopy revealed a protruding polypoid lesion.

Little is known about the precise mechanisms underlying calcified plaque. Although postmortem cases of coronary artery disease have been reported (3), the appearance of CN plaques in patients undergoing angiography has not been described. In clinical practice, CNs are often difficult to treat.

In this case, angiography revealed an eccentric calcified plaque in the distal SFA. IVUS images showed a convex and irregular intimal lesion with superficial hyperechoic signal accompanied by acoustic shadowing. Angioscopy revealed a cauliflower-like, reddish mass protruding into the vessel lumen. After observation with intravascular imaging, the calcified plaque was debulked using biopsy forceps and confirmed plaque in the tissues.

As previously reported, IVUS and OCT may be used to diagnose CN plaques in clinical practice (2). However, it is sometimes difficult to distinguish them from thrombotic lesions. As shown in Figure 2, high-resolution angioscopy can easily distinguish plaque from thrombotic lesions. In combination with angioscopy and IVUS or OCT, diagnostic accuracy can be further improved.

**FOLLOW-UP**

Eight months after the patient was treated, the SFA was checked using echography, because of intermittent claudication. Echography showed severe stenosis of the proximal left SFA.

When the proximal SFA lesion was checked, angiography, IVUS, and angioscopy were performed in the previously treated distal SFA lesion. This lesion showed mild stenosis in the angiogram and kept sufficient lumen area in the IVUS images and small CNs without thrombi in the angioscopy images (Figure 4).

**CONCLUSIONS**

CNs confirmed by angioscopy and histological examination in this case may help to elucidate the histophysics of this condition.

**AUTHOR RELATIONSHIP WITH INDUSTRY**

All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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**REFERENCES**

1. Virmani R, Burke AP, Farb A, Kolodgie FD, et al. Pathology of the vulnerable plaque. J Am Coll Cardiol 2006;47 Suppl 8:C13–8.
2. Karanasos A, Ligthart JM, Witberg KT, et al. Calcified nodules: an underrated mechanism of coronary thrombosis? J Am Coll Cardiol Img 2012;5:1071–2.
3. Hao H, Fuji K, Shibuya M, et al. Different findings in a calcified nodule between histology and intravascular imaging such as intravascular ultrasound, optical coherence tomography, and coronary angioscopy. J Am Coll Cardiol Img 2014;7:937–8.

**KEY WORDS** angioscopy, calcified nodules, histological examination, IVUS

**APPENDIX** For supplemental videos, please see the online version of this paper.
Systemic Allergic Contact Dermatitis Due to a GORE CARDIOFORM Septal Occluder Device
A Case Report and Literature Review

Charles D. Resor, MD, Ari M. Goldminz, MD, Prem Shekar, MD, Robert Padera, MD, PhD, Patrick T. O’Gara, MD, Pinak B. Shah, MD

ABSTRACT

Nickel hypersensitivity is a rarely reported complication of patent foramen ovale/atrial septal defect closure. Herein, we report a case of systemic allergic contact dermatitis to nickel present in a GORE CARDIOFORM (W.L. Gore, Flagstaff, Arizona) septal occluder that resolved following explanation. To our knowledge this is the first published case of nickel hypersensitivity associated with this device. (Level of Difficulty: Beginner.) (J Am Coll Cardiol Case Rep 2020;2:1867-71) © 2020 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Nickel hypersensitivity is a rarely reported complication of patent foramen ovale (PFO)/atrial septal defect (ASD) closure with percutaneous occluder devices. Herein, we report a case of systemic allergic contact dermatitis to nickel present in a GORE CARDIOFORM septal occluder (GSO) device (W.L. Gore, Flagstaff, Arizona) that completely resolved following explanation. To our knowledge this is the first published case of nickel hypersensitivity associated with this device.

HISTORY OF PRESENTATION

A 37-year-old female patient initially presented to our institution for evaluation of right-sided chamber enlargement detected by transthoracic echocardiography performed for evaluation of palpitations. A cardiac magnetic resonance imaging study was performed which revealed a septum secundum defect with Qp/Qs of 1.15 and borderline right-sided chamber enlargement (right ventricular end-diastolic volume index [RVEDVi], 90 ml/m2). Follow-up at 1 year with repeat magnetic resonance imaging revealed a mildly dilated right atrium and right ventricle (RVEDVi, 119 ml/m2) with Qp/Qs of 1.4. Given the mild but
progressive right-sided chamber enlargement, the patient was referred for percutaneous ASD closure.

She underwent uncomplicated implantation of a 30-mm GSO device under transesophageal echocardiographic guidance. She was administered a single dose of perioperative cefazolin and started on aspirin monotherapy post-procedure. She did well clinically post-procedure without any cardiovascular symptoms, but after 7 days began to develop generalized pruritus and diffuse urticaria over her torso and extremities (Figure 1). The patient’s medical history was notable only for palpitations and the above evaluation and treatment.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis included possible drug reaction and allergic reaction to the recently implanted device or other contact allergens.

INVESTIGATIONS

Given the suspicion of a possible drug reaction, aspirin was discontinued and replaced temporarily with clopidogrel. She was seen in the Dermatology Clinic where a systemic allergic contact dermatitis was among the diagnoses considered. The GSO contains nitinol (55% nickel and 45% titanium) and expanded polytetrafluoroethylene material. She underwent patch testing with allergens (Chemotechnique Diagnostics, Malmö, Sweden) placed in Finn Chambers (Smart Practice, Phoenix, Arizona) on Scanpore tape (Medline Industries, Inc., Northfield, Illinois). Allergens were adhered to the skin for 48 h. A first read was performed at the time of patch removal, showing a questionable reaction to nickel sulfate 5%. At the delayed, 72-h reading, the only positive reaction was to nickel sulfate 5% which showed an extreme (3+) reaction. Of note, testing to 4 titanium allergens as well as nickel sulfate 2.5% was negative. Direct skin testing to the device itself under occlusion on the skin for 7 days was negative. Laboratory testing including tryptase, erythrocyte sedimentation rate, complete blood count, serum immunoglobulin E as well as serum and urine nickel levels were within normal limits. A nickel spot test (dimethylglyoxime) was performed and did not detect nickel release from the device.

Over the ensuing 8 weeks, she followed allergen avoidance strategies, which included changes to her skin care products, a low-nickel diet, as well as antihistamines. However, her symptoms and urticaria continued to worsen.

MANAGEMENT

Given the extreme reaction to nickel on patch testing and persistent, severe urticaria despite allergen avoidance strategies, conservative therapy, and workup for other potential causes of her urticaria, the patient decided to undergo device explantation and bovine patch ASD repair via midline sternotomy. A polymer ZIPFIX system (DePuy Synthes, West Chester, Pennsylvania) was used as an alternative to metal sternotomy wires. She experienced an uneventful post-operative course. Her symptoms and urticaria resolved within 7 days of explantation and had not recurred as of her 1-month and 3-month follow-up visits. Histologic evaluation of the tissue surrounding the device showed a mixed chronic inflammatory infiltrate consisting of lymphocytes, plasma cells, and macrophages with a prominent eosinophilic component (Figure 2).

DISCUSSION

Nickel is the most prevalent contact allergen, with positive reactions occurring in approximately 20% of patients who undergo patch testing (1). Whereas rates of nickel sensitization are decreasing in Europe possibly due to regulations on nickel release from consumer items, sensitization rates may be increasing in North America (2). Despite the significant nickel content of all United States Food and Drug Administration-approved PFO/ASD closure devices, documented allergic reactions to these devices after implantation are relatively rare. One review estimated the rate of device-related allergic events at 1 per 17,000 (3).

In the current case, the diagnosis of allergic contact dermatitis secondary to the device is supported by the onset of urticaria 1 week after implantation, confirmation of contact allergy to one of the materials present in the device, and resolution within a week of explantation. Additionally, histologic evaluation of the tissue surrounding the device showed chronic inflammation with eosinophilia, also supporting the diagnosis of a hypersensitivity reaction. Although we did not specifically evaluate for polytetrafluoroethylene (PTFE) sensitization beyond skin testing to the device itself, PTFE is a rare contact allergen and the patient’s positive reaction to nickel allergen testing was extreme. To our knowledge, this is the
first reported case of nickel hypersensitivity associated with the GSO device.

Contact allergy secondary to the Amplatzer (St. Jude Medical, Inc., St. Paul, Minnesota) (4–6), PFO-Star (Cardia Inc., Burnsville, Minnesota) (7), and Gore Helex (8) devices have been described previously. The GSO, which has less exposed nickel than other approved devices, was shown to have in vitro nickel elution similar to placebo and significantly lower than the Amplatzer septal occlude (9). Therefore, the GSO has been thought to be a good alternative for percutaneous PFO/ASD closure in patients with nickel contact allergy.

In the 3 pivotal randomized trials on PFO closure published in 2017, which included more than 2,000 patients, only 1 device-related allergic reaction was reported among the adverse events (10–12). This occurred in a patient randomized to medical therapy in the RESPECT (Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment) trial of the Amplatzer device. Whether this patient crossed over to the device arm, received off label device implantation, or had an allergic reaction to an unrelated device is not clear. No device explantation was reported in any of the trials. Of note, patch testing to nickel was not
required in the studies and patient reported history of nickel allergy was not an exclusion criterion for any of the trials.

Nickel exposure is known to induce urticaria in a subset of patients with nickel allergy, and has been previously reported in association with various implants (13). As in the current case, systemic allergic contact dermatitis to nickel following implantation of an intracardiac device that resolved with explantation has been described (14). In this prior report, patch testing showed a 3+ reaction to nickel sulfate, whereas other investigations such as serum nickel testing and an evaluation of in vitro nickel elution from the device did not show elevated nickel levels.

Rates of device-related allergic reactions are difficult to estimate as the entity is poorly defined, not well understood mechanistically, and apparently rare (15). Previous case reports note signs or symptoms of nickel allergy related to PFO/ASD closure devices covering a wide range of symptomatology including chest pain, palpitations, pericarditis/effusion, dyspnea, bronchospasm, headache, rash, and fever. Medical treatments used in these cases have included antihistamines, steroids, and clopidogrel (16).

In a retrospective analysis of explantation rates for PFO/ASD occluder devices, 38 of 13,736 (0.28%) of patients undergoing percutaneous closure had device removal (17). Allergy was not listed as the primary cause of explantation in any cases, but among the 14 patients who required device explantation for chest pain, 7 were found to have a positive patch test for nickel. Additional reasons for device explantation included residual shunt, thrombus, effusion, and perforation.

Investigations of symptoms or other adverse events following percutaneous PFO/ASD closure with nickel-containing devices in patients with known nickel allergy have yielded conflicting results (18–20). Although these studies are limited by small sample sizes and generalizability, none reported cases of device failure or explantation. One study described a “device syndrome” marked by chest pain, dyspnea, fatigue, and mild leukocytosis that developed in 8 of 9 nickel-allergic patients within several days of implantation and resolved with prednisone and clopidogrel. The actual prevalence of these symptoms among nickel-allergic patients who receive percutaneous PFO/ASD closure with nickel-containing devices is unknown. Despite the high prevalence of nickel allergy among the general population, the current literature suggests low rates of allergic reactions to PFO/ASD closure devices. The current North American standard concentration for nickel patch testing of 2.5% may even underestimate the true prevalence of nickel allergy (2). In Europe, a 5% nickel concentration is typically used for screening. Some investigators have also advocated the use cobalt-chromium or stainless steel devices for use with other intracardiac devices in the setting of nickel allergy. However, intracoronary cobalt-chromium and stainless steel stents are thought to elute a greater amount of nickel than the nitinol-containing alternatives (21). Currently, all the approved PFO/ASD occluder devices contain nitinol.

The role of pre-implantation screening is a controversial topic given the currently low-reported incidence of device-related allergic syndromes particularly with the newer devices, uncertain relevance of positive patch test results, and presently limited alternative options for device materials. In patients with known nickel allergy under consideration for PFO/ASD closure, a discussion of the risks and benefits should include device-related allergic reactions. Post-implantation workup is also complicated by atypical presentations and symptomatology, the lack of evaluation techniques that establish definitive causation, and the potential risks of explantation without a guarantee of symptom resolution. Further research is required to help guide the decision process particularly for patients with known nickel hypersensitivity and to stratify risk for the development of device-related reactions during the pre-operative evaluation process.

**FOLLOW-UP**

As of 3 months post-procedure, the patient has done well clinically and has remained free of urticaria or any allergic or cardiovascular symptoms.

**CONCLUSIONS**

Nickel hypersensitivity is a rarely reported complication of PFO/ASD closure with percutaneous occluder devices. To our knowledge this is the first published case of nickel hypersensitivity associated with the GSO device.

**AUTHOR RELATIONSHIP WITH INDUSTRY**

Dr. Goldminz’s wife owns stock in Johnson and Johnson. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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REFERENCES

1. DeKoven JG, Warshaw EM, Zug KA, et al. North American Contact Dermatitis Group patch test results: 2015–2016. Dermatitis 2018;29:297–309.
2. Goldminz AM, Scheinman PL. Comparison of nickel sulfate 2.5% and nickel sulfate 5% for detecting nickel contact allergy. Dermatitis 2018;29:321–3.
3. Schram SE, Warshaw EM, Laumann A. Nickel hypersensitivity: a clinical review and call to action. Int J Dermatol 2010;49:115–25.
4. Dickison P, Harris V, Smith SD. Nickel hypersensitivity following closure of atrial septal defect: a case report and review of the literature. Australas J Dermatol 2018;59:220–2.
5. Lai DW, Saver JL, Araujo JA, Reidl M, Tobis J. Pericarditis associated with nickel hypersensitivity to the Amplatzer occluder device: a case report. Catheter Cardiovasc Interv 2005;66:424–6.
6. Jain M, Singh S, Cadeiras M. A case of nitrinol allergy causing pericardial tamponade. J Invasive Cardiol 2013;25:E180–2.
7. Fukahara K, Minami K, Reiss N, Fassbender D, Koerfer R. Systemic allergic reaction to the percutaneous patent foramen ovale occluder. J Thorac Cardiovasc Surg 2003;125:213–4.
8. Basika UK, Kanter KR, Vincent R. Nickel allergy to the percutaneous patent foramen ovale occluder and subsequent systemic nickel allergy. J Thorac Cardiovasc Surg 2003;126:2112.
9. Verma DR, Khan MF, Tandar A, et al. Nickel elution properties of contemporary interatrial shunt closure devices. J Invasive Cardiol 2015;27:99–104.
10. Saver JL, Carroll JD, Thaler DE, et al. Long-term outcomes of patent foramen ovale closure or medical therapy after stroke. N Engl J Med 2017;377:1022–32.
11. Mas JL, Derumeaux G, Guillot B, et al. Patent foramen ovale closure or anticoagulation vs. antiplatelets after stroke. N Engl J Med 2017;377:1011–21.
12. Sondergaard L, Kasner SE, Rhodes JF, et al. Patent foramen ovale closure or antiplatelet therapy for cryptogenic stroke. N Engl J Med 2017;377:1033–42.
13. Hession MT, Scheinman PL. The role of contact allergens in chronic idiopathic urticaria. Dermatitis 2012;23:110–6.
14. Diaz Palacios MA, Lopez-Salguero R, Mercia Sanchez G, Martinez Romero A, Morales-Rubio A, Hernandez Fernandez de Rojas D. Chronic urticaria after implantation of a mitral annuloplasty ring in a nickel-allergic patient. J Investig Allergol Clin Immunol 2017;27:74–5.
15. Mohshedii MM, Kinney TB. Nickel hypersensitivity in patients with inferior vena cava filters: case report and literature and MAUDE database review. J Vasc Interv Radiol 2014;25:1187–91.
16. Jalal Z, Hascoet S, Baruteau AE, et al. Long-term complications after transcatheter atrial septal defect closure: a review of the medical literature. Can J Cardiol 2016;32:1315–20.
17. Verma SK, Tobis JM. Explantation of patent foramen ovale closure devices: a multicenter survey. J Am Coll Cardiol Intv 2011;4:579–85.
18. Rigatelli G, Cardioli P, Giordan M, et al. Nickel allergy in interatrial shunt device-based closure patients. Congenit Heart Dis 2007;2:416–20.
19. Kim HJ, Shin JU, Lee J, et al. Positive reactions to nickel on a patch test do not predict clinical outcome of nickel alloy-based atrial septal defect occluder implantation. Dermatology 2015;230:184–8.
20. Reddy BT, Patel JB, Powell DL, Michaels AD. Interatrial shunt closure devices in patients with nickel allergy. Catheter Cardiovasc Interv 2009;74:647–51.
21. Honari G, Ellis SG, Wilkoff BL, Aronica MA, Svensson LG, Taylor JS. Hypersensitivity reactions associated with endovascular devices. Contact Dermatitis 2008;59:7–22.

KEY WORDS allergy, Gore Septal Occluder, nickel
A 75-year-old female patient on hemodialysis presented with non–ST-segment elevation myocardial infarction. After successful primary percutaneous coronary intervention, in-stent restenosis (ISR) occurred 3 consecutive times. Intravascular imaging assessment during the repeated percutaneous coronary intervention indicated that the ISR was not associated with neointimal hyperplasia but was mainly attributed to a calcified nodule, which protruded into the lumen. We applied excimer laser catheter ablation to avoid another ISR. (Level of Difficulty: Intermediate.) (J Am Coll Cardiol Case Rep 2020;2:1872–8) © 2020 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).
(Video 1), whereas there was no significant stenosis in the left coronary artery. Following coronary angiography, primary percutaneous coronary intervention (PCI) was performed.

**MANAGEMENT**

Intravascular ultrasound (IVUS) was used to evaluate the culprit lesion before PCI. It visualized the protruding shape of multiple calcification plates suggestive of a calcified nodule (CN) (Figure 1D, Video 2). After balloon angioplasty, one 3.5 mm × 18 mm biolimus-eluting stent (Nobori, Terumo, Tokyo, Japan) was implanted, which enabled to compress protruding calcium plates with minimum stent area at 8.64 mm² (Figure 1E, Video 3). She was discharged following the commencement of 100-mg aspirin and 75-mg clopidogrel.

Eight months later, she presented our emergency room again because of the recurrence of chest pain under the aforementioned dual antiplatelet therapy (DAPT). Troponin T level was 0.224 ng/ml. A hypokinetic inferior wall was observed by echocardiography. Coronary angiography revealed in-stent restenosis (ISR) within the previously implanted drug-eluting stent (DES) (Figure 2A). IVUS showed the reprotrusion of calcification plates into the lumen. On optical coherence tomography (OCT) imaging, in addition to neointimal hyperplasia, multiple high-intensity signals with its substantial attenuation existed and caused lumen narrowing at the ISR site. These findings indicated that ISR was attributable to mainly eruptive CN (Figure 2D, Supplemental Figure 1).
Figures 1 and 2, Video 4). Culprit lesion was treated by a 4.0-mm drug-coating balloon (SeQuent Please, B. Braun Berlin, Germany) (Figure 2F, Video 5). Given that P2Y₁₂ reaction units measured by VerifyNow (Instrumentation Laboratory, Bedford, Massachusetts) were 295 under 75-mg clopidogrel use, it was switched to 3.75-mg prasugrel.

She required the third urgent hospitalization because of non-ST-segment elevation ACS 3 months after the second PCI. This recurrence of ACS was because of the second ISR in the RCA confirmed by coronary angiography. OCT prior to PCI demonstrated protruding mass characterized by high signal intensity with remarkable attenuation, suggesting the presence of a CN (Figure 3D, Supplemental Figure 3, Video 6). Of note, there was red thrombus attaching to the CN despite continuing same DAPT regimen. A 4.0 mm × 15 mm additional everolimus-eluting stent (Xience, Abbott Vascular, Santa Clara, California) was implanted to cover the protruding mass and thrombus (Figure 3E, Video 7).

She was rehospitalized because of non-ST-segment elevation ACS 6 months after the third PCI, although she was taking DAPT. Again, OCT imaging elucidated neointimal hyperplasia as well as protruding high-intensity mass with remarkable attenuation (Figure 4E, Supplemental Figure 4, Video 8). Debulking with excimer laser catheter ablation (ELCA) (1.7-mm Vitesse-Cos RX catheter, Spectranetics, Colorado Springs, Colorado) was performed with an incremental energy setting at 40 mJ/60 Hz. OCT imaging after ELCA revealed the effective ablation of the CN (Figure 4G, Video 9). Procedural-related minor coronary perforation was resolved by 3.5-mm
perfusion balloon (Ryusei, KANEKA Medics, Osaka, Japan) (Figure 4B, Video 10). A 3.5-mm drug-coating balloon (SeQuent Please, B. Braun, Berlin, Germany) was used to optimize this PCI procedure.

**DISCUSSION**

This case provides mechanistic insights into the refractory ISR at the CN (1–6). In this case, the implantation of a biolimus-eluting stent enabled the acquisition of optimal stent expansion. However, ISR occurred and it was presumably driven by the protrusion of the CN, rather than neointimal hyperplasia. Moreover, this dynamic response of the CN after favorable dilatation was repeatedly observed at every ISR. Recent pathohistological study reported 2 different mechanisms of ISR at the CN, which included: 1) protrusion of the CN through the stent struts; or 2) calcification of thrombus or neointima within the implanted stent (7). The protruding mass characterized by high signal intensity with remarkable attenuation on OCT was identified at the culprit lesion under DAPT. Therefore, the former mechanism seems more likely to be responsible for the refractory ISR in our case.

Every ISR occurred between 3 and 8 months after PCI and presented as ACS. Because ISR is generally observed around 8 months following PCI, the timing of every ISR in this case was quite earlier compared with findings from clinical trials. CN has been reported to be more frequently located at the middle segment of RCA, which receives much mechanical stress because of coronary hinge motion through beating (8). Moreover, stent implantation at this segment may make it more rigid. As such, more susceptible nature of coronary
segment to stress as well as its stent-induced greater rigidity may be a potential substrate for causing much stress, thereby resulting in the rapid and repeated eruption of the CN.

The current case indicates a potential benefit of the debulking procedure for CN. Currently, there is no evidence about its efficacy and difference in each debulking device. In our case, target lesion revascularization was not needed for 2 years after ELCA use. Orbital atherectomy is a recently developed coronary atherectomy device. It enables the modulation of calcification by both its advancement and pullback via wire bias. This feature may effectively modify the CN with its eccentric structure. Further investigation is warranted to elucidate a lesion-modification strategy with orbital atherectomy, ELCA, and other devices for CN.

In this case, coronary artery bypass surgery was an alternative option for revascularization. Because any significant stenosis was not identified in the left coronary artery throughout her clinical course, we selected PCI for repeated ISR.

**FOLLOW-UP**

Follow-up coronary angiography 12 months after the last PCI showed a fourth restenosis at the CN lesion. However, PCI was deferred because of its fractional flow reserve at 0.86 (Figures 5A and 5B). OCT imaging visualized the presence of multiple protruding CNs, but the lumen area was not substantially compromised. The repeated coronary angiography 2 years after the last PCI identified that the degree of stenosis at the ISR lesion did not change (Figure 5C). She continued to take DAPT after the last PCI.

**CONCLUSIONS**

In the current case, the CN exhibited refractory ISR following newer-generation DES implantation.
Intravascular imaging elucidated a distinct mechanism of ISR, which is presumably derived by repeated protrusion of a CN. These findings highlight CN as a high-risk plaque phenotype which requires repeat revascularization. Considering that debulking with ELCA effectively modulated the CN and the recurrence of ISR did not occur after the procedure, this strategy may be a potential first-line approach to treat the CN prior to stent implantation. Future studies are warranted to evaluate the efficacy of debulking devices including ELCA, rotablator, orbital atherectomy, and lithotripsy on CN.

**AUTHOR RELATIONSHIP WITH INDUSTRY**

The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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**REFERENCES**

1. Bentzon JF, Otsuka F, Virmani R, Falk E. Mechanisms of plaque formation and rupture. Circ Res 2014;114:1852-66.
2. Lee JB, Mintz GS, Lisauskas JB, et al. Histopathologic validation of the intravascular ultrasound diagnosis of calcified coronary artery nodules. Am J Cardiol 2011;108:1547-51.
3. Jia H, Abtahian F, Aguirre AD, et al. In vivo diagnosis of plaque erosion and calcified nodule in patients with acute coronary syndrome by intravascular optical coherence tomography. J Am Coll Cardiol 2013;62:1748-58.
4. Kawakami R, Hao H, Takagi Y, et al. Drug-eluting stent implantation on calcified nodule: ex vivo intravascular images and histopathology. J Am Coll Cardiol Intv 2015;8:e127-8.
5. Higuma T, Soeda T, Abe N, et al. A combined optical coherence tomography and intravascular ultrasound study on plaque rupture, plaque erosion, and calcified nodule in patients with ST-segment elevation myocardial...
infarction: incidence, morphologic characteristics, and outcomes after percutaneous coronary intervention. J Am Coll Cardiol Intv 2015;8:1166-76.

6. Otsuka F, Sakakura K, Yahagi K, Joner M, Virmani R. Has our understanding of calcification in human coronary atherosclerosis progressed? Arterioscler Thromb Vasc Biol 2014;34:724-36.

7. Mori H, Finn AV, Atkinson JB, Lutter C, Narula J, Virmani R. Calcified nodule: an early and late cause of in-stent failure. J Am Coll Cardiol Intv 2016;9:e125-6.

8. Lee T, Mintz GS, Matsumura M, et al. Prevalence, predictors, and clinical presentation of a calcified nodule as assessed by optical coherence tomography. J Am Coll Cardiol Img 2017;10:883-91.

KEY WORDS calcified nodule, in-stent restenosis, intravascular imaging, percutaneous coronary intervention

APPENDIX For supplemental videos and figures, please see the online version of this paper.
Recognition of Recurrent Stent Failure Due to Calcified Nodule Between a Rock and a Hard Place*

Jeffrey W. Moses, MD,a,b,c Eisuke Usui, MD,a,b Akiko Maehara, MDa,b

Calcified nodule (CN) is known as the least frequent (~5%) morphology causing thrombotic acute coronary syndrome. CN is an accumulation of small calcium fragments accompanying fibrin or platelet-rich thrombi, presumably a disruption of a fibrous cap due to a fracture of an underlying calcified plate (1). The prevalence of CN has been reported as 16% per vessel and 30% per patient in the nonculprit lesions using 3-vessel intravascular ultrasound (IVUS) (2) and 4.2% of culprit lesions using optical coherence tomography (OCT). Maximum calcium angle, coronary artery hinge motion, and hemodialysis are associated with the presence of CN (3). Morofuji et al. (4) reported that half of the heavily calcified lesions requiring rotational atherectomy had CN and that CN was associated with the worse 5-year adverse events, suggesting a mechanism of stent failure by CN that may not be resolved simply by adequate stent expansion.

Mori et al. (5) reported 2 different types of CN-related in-stent thrombosis in autopsy cases: 1) CN within the neointima (neoatherosclerosis) causing a thrombotic occlusion; and 2) CN without neointimal hyperplasia, suggesting early luminal thrombosis due to a reprotrusion of the CN through the stent. The first one is a similar mechanism of thrombosis to de novo CN, while the second one seems to be a unique phenomenon related to the CN in the stent (5).

In this issue of JACC: Case Reports, Nakano et al. (6) described a challenging case of a 75-year-old woman on hemodialysis who presented non-ST-segment elevation myocardial infarction and CN in the culprit lesion was treated with a drug-eluting stent. This patient presented at 8, 11, and 17 months with repeated non-ST-segment elevation myocardial infarction each time due to reprotrusion of the CN into the lumen without significant neointimal hyperplasia as determined by OCT or IVUS. Finally, after laser atherectomy, the culprit lesion remains non-obstructive, though follow-up OCT still demonstrated a non-flow-limiting reprotruding CN. Mechanism of this case seems to be the second type of CN-related thrombotic event described by Mori et al. (5).

Table 1 summarizes 6 cases reports (current and 5 others) describing recurrent in-stent restenosis (ISR) of which mechanism was confirmed as reprotruding CN by OCT or IVUS without significant neointimal hyperplasia at the CN site (i.e., those CNs were not a part of neoatherosclerotic process, but rather reprotrusion of original de novo CN through the stent) (7-11). Clinical and lesion characteristics include: 1) 4 patients on hemodialysis due to diabetic nephropathy; 2) myocardial infarction presentation in 4 patients at the time of ISR; 3) time to event being relatively early compared with regular ISR (median of 5.5 months from index procedure); 4) recurrent ISRs in 3 patients; 5) 3 cases being in proximal to mid right coronary artery and 1 case being at the hinge motion of saphenous vein graft; and 6) 2 cases with stent fractures at the site of CN. In summary, de novo CN appears at the hinge motion of severely calcified coronary artery, and the stented CN still has

*Editorials published in JACC: Case Reports reflect the views of the authors and do not necessarily represent the views of JACC: Case Reports or the American College of Cardiology.

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors’ institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the JACC: Case Reports author instructions page.

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TABLE 1 Case Reports Describing Recurrent Events After Stenting on CN

| First Author (Ref. #) | Patient Presentation, Imaging Findings, Treatment, and Outcome |
|-----------------------|---------------------------------------------------------------|
| Current report (6)    | CN in the mid RCA caused NSTEMI and treated with stent. At 8, 11, and 17 months, the patient experienced 3 NSTEMIs due to reprotruding CN in the stent. Treatments includes drug-coating balloon at first ISR, new stent at second ISR, and laser at third ISR. In the subsequent 2 yrs, patient did not have clinical event, though follow-up OCT showed non-flow-limiting reprotruding CN. |
| Yumoto et al. (7)     | CN in the proximal RCA caused stable angina and treated with scoring balloon and stent. At 5 months, the patient experienced STEMI due to reprotruding CN in the stent. |
| Kawai et al. (8)      | CN in the mid left circumflex artery caused NSTEMI and was treated with stent. At 4 and 9 months, the patient experienced 2 NSTEMIs due to reprotruding CN in the stent. Treatments includes scoring balloon and stent at first ISR and coronary bypass at second ISR because of multivessel disease. |
| Kawai et al. (9)      | CN in the mid left anterior descending artery caused unstable angina and treated with scoring balloon and stent. At 9 months, patient experienced stable angina due to reprotruding CN and neointimal hyperplasia in the stent, which was treated by cutting balloon. |
| McCutcheon et al. (10)| A proximal RCA lesion was treated by stent. At 6 months and 2 yrs, the patient experienced ISR, and OCT diagnosed protruding CN in the stent at 2 yrs. Eight years later, patient presented with unstable angina due to reprotruding CN through the fractured stent. Following lithotripsy, additional stents were implanted. |
| Uemura et al. (11)    | CN in a 36-year-old saphenous vein graft caused stable angina and was treated with stent. At 3 months, 2 weeks after cessation of P2Y12 inhibitor, the patient experienced STEMI due to reprotruding CN through stent fracture. |

CN = calcified nodule; ISR = in-stent restenosis; NSTEMI = non-ST-segment elevation myocardial infarction; OCT = optical coherence tomography; RCA = right coronary artery; STEMI = ST-segment elevation myocardial infarction.

mechanical stresses, resulting in reprotrusion of CN with or without visible stent fracture and frequently causes recurrent thrombotic events. Because of incomplete noncompliant balloon expansion, scoring or cutting balloon was used in 3 cases, lithotripsy was used in 1 case, and the current case was treated by laser atherectomy. Considering the mechanism of ISR (reprotrusion of CN) and a high prevalence of stent fracture, debulking of CN without a stent at the first time could be considered (12). However, because CN is protruding into the lumen and its eccentric shape, a caution must be taken to avoid perforation due to a wire bias to the normal site, which was observed in the current case.

One can speculate as to the mechanism of action of the laser: as excimer laser ablates only on contact, one wonders whether the acoustic effects of laser energy-fractured calcific segments that allowed more successful balloon compression and less reprotrusion. The authors do appropriately cite orbital atherectomy and intravascular lithotripsy as potential alternatives as well.

In summary, this case highlights an infrequent but vexing problem in percutaneous coronary intervention treatment of acute coronary syndromes and demonstrates the value of novel case reports in stimulating new approaches to rare problems.

AUTHOR RELATIONSHIP WITH INDUSTRY

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REFERENCES

1. Virmani R, Kolodgie FD, Burke AP, Farb A, Schwartz SM. Lessons from sudden coronary death. Arterioscler Thromb Vasc Biol 2000;20:1262–75.
2. Xu Y, Mintz GS, Tam A, et al. Prevalence, distribution, predictors, and outcomes of patients with calcified nodules in native coronary arteries: a 3-vessel intravascular ultrasound analysis from providing regional observations to study predictors of events in the coronary tree (PROSPECT). Circulation 2012;126:537–45.
3. Lee T, Mintz GS, Matsumura M, et al. Prevalence, predictors, and clinical presentation of a calcified nodule as assessed by optical coherence tomography. J Am Coll Cardiol Img 2017;10:883–91.
4. Morofuji T, Kuramitsu S, Shinozaki T, et al. Clinical impact of calcified nodule in patients with heavily calcified lesions requiring rotational atherectomy. Catheter Cardiovasc Interv 2020 Apr 7 [E-pub ahead of print].
5. Mori H, Finn AV, Atkinson JB, Lutter C, Narula J, Virmani R. Calcified nodule: an early and late cause of in-stent failure. J Am Coll Cardiol Intv 2016;9:e125–6.
6. Nakano H, Kataoka Y, Otsuka F, et al. Refractory in-stent restenosis attributable to eruptive calcified nodule. J Am Coll Cardiol Case Rep 2020, 2:1872–8.
7. Yumoto K, Kanaya T, Tanaka S, Fukuzawa T, Watanabe T, Aoki H. Calcified nodule as an unsolved cause of coronary stent thrombosis in the new-generation drug-eluting stent era. Cardiovasc Interv Ther 2018;33:169–70.
8. Kawai K, Alahori H, Imanaka T, et al. Coronary restenosis of in-stent protruding bump with rapid progression: optical frequency domain imaging and angioscopic observation. J Cardiol Cases 2019;19:12–4.
9. Kahiira T, Higuma T, Kotoku N, et al. Calcified nodule protruding into the lumen through stent...
10. McCutcheon K, Bennett J, Adriaenssens T. Double stent fracture and in-stent restenosis due to nodular calcification treated with Shockwave coronary intravascular lithotripsy. Catheter Cardiovasc Interv 2020 Jan 16 [E-pub ahead of print].

11. Uemura Y, Tanaka A, Takemoto K, et al. Late stent thrombosis concurrent with stent fracture at calcified nodule lesion in saphenous vein graft. J Am Coll Cardiol Intv 2019;12:e199–200.

12. Matsuda Y, Ashikaga T, Sasaoka T, et al. Ostial left circumflex lesion with calcified nodule successfully treated with excimer laser coronary atherectomy and drug-coated balloon. J Cardiol Cases 2020;22:32–3.

**KEY WORDS** acute coronary syndrome, atherosclerosis, percutaneous coronary intervention, stents
ABSTRACT

High-risk percutaneous coronary intervention may lead to undesirable clinical scenarios such as cardiogenic shock. We describe the hemodynamic changes using pressure-volume loop analyses in percutaneous coronary intervention-induced shock. (PULsecath mechanicaL Support Evaluation [PULSE]; NCT03200990) (Level of Difficulty: Intermediate.) (J Am Coll Cardiol Case Rep 2020;2:1882–3) © 2020 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

A 66-year-old male with no known cardiovascular disease was admitted after successful cardiopulmonary resuscitation following out-of-hospital cardiac arrest. Echocardiography showed poor left ventricular (LV) function without significant valve disease. Coronary angiography revealed chronic total occlusions of the right and left circumflex coronary arteries, and a complex, heavily calcified bifurcation lesion of the left anterior descending (LAD) coronary artery (Figure 1, right panel). Cardiac magnetic resonance imaging confirmed severely reduced LV ejection fraction of 28% but myocardial viability in all segments. There was heart team consensus for high-risk percutaneous coronary intervention under mechanical circulatory support.

A pulsatile LV assist device (model iVAC2L, PulseCath BV, Amsterdam, the Netherlands) was implanted through right femoral access. Invasive LV pressure-volume loops and pulmonary artery pressures were recorded as part of a research protocol (PULSE [PULsecath mechanicaL Support Evaluation]). Following balloon inflation in the LAD, progressive hemodynamic deterioration ensued (Figure 1, red/brown loops). The pressure-volume loop shifted further to the right with markedly reduced systolic and increased diastolic LV pressures resulting in a dramatic reduction in stroke volume. The patient developed bradycardia and severe hypotension (Figure 1, green loop), necessitating insertion of a temporary pacemaker. After initial recovery with vasopressor therapy, and upon continuation of the procedure, the patient developed refractory ventricular fibrillation. Cardiopulmonary resuscitation was initiated with effective chest compressions as illustrated by markedly increased systolic and lower diastolic pressures in combination with larger stroke volume (Figure 1, gray/yellow loops). Escalation of mechanical circulatory support from the iVAC2L to the Impella CP (Abiomed, Danvers, Massachusetts) was ineffective, and ventricular fibrillation persisted despite multiple defibrillations. Eventually, venoarterial extracorporeal membrane oxygenation was initiated, enabling a successful percutaneous coronary intervention of the LAD while the patient remained in ventricular fibrillation, despite multiple
attempts of electrical defibrillation. After LAD revascularization, sinus rhythm was restored successfully. The patient was transferred to the intensive care unit for further recovery.

**AUTHOR RELATIONSHIP WITH INDUSTRY**

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**KEY WORDS** cardiac assist devices, hemodynamics, percutaneous coronary intervention

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**FIGURE 1** Pressure-Volume Loops Show Subsequent Changes During Complicated High-Risk PCI

(Left) Pressure-volume loops show subsequent changes during complicated high-risk percutaneous coronary intervention (PCI). (Right) (Top) Angiographic right superior oblique view of the LAD prior and (bottom) after PCI. CPR = cardiopulmonary resuscitation; LAD = left anterior descending coronary artery.

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**ABBREVIATIONS AND ACRONYMS**

ICU = intensive care unit  
LAD = left anterior descending coronary artery  
LV = left ventricle
We describe a novel approach for percutaneous insertion of the Impella 2.5 (Abiomed Inc., Danvers, Massachusetts) through the brachial artery in 2 patients with inaccessible femoral arteries. Placement of the Impella 2.5 via the brachial artery was feasible and enabled the required hemodynamic support, with no procedural complications. (Level of Difficulty: Intermediate.) (J Am Coll Cardiol Case Rep 2020;2:1884–7) © 2020 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

The Impella device (Abiomed Inc., Danvers, Massachusetts) is frequently used for hemodynamic support in the setting of high-risk percutaneous coronary intervention (PCI) or during cardiogenic shock (1). The most frequent access route of the Impella 2.5 is the femoral artery. However, in selected patients, an alternative approach may be preferable or even necessary. Alternative insertion methods using the axillary or subclavian artery have been described, but these approaches have greater risk of complications such as access site hematoma, hemothorax, and neurovascular injury (2,3). The brachial artery has been described as an access route for PCI when radial or femoral access could not be obtained (4). The brachial artery could also be a potential alternative for Impella 2.5 insertion, as its more distal location provides easier and more controlled access compared with the axillary and subclavian artery, with potentially lower risks of complications.

Here, we describe the novel approach of percutaneous insertion and removal of the Impella 2.5 via the brachial artery in two cases: a patient with morbid obesity and poor left ventricular ejection fraction (LVEF) undergoing high-risk PCI, and a patient with cardiogenic shock after acute anterior myocardial infarction who required hemodynamic support.
left anterior descending artery (LAD) was diffusely diseased with several 90% proximal and distal stenoses. Also, there was a chronic total occlusion (CTO) of the large and left dominant circumflex artery and a CTO of the small right coronary artery (RCA). The LVEF of the patient was 24%. Myocardial perfusion scintigraphy showed no viability in the left dominant circumflex artery area but ischemia in the LAD territory.

The patient was initially refused for cardiac surgery and PCI in 2 hospitals because of his morbid obesity and poor left ventricular function. He was presented to our hospital for last resort therapy because of severe shortness of breath. Because of the ischemia and a significant stenosis in the last remaining vessel, the patient was considered for protected high-risk PCI of the LM/LAD with Impella 2.5 support.

We chose an alternative access via the brachial artery; a conventional insertion method of the Impella 2.5 was not possible because of inaccessible femoral arteries due to the patient’s excessive body weight. Pre-procedural Duplex ultrasound of the upper limb vasculature revealed a diameter of at least 4 mm of both brachial arteries. The Impella 2.5 was positioned via the left brachial artery through a 13-F sheath under angiographic guidance. Figure 1 shows the patient during the procedure with the Impella 2.5 in situ via the left brachial artery. Subsequent PCI via the right radial artery of the LM and LAD was performed with 3 drug-eluting stents, with good angiographic result. Videos 1 and 2 show the coronary angiography before and after PCI, respectively. Almost directly after first wire insertion, the pulsatility of the blood pressure disappeared and reappeared again at the end of the procedure. The Impella device was removed directly after the procedure. The sheath was removed 1 h after heparin cessation, and hemostasis was achieved with manual compression. Follow-up Duplex ultrasound of the left upper extremity showed good patency of the artery and no signs of arterial stenosis, aneurysm, or fistula.

**CLINICAL OUTCOMES.** The patient recovered quickly without any chest complaints. There were no signs of neurovascular injury, ischemia, or other procedural complications, and he was discharged the next day. He has resumed his activities and no longer experiences shortness of breath. His LVEF has improved from 24% to 34% at 6 months post-procedure.

**CASE 2**

Our second case was treated some years ago. Briefly, a 51-year-old man, without medical history, presented with an out-of-hospital cardiac arrest. After successful defibrillation in the ambulance, the electrocardiogram showed signs of an acute anterior myocardial infarction. A primary PCI was performed of the LM and proximal LAD via the right radial artery, with good angiographic result. During primary PCI, the hemodynamic status of the patient deteriorated, most likely due to microvascular obstruction and/or distal embolization. Insertion of an intra-aortic balloon pump was attempted but failed because crossing of the device through the femoral arteries or iliac arteries was not possible. Later, computed tomography imaging confirmed occlusion of the femoral and iliac arteries. The patient was admitted to the cardiac care unit and remained hemodynamically unstable despite pharmacological therapy. Additional mechanical support was deemed necessary, and Impella insertion was considered. Because of the inaccessible femoral arteries, we chose to use the right brachial artery as an alternative access route. Puncture of the brachial artery was successful, and 6-F and 10-F sheaths were inserted before inserting the Impella sheath. Subsequently, the Impella device was inserted and positioned without any complications.

**CLINICAL OUTCOMES.** Access through the brachial artery allowed insertion of the Impella device in a patient with cardiogenic shock refractory to pharmacological therapy. Initially, the clinical status and hemodynamics of the patient improved with Impella support and allowed weaning and extraction of the Impella device 4 days later. However, during his intensive care unit stay, the patient developed a necrotic foot and cerebral infarction and died of multiorgan failure.

**DISCUSSION**

We illustrate the feasibility of an alternative insertion of the Impella 2.5 through the brachial artery in 2 patients with inaccessible femoral arteries. Traditionally, the common femoral artery has been used as the preferred access route for Impella placement. However, many patients undergoing high-risk PCI have concomitant peripheral artery disease, precluding femoral access. This novel approach provides further options in patients with need for hemodynamic support but who have concomitant conditions that impede conventional insertion. Moreover, this brachial insertion method could facilitate quicker rehabilitation of patients, as the required bed-rest in case of femoral insertion of the Impella is not
necessary. The use of larger sheaths in the brachial artery may hold an increased risk of compartment syndrome of the forearm (5). However, the upper limb is known to have a large capability to recruit collateral circulation. Therefore, even longer use of the brachial artery for device insertion is feasible, provided careful monitoring of the upper limb circulation is performed as with femoral device access. Ideally, pre-procedural duplex ultrasound examination of the brachial artery is obtained in patients undergoing elective procedures.

Also, preferably smaller size sheaths are inserted first under fluoroscopic/angiographic guidance before inserting the large-bore sheaths. Closure of the brachial access in these 2 cases was performed with 30-min manual compression after heparin had been discontinued for 1 h. Alternatively, closure devices may be used as described for an axillary approach, although manual compression is likely to be the safest method for brachial artery access closure.

Here, we have presented a case series of short-term and longer term Impella support through brachial artery access as a feasible and possibly safer alternative to axillary access. Insertion via the brachial artery has advantages over an axillary approach because of its easier access and more distal location, potentially limiting the risk of complications.

Provided careful pre-procedural and post-procedural monitoring of the upper limb is performed, brachial device insertion may offer the opportunity to insert larger bore devices than thus far anticipated. Further exploration of brachial access for large-bore device insertion is necessary in larger patient populations.

**AUTHOR RELATIONSHIP WITH INDUSTRY**

The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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REFERENCES

1. Vetrovec GW, Anderson M, Schreiber T, et al. The cVAD registry for percutaneous temporary hemodynamic support: a prospective registry of Impella mechanical circulatory support use in high-risk PCI, cardiogenic shock, and decompenedated heart failure. Am Heart J 2018;199:115-21.

2. Bertoglio L, Katsarou M, Scandroglio M, Bertoldi L, Chiesa R, Pappalardo F. Surgical transaxillary placement of the Impella 5.0 ventricular assist device. J Card Surg 2019;34:92-8.

3. Truong HTD, Hunter G, Lotun K, et al. Insertion of the Impella via the axillary artery for high-risk percutaneous coronary intervention. Cardiovasc Revasc Med 2018;19:540-4.

4. Parviz Y, Rowe R, Vijayan S, et al. Percutaneous brachial artery access for coronary artery procedures: feasible and safe in the current era. Cardiovasc Revasc Med 2015;16:447-9.

5. Omori S, Miyake J, Hamada K, Naka N, Araki N, Yoshikawa H. Compartment syndrome of the arm caused by transcatheter angiography or angioplasty. Orthopedics 2013;36:e121-5.

KEY WORDS brachial artery, coronary artery disease, Impella, percutaneous coronary intervention, vascular access

APPENDIX For supplemental videos, please see the online version of this paper.
Impella 2.5 Insertion
Which Artery to Access When Femoral Is not an Option?*
Efstratios Koutroumpakis, MD

Transcutaneous left ventricular assist devices have been used for hemodynamic support in the setting of cardiogenic shock, or prophylactically before high-risk percutaneous coronary interventions (PCI). Impella 2.5 (Abiomed Inc., Danvers, Massachusetts) is a miniaturized, catheter-based, rotary blood pump that is placed retrogradely across the aortic valve and which can provide up to 2.5 l/min forward flow from the left ventricle to the ascending aorta (1). Since the introduction of Impella 2.5 in 2004, several studies have described its beneficial role in unloading the left ventricle and improving cardiac output, as well as augmenting coronary perfusion in the setting of cardiogenic shock and during high-risk PCI (2–6). PROTECT I (A Prospective Feasibility Trial Investigating the Use of IMPELLA RECOVER LP 2.5 System in Patients Undergoing High Risk PCI) demonstrated feasibility and overall safety of Impella 2.5, which, when used during high-risk PCI, prevented intraprocedural hemodynamic compromise (defined as mean arterial blood pressure <60 mm Hg for >10 min) (7). The role of Impella 2.5 in patients with cardiogenic shock after acute myocardial infarction was evaluated in the Impella-EUROSHOCK-registry (8). Placement of Impella 2.5 in the setting of cardiogenic shock was found to be feasible and resulted in improved serum lactate levels, suggesting improved organ perfusion.

No significant improvement in mortality has been reported.
Impella 2.5 is usually inserted percutaneously through a 13-F femoral sheath. Other arterial sites of insertion have been used in the presence of significant iliofemoral arterial disease that precludes femoral access. The axillary artery can typically accommodate the insertion of large sheaths (up to 18-F), and it is infrequently affected by atherosclerotic disease (9). Furthermore, the presence of collateral circulation decreases the likelihood of periprocedural limb ischemia. As a result, axillary access is usually the alternative approach for the insertion of Impella 2.5 in the absence of a suitable aorto-iliac-femoral arterial axis (10–13). However, concerns about potential nerve damage and inability to achieve good hemostasis due to lack of compressibility of the arteriotomy site against bony structures have been raised.

In this issue of JACC: Case Reports, Karimi et al. (14) describe the successful placement of Impella 2.5 using the brachial artery as an alternative access site when femoral access is not feasible. Impella 2.5 was uneventfully inserted and removed in 2 patients, 1 undergoing high-risk PCI and the other experiencing cardiogenic shock after acute myocardial infarction. Pre-procedural Duplex ultrasound of the upper limb of the first patient revealed a brachial artery diameter of at least 4 mm. Pre-procedural imaging assessing the brachial artery diameter of the second patient was not reported. The 13-F (4.33 mm) arterial sheath of Impella 2.5 was inserted following serial dilations of the brachial arteriotomy. No vascular or other complications were reported peri-procedurally in either of the patients. Impella 2.5 prevented hemodynamic compromise of the first patient during PCI to the left main coronary artery, and it helped the second patient transiently recover from cardiogenic shock, before he died due to multiorgan failure.

Although using the brachial artery (as an alternative to femoral) for the insertion of Impella 2.5 was
successful in the 2 patients presented (14), the generalizability of this approach requires further investigation in larger studies. The diameter of the brachial artery is 3.9 ± 0.5 mm when assessed by ultrasound, and it varies depending on patient demographic characteristics (15). Whether the 4.33 mm (13-F) arterial sheath of Impella 2.5 can be safely inserted, without increasing the risk of periprocedural limb ischemia or other vascular complications, must be carefully assessed by pre-procedural evaluation of the brachial artery. Duplex ultrasound, computed tomography angiogram, or peripheral angiography under fluoroscopy can be used for that purpose.

In addition to the limited studies evaluating the nonfenoral insertion of Impella 2.5, there are rapidly growing data supporting the transaxillary insertion of large-bore devices, including the transcatheter aortic valve replacement (TAVR) delivery system (16–18). A recent study of >3,600 patients who underwent TAVR reported a success rate with the transaxillary approach of 97.3% (18). The number of transaxillary TAVRs doubled over the 3 years of the study and represented one-half of the TAVRs during the last quarter of 2017. Thirty-day mortality was lower (5.3% vs. 8.4%; p < 0.01) and intensive care unit and hospital stay were shorter compared with the transapical or transaortic approaches. Stroke rates were 6.3%, whereas the major vascular complication rate was 2.5%. Whether brachial access is as successful as axillary access for the insertion of large-bore devices and whether it is associated with fewer neurological and bleeding complications must be answered by large prospective studies. Furthermore, as experience with transaxillary insertion of large-bore devices increases and the technique is being optimized (19), another question that arises is whether the axillary approach has now equal or better outcomes compared with the femoral approach and whether it can be used even in the setting of intact iliofemoral arteries (16,17).

In conclusion, insertion of Impella 2.5 using brachial arterial access is feasible in patients with unfavorable iliofemoral anatomy. An individualized approach with preprocedural evaluation of the brachial artery diameter should be followed. Large studies are needed to determine feasibility of the brachial approach in the general population and evaluate complication rates compared with the axillary approach, which is currently the most popular insertion site of large-bore devices in the setting of a hostile iliofemoral environment.

**AUTHOR RELATIONSHIP WITH INDUSTRY**

Dr. Koutroumpakis has reported that he has no relationships relevant to the contents of this paper to disclose.

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**REFERENCES**

1. Meyns B, Stolinski J, Leunens V, Verbelen E, Flameng W. Left ventricular support by catheter-mounted axial flow pump reduces infarct size. J Am Coll Cardiol 2003;41:1087–95.

2. Valgimigli M, Steendijk P, Sianos G, Onderwater E, Serruys PW. Left ventricular unloading and concomitant total cardiac output increase by the use of percutaneous Impella Recover LP 2.5 assist device during high-risk coronary intervention. Catheter Cardiovasc Interv 2005;65:263–7.

3. Remmelink M, Sjauw KD, Henriques JP, et al. Effects of left ventricular unloading by Impella recovery LP 2.5 on coronary hemodynamics. Catheter Cardiovasc Interv 2007;70:532–7.

4. Sjauw KD, Remmelink M, Baan J Jr, et al. Left ventricular unloading in acute ST-segment elevation myocardial infarction patients is safe and feasible and provides acute and sustained left ventricular recovery. J Am Coll Cardiol 2008;51:1044–6.

5. Seyfarth M, Sibbing D, Bauer I, et al. A randomized clinical trial to evaluate the safety and efficacy of a percutaneous left ventricular assist device versus intra-aortic balloon pumping for treatment of cardiogenic shock caused by myocardial infarction. J Am Coll Cardiol 2008;52:1584–8.

6. Remmelink M, Sjauw KD, Henriques JP, et al. Effects of mechanical left ventricular unloading by Impella on left ventricular dynamics in high-risk and primary percutaneous coronary intervention patients. Catheter Cardiovasc Interv 2010;75:187–94.

7. Dixon SR, Henriques JP, Mauri L, et al. A prospective feasibility trial investigating the use of the Impella 2.5 system in patients undergoing high-risk percutaneous coronary intervention (The PROTECT I Trial): initial U.S. experience. J Am Coll Cardiol Intv 2009;2:91–6.

8. Lauten A, Engström AE, Jung C, et al. Percutaneous left-ventricular support with the Impella 2.5-assist device in acute cardiogenic shock: results of the Impella-EUROSHOCK-registry. Circ Heart Fail 2013;6:23–30.

9. Tayal R, Ifišáh H, Lešar B, et al. CT angiography analysis of axillary artery diameter versus common femoral artery diameter: implications for axillary approach for transcatheter aortic valve replacement in patients with hostile aortoiliac segment and advanced lung disease. Int J Vasc Med 2016;2016:3610705.

10. Tayal R, Barvalia M, Rana Z, et al. Totally percutaneous insertion and removal of Impella device using axillary artery in the setting of advanced peripheral artery disease. J Invasive Cardiol 2016;28:374–80.

11. Lotun K, Shetty R, Patel M, Arain SA. Percutaneous left axillary artery approach for Impella 2.5 liter circulatory support for patients with severe aortoiliac arterial disease undergoing high-risk percutaneous coronary intervention. J Interv Cardiol 2012;25:200–1.

12. Kaki A, Blank N, Alraies MC, et al. Axillary artery access for mechanical circulatory support devices in patients with prohibitive peripheral arterial disease presenting with cardiogenic shock. Am J Cardiol 2019;123:1715–21.

13. Truong HTD, Hunter G, Lotun K, et al. Insertion of the Impella via the axillary artery for high-risk percutaneous coronary intervention. Cardiovasc Revasc Med 2018;19:540–4.
14. Karami M, van Veelen A, Henriques J. Brachial artery access as a novel alternative for Impella 2.5 insertion. J Am Coll Cardiol Case Rep 2020;2:1884–7.

15. Tomiyama Y, Yoshinaga K, Fujii S, et al. Accurate quantitative measurements of brachial artery cross-sectional vascular area and vascular volume elastic modulus using automated oscillometric measurements: comparison with brachial artery ultrasound. Hypertens Res 2015;38:478–84.

16. Gleason TG, Schindler JT, Hagberg RC, et al. Subclavian/axillary access for self-expanding transcatheter aortic valve replacement renders equivalent outcomes as transfemoral. Ann Thorac Surg 2018;105:477–83.

17. Petronio AS, De Carlo M, Bedogni F, et al. 2-Year results of CoreValve implantation through the subclavian access: a propensity-matched comparison with the femoral access. J Am Coll Cardiol 2012;60:502–7.

18. Dahle TG, Kaneko T, McCabe JM. Outcomes following subclavian and axillary artery access for transcatheter aortic valve replacement: Society of the Thoracic Surgeons/American College of Cardiology TVT Registry Report. J Am Coll Cardiol Intv 2019;12:662–9.

19. De Palma R, Rück A, Settergren M, Saleh N. Percutaneous axillary arteriotomy closure during transcatheter aortic valve replacement using the MANTA device. Catheter Cardiovasc Interv 2018;92:998–1001.

KEY WORDS cardiac assist devices, hemodynamics, percutaneous coronary intervention
Use of Lithotripsy in a Calcified Saphenous Vein Graft

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ABSTRACT

Percutaneous coronary interventions in saphenous vein grafts can pose a variety of challenges, such as severely calcified lesions. If these lesions are nondilatable, lithotripsy can arguably be a proper tool for lesion preparation. We present a case in which a nondilatable, calcified saphenous vein graft was successfully treated using Shockwave lithotripsy.

History of Presentation

A 74-year-old man was admitted to the cardiology department with progressively worsening retrosternal chest pain for several weeks. He had now developed chest pain at rest that improved within 5 min after nitroglycerin administration. Physical examination was unremarkable and vital signs were normal (heart rate 52 beats/min, blood pressure 155/70 mm Hg after nitroglycerin).

Medical History

The patient’s medical history included non-insulin-dependent diabetes, hypertension, inferior wall myocardial infarction in 1980, coronary artery bypass grafting in 1985 (left internal mammary artery [LIMA] to left anterior descending coronary artery and a sequential saphenous vein graft [SVG] to a diagonal branch, an obtuse marginal branch, and the posterior descending artery), and sustained fast ventricular tachycardia followed by percutaneous coronary intervention (PCI) with drug-eluting stent (DES) implantation in the proximal SVG in 2014.

Differential Diagnosis

Clinical presentation and medical history were highly suggestive for a recurrent acute coronary syndrome. Theoretically, the patient could also have had hypertension or intermittent arrhythmias.
INVESTIGATIONS

The electrocardiogram was unchanged from previous outpatient electrocardiograms (sinus rhythm, heart rate 54 beats/min, negative T waves in the inferior leads). Serial high-sensitivity troponin and creatine kinase measurements were successfully used to rule out an acute myocardial infarction. Cardiac ultrasound showed known mildly impaired systolic left ventricular function without significant valvular disease. Because the diagnosis was unstable angina, coronary angiography was scheduled and revealed occlusion of all 3 native vessels. LIMA function was normal. The proximal SVG contained an in-stent restenosis. In addition, a short calcified stenosis was seen in the segment between the anastomoses with the diagonal and the obtuse marginal branches (Figure 1A, Video 1).

MANAGEMENT

The patient was discussed by the heart team and accepted for PCI of the SVG. PCI of the native vessels and redo coronary artery bypass graft surgery (considering the normal LIMA function) were considered inferior options.

During a transradial procedure, the in-stent restenosis in the proximal segment of the saphenous graft was successfully treated with a DES. Because this was a tight stenosis, it had to be treated before balloons with diameter >3 mm could be advanced toward the new stenosis. An attempt to treat this new stenosis was unsuccessful; the calcified lesion was resistant to high pressure (24 atm) dilation with noncompliant (NC) balloons up to 3.5 mm.

After team discussion, the patient was scheduled for a second attempt, with anticipated rotational atherectomy or lithotripsy. Transfemoral access was obtained to allow the use of an 8-F left Amplatz 1.0 guiding catheter.

Optical coherence tomography was performed to guide further treatment selection and confirmed the anticipated presence of excessive calcification; circumferential calcium (360°) was found over the entire length of the graft but in particular at the site of the stenosis (Figures 2A, 2B, and 2E, Video 2). Lithotripsy was considered the most appropriate method to prepare the lesion.

Optical coherence tomographic evaluation revealed a crack in the calcification (Figure 2C, Video 3) after application of 8 cycles of 10 pulses using a 3.5 × 12 mm Shockwave lithotripsy balloon (Shockwave Medical, Santa Clara, California). Pre-dilation was successfully performed using a 3.75-mm NC balloon, followed by implantation of a 3.5 × 13 mm DES. A 4.0-mm NC balloon was used to perform post-dilation. The final angiographic result can be appreciated in Figure 1B and Video 4. Normal coronary blood flow was present during this injection (TIMI [Thrombolysis In Myocardial Infarction] flow grade 3).

Optimal stent apposition and expansion were confirmed during the final optical coherence tomographic run (Figure 2D, Video 5).

DISCUSSION

In contrast to native artery calcification, the process of calcification within an SVG is not limited to the plaque but occurs predominantly in the vessel wall. This is considered to be the result of arterialization: fibrous thickening, medial hypertrophy, and lipid deposition caused by the hemodynamic stress on the graft (1).

The resulting calcifications of this process can clearly be seen in the presented case (Figure 2). The combination of these circumferential wall calcifications and an eccentric, severely calcified plaque caused the difficult lesion in this case. Proper lesion...
Imaging performed before lithotripsy reveals circular calcifications (marked by an asterisk in A; a distal reference close to the focal tight lesion). At the site of maximal stenosis, a large amount of superficial eccentric calcification can be seen in addition to the deep calcification (marked by an asterisk in B). Following lithotripsy, disruption of the arc of calcification can be seen at 11 o’clock (marked by an arrow in C). Proper expansion and apposition of the stent after post-dilation are shown in D (several stent struts are marked by an asterisk). A longitudinal view (E) reveals calcifications covering the entire length of the venous graft. A and B are cross-sectional views at the level of the red and blue arrows, respectively. See Videos 2, 4, and 5.
preparation using rotational atherectomy or lithotripsy, a technique in which calcium is cracked by sonic pressure waves, was therefore required.

Given the amount and depth of the calcium revealed by optical coherence tomography, scoring (or cutting) balloon lesion preparation was not considered sufficient and therefore not attempted. Contemporary imaging-supported decision algorithms, although not specifically designed for SVG lesions, support this assumption (2–4). However, an attempt to crack the calcium with a scoring balloon could have been performed during the index procedure.

Although rotational atherectomy using a Rotablator (Boston Scientific, Marlborough, Massachusetts) has not been approved for use in an SVG, successful rotational atherectomy has been described in degenerated grafts (5). This approach was therefore considered in this patient as well but eventually appeared to be a less suitable lesion preparation tool than lithotripsy in this case because of the eccentric, circular, thick, and deep calcifications. Furthermore, we hoped to minimize risk for distal embolization in a vessel prone to embolization in combination with a technique prone to distal embolization.

Although lithotripsy has proved to be an effective tool to prepare severely circumferential calcified stenoses in native coronary arteries (6), its use within venous grafts has not been described previously.

In this case, lesion preparation by lithotripsy allowed straightforward successful treatment of a calcified lesion in a 34-year-old SVG that was resistant to high-pressure NC balloon inflations.

FOLLOW-UP

Six months after the procedure, the patient is still free from angina.

CONCLUSIONS

In selected cases, lithotripsy appears to be a feasible option for severely calcified SVG stenoses that are resistant to NC balloon dilation.

AUTHOR RELATIONSHIP WITH INDUSTRY

The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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REFERENCES

1. Castagna MT, Mintz GS, Ohlmann P, et al. Incidence, location, magnitude, and clinical correlates of saphenous vein graft calcification: an intravascular ultrasound and angiographic study. Circulation 2005;111:1148-52.
2. Barbato E, Shlofmitz E, Milkas A, Shlofmitz R, Azzalini L, Colombo A. State of the art: evolving concepts in the treatment of heavily calcified and undilatable coronary stenoses—from debulking to plaque modification, a 40-year-long journey. EuroIntervention 2017;13:696-705.
3. Fujino A, Mintz GS, Matsumura M, et al. A new optical coherence tomography-based calcium scoring system to predict stent underexpansion. EuroIntervention 2018;13:e2182-9.
4. Sorini Dini C, Nardi G, Ristalli F, Mattesini A, Hamiti B, Di Mario C. Contemporary approach to heavily calcified coronary lesions. Interv Cardiol 2019;14:154-63.
5. Pellicano M, Flore V, Barbato E, De Bruyne B. From debulking to delivery: sequential use of rotational atherectomy and Guidezilla for complex saphenous vein grafts intervention. BMC Cardiovasc Disord 2018;18:122.
6. Alsayo A, Salazar C, Becher MU, et al. Intravascular lithotripsy in calcified coronary lesions: a prospective, observational, multicenter registry. Circ Cardiovasc Interv 2019;12:e008154.

KEY WORDS coronary artery bypass, percutaneous coronary intervention, stenosis, stents

APPENDIX For supplemental videos, please see the online version of this paper.
Endovascular Repair of Thoracic Aortic Pseudoaneurysms in Children

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ABSTRACT

Pediatric aortic pseudoaneurysms are rare and can result in life-threatening sequelae. We describe 2 cases of exclusion of descending thoracic aortic pseudoaneurysm by different approaches, chosen based on the anatomy and cause of the lesions. (Level of Difficulty: Beginner.) (J Am Coll Cardiol Case Rep 2020;2:1895–8) © 2020 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

CASE 1

A new-born male received a diagnosis of tetralogy of Fallot, pulmonary atresia, hypoplastic pulmonary arteries, and aortopulmonary collaterals (MAPCAs). During hospitalization he was treated for a methicillin-resistant Staphylococcus bacteremia related to an indwelling arterial umbilical catheter. Ultimately, he underwent 4-mm aortopulmonary shunt placement.

At 8 months of age, cardiac catheterization was performed for surgical staging. Vitals were heart rate of 115 beats/min, blood pressure of 106/52 mm Hg, and oxygen saturation (SaO₂) of 85%. Examination revealed a normal S1, a single S2, and a grade-3 continuous murmur. Aortic angiography demonstrated a saccular pseudoaneurysm of the descending thoracic aorta at thoracic levels T8 to T9 (Figure 1, Video 1). It measured 10 mm in length and 14 mm in diameter and with a 6-mm neck. This pseudoaneurysm was presumed to be mycotic, given the prior umbilical artery catheter infection. A decision was made to exclude the aneurysm by an endovascular approach prior to surgical repair of tetralogy of Fallot to lessen the complexity and duration of surgery. Shortly thereafter, the patient was returned to the catheterization laboratory, weighing 7.8 kg. Arterial access was obtained, and a descending aortic angiogram was performed. Endovascular stenting was precluded in this patient based on his size. An Azur Framing coil, 0.035-inch, 14 mm × 34 cm (Terumo, Somerset, New Jersey) was deployed in the pseudoaneurysm lumen. This was followed by deployment of 2 Azur detachable hydrocoils (0.035-inch, 12 mm × 20 cm; and 0.035-inch 8 mm × 15 cm) to fill the lumen of the saccular pseudoaneurysm. An aortogram confirmed complete exclusion. Dual-supply MAPCAs were embolized during this procedure. Total procedural and fluoroscopy times were 60 min and 13 min,

LEARNING OBJECTIVES

- A minimally invasive endovascular approach may be considered for repair of thoracic descending aortic pseudoaneurysms in children with higher surgical risk.
- Strategies should be chosen based on associated risks and benefits of various approaches and specific anatomy and cause.

From the Division of Pediatric Cardiology, Department of Pediatrics, Louisiana State University, New Orleans, Louisiana. The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors’ institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the JACC: Case Reports author instructions page.

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respectively. There were no periprocedural complications. Surgical right ventricle-pulmonary artery conduit placement, VSD closure, and pulmonary arterioplasty were performed the following day. A computed tomography (CT) angiogram obtained 1 week later and cardiac catheterization at 17 months of age confirmed exclusion of the pseudoaneurysm (Figure 2, Video 2).

**CASE 2**

A 3-year-old, 15-kg male presented to an outside hospital after a high-speed motor vehicle accident. Cardiac contusion based on elevated troponin concentrations (47 ng/dl) and a flail anterior tricuspid valve leaflet with severe regurgitation on echocardiography were diagnosed. The patient developed hypotension requiring fluid resuscitation. Chest CT revealed a saccular descending aortic pseudoaneurysm measuring 5 × 5 mm at the thoracic T7 to T8 level (Figure 3). Vital signs at the time of transfer were heart rate of 144 beats/min, a blood pressure of 90/53 mm Hg, and an oxygen saturation (SaO2) of 100%. On examination, a normal S1, S2, and grade 3 pansystolic murmur were auscultated along the left sternal border. Due to the severe tricuspid regurgitation and evolving clinical decompensation, the decision was made to surgically repair the tricuspid valve after exclusion of the aneurysm. Endovascular repair of the pseudoaneurysm was chosen to obviate the need for 2 surgical entry sites, to mitigate the risk of rupture with cannulation, and to limit cardiopulmonary bypass time.

In the catheterization laboratory, a 4-F sheath was placed in the left femoral artery (LFA). Aortic angiography showed the saccular pseudoaneurysm measured 5 × 5 mm with maximal aortic diameter at the level measuring 8.5 mm (Video 3). The aortic diameters proximal and distal to the pseudoaneurysm were 8.3 mm and 8 mm, respectively.

The LFA was serially dilated after measurements of LFA, and the iliac artery was believed to be of adequate size. A 12-F Flexor (Cook Medical, Bloomington, Indiana) long arterial sheath was introduced. A 2.2-cm covered Cheatham-Platinum stent (NuMed, Hopkinton, New York) was mounted on a 10-mm × 2.5-cm Balloon-in-Balloon catheter (NuMed, Hopkinton, New York). The covered stent was deployed after confirming the position angiographically. Final angiograms demonstrated an aortic luminal diameter of 10 mm with complete exclusion of the pseudoaneurysm (Figure 4, Video 4). Procedural and fluoroscopy times were 26 min and 5.2 min, respectively.

Immediately following this, the patient underwent surgical tricuspid valve replacement using a 19-mm mechanical valve (St. Jude, Minneapolis, Minnesota) after an unsuccessful attempt at tricuspid valve replacement.
repair. The postoperative recovery was uneventful. The patient was discharged on warfarin and aspirin prophylaxis. He has had frequent follow-up examinations and admissions since surgery for warfarin management and noncompliance. At his most recent follow-up, 10 months after the procedure, the stent appeared intact with no evidence of turbulence or narrowing on transthoracic echocardiography. A CT angiogram will be performed within 1 year after the procedure to ensure there is no recurrence of the aneurysm.

**DISCUSSION**

Aortic pseudoaneurysms are rarely seen in children. Many are asymptomatic and are discovered incidentally (1). A pseudoaneurysm is a localized dilation of the vessel that occurs due to transmural disruption of the arterial wall. Important causes include infection, trauma, and previous cardiovascular surgery, or they may be iatrogenic. They can result in thromboembolism or fatal rupture when untreated. Open surgery has been the gold standard for repair (1–3). The advent of endovascular repair has altered the management of these lesions in adults and has been used in a small number of children (3,4).

This paper presents 2 children whose endovascular treatment approaches were chosen based on the causes and anatomy of the lesions. In the first patient, a detachable hydrocoil (Terumo) embolization technique was chosen for exclusion of the pseudoaneurysm due to the presence of a narrow neck, minimizing migration risk, and the aneurysm’s long-standing presence, making the risk of rupture less...
likely. Coil exclusion of an aneurysm, if successful, can be curative as opposed to covered stent placement that may need reintervention.

A hydrocoil consists of a Platinum coil with an expandable hydrogel polymer that expands when in contact with blood. There is limited expansion in the first 3 min, providing the operator a window for repositioning or retrieval. Maximum expansion occurs in 20 min. The coil expands to 3 to 4 times its original diameter, decreasing the number of coils required. Most of the aneurysm is filled by expansion of the hydrocoil, promoting organized thrombus. Histologic specimens of aneurysms embolized with hydrocoils in animal models revealed the aneurysm filled by coils, hydrogel, neointima, and minimal thrombus. Consequently, the incidence of recanalization due to thrombolysis and aneurysm regrowth is low. This technique is preferable in small children as the 0.018-inch coils can be deployed using a microcatheter. Embolization can be safely performed when there is a risk for adjacent aortic branch occlusion, as with covered stents. The need for reintervention is less likely in comparison to that with covered stent placement, given the need for redilation with somatic growth. Complications of hydrocoil embolization include recurrence of the aneurysm due to incomplete packing and coil migration (5,6).

In the second patient, given the uncertainty of aneurysmal wall integrity following the trauma and the wide neck of the aneurysm, covered stent placement was preferred over coil embolization. Covered Cheatham Platinum stents (NuMed) used for endovascular repair of recurrent coarctation of aorta have been used in pediatric patients >20 kg for exclusion of aortic aneurysms. These balloon-expandable stents were chosen due to comparatively smaller sheaths required for deployment of the stent and the ability to redilate the stent later if needed (4). Balloon-expandable stents can be mounted on balloons of various diameters, which facilitates placing the stent in vessels with a wide range of diameters. The present patient received a 2.2-cm stent diluted to 10 mm that could be expanded up to 24 mm in diameter. Based on available studies, this patient might have been the youngest patient in whom a balloon-expandable covered stent was deployed for exclusion of post-traumatic aortic pseudoaneurysm (4). Adverse events associated with this procedure include endoleaks, stent migration, stent fracture, vascular injury, atheroembolism, and distal lower limb ischemia (4,7).

CONCLUSIONS

An endovascular approach for exclusion of thoracic descending aortic pseudoaneurysm is less invasive. It may be an option in relatively young children with favorable anatomy who are deemed to have a higher surgical risk.

AUTHOR RELATIONSHIP WITH INDUSTRY

The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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REFERENCES

1. Mendeloff J, Stallion A, Hutton M, Goldstone J. Aortic aneurysm resulting from umbilical artery catheterization: case report, literature review, and management algorithm. J Vasc Surg 2001;33:419-24.
2. Jaffer U, Gibbs R. Mycotic thoracoabdominal aneurysms. Ann Cardiothoracic Surg 2012;1:417-25.
3. Menini Stahlschmidt CM, Von Bahten LC, Leal Nicoluzzi JE, et al. Successful endovascular management of a traumatic aortic rupture in a pediatric patient: case report and literature review.Ulus Travma Acil Cerrahi Derg 2010;16:84-6.
4. Goldstein BH, Hirsch R, Zussman ME, et al. Percutaneous balloon-expandable covered stent implantation for treatment of traumatic aortic injury in children and adolescents. Am J Cardiol 2012;110:1541-5.
5. Kallmes DF, Fujiwara NH. New expandable hydrogel-Platinum coil hybrid device for aneurysm embolization. AJNR Am J Neuroradiol 2002;23:1580-8.
6. Ferral H. Hydrogel-coated coils: product description and clinical applications. Semin Intervent Radiol 2015;32:343-8.
7. Medical Advisory Secretariat. Endovascular repair of descending thoracic aortic aneurysm: an evidence-based analysis. Ont Health Technol Assess Ser 2005;5:1-59.

KEY WORDS covered stent, hydrocoil embolization, traumatic pseudoaneurysm

APPENDIX For supplemental videos, please see the online version of this paper.
A 37-year-old woman presented with chest pain and shortness of breath in the third trimester of pregnancy. Diagnostic imaging demonstrated a saddle pulmonary embolism, severe impairment of right ventricular function, and an extensive deep venous thrombus. She underwent catheter-directed thrombolysis with tissue plasminogen activator and delivered a healthy infant at term. (Level of Difficulty: Intermediate.) (J Am Coll Cardiol Case Rep 2020;2:1899–904) © 2020 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

PRESENTATION

A 37-year-old nullipara presented to the emergency department at 33 weeks 2 days gestational age with several hours of shortness of breath and chest pain. Initial evaluation was notable for tachycardia to 120 beats/min, tachypnea with a respiratory rate of 30 breaths/min, and oxygen desaturation requiring 4 liters of supplemental oxygen through high-flow nasal cannula to maintain saturations above 94%. Blood pressure was normal at 112/70 mm Hg. She was dyspneic at rest and became increasingly dyspneic with speaking. On examination, jugular venous pressure was elevated to 6 cm above the sternal angle, and a right ventricle (RV) heave was palpated. Heart sounds S1 and S2 were normal, without accentuation of S2. S2 was not palpable. Breath sounds were decreased bilaterally, and asymmetrical swelling of the right lower extremity was present.

LEARNING OBJECTIVES

- To describe unique considerations for treatment of a pulmonary embolism in pregnancy.
- To illustrate a novel way of treating a submassive pulmonary embolism in pregnancy.
- To review the published medical literature surrounding the use of catheter-directed thrombolysis for treatment of pulmonary embolism in pregnancy.

MEDICAL HISTORY

The patient had been found to be heterozygous for the prothrombin gene mutation G20210A 2 years prior on elective carrier screening. She also had a recent
history of immobility after a soft tissue injury of the right knee 2 weeks prior to presentation. She denied any other medical history.

**DIFFERENTIAL DIAGNOSIS**

Given her history, symptoms, and vital sign abnormalities, differential diagnosis included pulmonary embolism, cardiac arrhythmia, undiagnosed cardiac structural abnormality, pregnancy-related cardiomyopathy, and infectious causes such as pneumonia with pleurisy or pleural effusion and pericarditis.

**INVESTIGATIONS**

The patient’s laboratory results were notable for a hemoglobin of 11.1 g/dl, white blood cell count of 10.1 x 10^9 l; and platelet count of 175 x 10^9 l. Her serum lactate was 0.9 mmol/l. Her initial troponin was 0.48 ng/ml (reference range: <0.05 ng/l). Electrocardiography showed sinus tachycardia. There was high suspicion for pulmonary embolism with concern for impending hemodynamic instability based on vital signs and physical examination findings. Thus, the decision was made to forego lower extremity Doppler ultrasonography as the initial study and to proceed directly to computed tomography angiography (CTA). The benefit of reaching a prompt diagnosis and rapid initiation of treatment was thought to outweigh the minimal risks of radiation to the fetus, and the patient was amenable to this treatment. Of note, the fetal radiation exposure associated with CTA is estimated at a maximum of 0.66 mGy, which is well below the 50-mGy threshold of significant adverse neurodevelopmental outcomes (1).

CTA with intravenous (IV) iohexol (Omnipaque 350, GE Healthcare, Chicago, Illinois) in a solution of 100 ml with abdominal shielding was performed and demonstrated a saddle pulmonary embolism (PE) (Figure 1). Transthoracic echocardiography demonstrated a flattened interventricular septum in diastole, consistent with RV volume overload, an elevated estimated systolic pulmonary artery (PA) pressure of 46 mm Hg and thrombus in the main PA and PA branches (Figure 2). Lower extremity Doppler ultrasonography demonstrated an extensive, occlusive, right-sided deep venous thrombosis extending from the popliteal vein up to the femoral vein.

**MANAGEMENT**

Following the results of the CTA, IV unfractionated heparin (UFH) was initiated. The patient’s clinical status was reviewed by a multidisciplinary team including specialists in maternal fetal medicine, cardiology, obstetric anesthesia, interventional radiology, and critical care. Based on the patient’s worsening tachycardia, tachypnea, and oxygen requirement and increasing troponin concentrations (to 0.51 µg/l) over 18 h of IV UFH treatment, the multidisciplinary team expressed concern for impending hemodynamic instability. Re-evaluation for clinical improvement after 24 to 48 h of IV UFH was deemed imprudent due to the potential for rapid deterioration in maternal status that would prompt emergent delivery and resuscitation, which would be catastrophic in the setting of RV dysfunction.

In the setting of the large clot in the main PA, evidence of severe RV dysfunction, and concern for worsening cardiac status during 6 additional weeks of pregnancy, followed by delivery, catheter-directed thrombolysis (CDT) using tissue plasminogen activator was recommended. The recommendation was also made for an inferior vena cava filter placement, due to the significant lower extremity clot burden and the need to discontinue anticoagulation during delivery. The multidisciplinary members shared their decisions with the patient, with careful consideration of the risks, benefits, and alternatives to this therapy, including continuing UFH for at least 24 to 48 h. The team discussed the fact that CDT could help remove clot burden and allow for improvement in RV function before her anticipated delivery in 6 weeks.

The team also discussed the fact that the maternal and fetal risks associated with this intervention were hard to calculate, given the limited available medical literature regarding use of CDT in pregnancy but that the few case reports in pregnancy had favorable outcomes. The fetal risk of radiation exposure with CDT and inferior vena cava filter placement were also reviewed, which is considered low in the third trimester and outweighed by the maternal benefits (1).

Following appropriate patient counseling and informed consent, bilateral ultrasonography-assisted thrombolysis catheters and suprarenal inferior vena cava filter were placed in the interventional radiology suite (Figure 3). IV iohexol 350 in a solution of 50 ml was used during fluoroscopy. Tissue plasminogen activator was infused at a rate of 1.0 mg/h along with UFH through the ultrasonography-assisted thrombolysis catheters for 24 h while the patient remained in the intensive care unit for close monitoring and continuation of IV UFH. Continuous electronic fetal heart rate monitoring was performed during this time.

On post-operative day (POD) 1, ultrasonography-assisted thrombolysis catheters were removed,
with improvement in RV size and function and troponin decrease to 0.35 ng/ml. By POD 2, the patient was able to maintain saturations ≥99% on room air. Subcutaneous low-molecular-weight heparin was initiated on POD 2, with a target peak concentration of 0.8 to 1.2 U/ml and a trough concentration >0.6 U/ml to avoid supratherapeutic and subtherapeutic effects, respectively. On POD 3, transthoracic echocardiography demonstrated a 12-mm Hg decrease in estimated PA systolic pressure, further indicating hemodynamic improvement. The patient was discharged at 34 weeks 2 days gestation with a plan for close outpatient follow-up. Fetal monitoring throughout her hospital admission was reassuring.

DISCUSSION

PE is one of the leading causes of maternal morbidity and mortality in the United States, accounting for 9.5% of pregnancy-related deaths from 2008 to 2017 (2). The hypercoagulable state of pregnancy increases the risk of venous thromboembolism 4-fold above the general population, for an overall venous thromboembolism incidence of 0.5 to 2 per 1,000 pregnancies (3). Inherited thrombophilias increase the risk of venous thromboembolism in pregnancy; for example, the prothrombin G20210A mutation is associated with a 2- to 3-fold increased risk of venous thromboembolism (4). However, the overall risk of venous thromboembolism in pregnancy remains <1% for a

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FIGURE 1: Chest Computed Tomography

Chest computed tomography shows (A) axial image of saddle pulmonary embolus and (B) right ventricular dilation with right-to-left ventricle diameter (RV/LV) ratio >1.

FIGURE 2: Transthoracic Echocardiogram

Transthoracic echocardiogram shows (A) flattening of interventricular septum (arrowheads) during diastole, consistent with right ventricular volume overload, and (B) visible thrombus in the main pulmonary artery (solid arrow) and pulmonary artery branches (dashed arrows).
prothrombin gene heterozygote with no history of venous thromboembolism, thus, the standard practice is to not initiate anticoagulation in these patients in pregnancy.

When a pregnant patient does receive a diagnosis of venous thromboembolism, the standard treatment for PE in pregnancy is systemic anticoagulation, regardless of PE classification (3). In the nonpregnant population, however, treatment varies based on PE classification (5). Despite the lack of high-quality data to support its use, thrombolytic therapy for PE in pregnancy has been documented in a handful of case reports and observational studies.

In the present case, CDT is described as the first-line treatment for a submassive PE in the third trimester of pregnancy. Because there are currently no guidelines regarding thrombolysis for PE in pregnancy, providers interested in using this treatment must extrapolate from data in the nonpregnant population. According to the 2016 guidelines from the American College of Chest physicians, systemic thrombolytic therapy is recommended only for patients with a massive PE and for patients with a submassive PE who clinically deteriorate despite systemic anticoagulation (6). There is currently no consensus surrounding the use of systemic or catheter direct thrombolysis as a primary treatment for patients who present with a submassive PE, due to controversy regarding risk-benefit ratio. Compared to systemic thrombolysis, CDT has the potential to lower the risk of bleeding by localizing drug delivery directly to the area of interest, allowing for a two-thirds reduction in the required dose (7). Numerous studies have demonstrated the efficacy and safety of CDT for PE in the general population. For example, 2 prospective observational studies each with 100 patients demonstrated significant reduction in right ventricle-to-left ventricle (RV/LV) ratios, significant improvement in PA pressures, and 80% clinical success rate when using CDT for massive and submassive PEs (5). A third prospective study was a randomized controlled trial that demonstrated more rapid normalization of the RV/LV ratio with CDT compared to UFH in patients with a submassive PE (5). The overall bleeding rates in these 3 studies were low, with only 1 severe incidence of bleeding and 16 moderate incidences of bleeding in a total of 280 cases. Although these studies demonstrate the efficacy and safety of CDT, there have been no direct comparisons of CDT to systemic thrombolysis. As such, the most recent CHEST guidelines recommend reserving CDT for cases with a particularly high risk of bleeding (6).

Whether thrombolysis should be used in pregnancy, whether thrombolysis should be used in submassive PEs in all subjects, and whether thrombolysis should be given systemically or in a catheter-directed fashion are all topics of ongoing debate. Thus, the use of CDT as first-line treatment for a submassive PE in pregnancy makes the present case a unique situation. In this case, the decision was made based on multidisciplinary discussion among specialty providers and shared with
the patient, with careful consideration of the risks, benefits, and alternatives to this therapy, as outlined above. Particular emphasis was given to the interaction between ongoing RV dysfunction and the cardiovascular burden of 6 additional weeks of pregnancy followed by labor and delivery. Pregnancy is a state of increased cardiac output and blood volume, and the normal physiologic changes of pregnancy, labor, and delivery often worsen underlying cardiac dysfunction. The primary concern for this patient was that without thrombolysis, cardiac dysfunction would worsen with ongoing pregnancy, with the potential for catastrophic urgent preterm delivery or decompensation during term delivery. CDT was chosen over systemic thrombolysis to minimize the dose of tissue plasminogen activator, given concerns regarding risk of bleeding and possible fetal effects (7).

This case adds to the limited studies regarding use of CDT in pregnancy. In the review, 5 case reports of CDT were identified for PE in pregnancy (Table 1) (8-12). In 1 case of submassive PE, CDT was used only after the patient developed severe RV dysfunction despite therapeutic anticoagulation. There were no maternal complications in any of the cases. In 1 case, an intrauterine fetal demise occurred 1 day after CDT; however, this fetal death was attributed to maternal acuity. None of the prior cases report long-term maternal outcomes.

This is the third case report to describe CDT as treatment for a PE in the third trimester of pregnancy. In any trimester of pregnancy, CDT for massive or submassive PE can be considered for patients with current or impending hemodynamic instability. In the third trimester, special consideration should be given to CDT as the first-line treatment for any submassive PE due to the potential catastrophic events that acute decompensation could prompt, including the need for premature delivery with the myriad of short- and long-term complications of prematurity and the further deterioration of maternal status when the hemodynamic burden of an emergency delivery is superimposed on significant cardiopulmonary dysfunction. Furthermore, given the inherent limitations of gestation, patients in the third trimester have less time for cardiac function to improve before the intense cardiovascular stress of labor and delivery.

**FOLLOW-UP.** The patient presented at 38 weeks 5 days gestation for a scheduled induction of labor. Low-molecular-weight heparin was discontinued, and IV UFH was initiated, with monitoring of activated partial thromboplastin time. The patient delivered a healthy infant weighing 3,735 g at 39 weeks 0 days gestation. On postpartum day 1, she was transitioned back to weight-based therapeutic low-molecular-weight heparin, with the plan to continue this for 6 months. The remainder of her postpartum course was unremarkable, and she and the infant were discharged home on postpartum day 4. The inferior vena cava filter was removed 2 months postpartum. The filter was kept in place longer than the standard 4-week period due to the unique hypercoagulability of the postpartum state and the patient’s extensive lower extremity clot burden. At a follow-up visit 6 months after CDT, the patient was doing well and reported a healthy infant who was meeting all pediatric milestones.

**CONCLUSIONS**

In summary, this paper describes the case with excellent maternal and neonatal outcome following CDT as first-line treatment for a submassive PE in the third trimester of pregnancy. Further research should explore the efficacy and safety of this treatment in pregnancy. Due to the complex physiologic changes in pregnancy and the cardiovascular strain associated with delivery, pregnant patients in the third trimester with submassive PE may derive the most benefit from

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**TABLE 1 5 Previous Case Reports Describing the Use of CDT for PE in Pregnancy**

| First Author, Year (Ref. #) | GA at Diagnosis | Type of PE | Maternal Outcome | Fetal/Neonatal Outcome |
|----------------------------|-----------------|------------|------------------|------------------------|
| Gowda et al., 2019 (8)     | 9 weeks         | Massive    | Pulmonary infarct | Through delivery        |
| Sofocleous et al., 2001 (10) | 15 weeks      | Massive    | Major bleeding*  | Through delivery        |
| Pick et al., 2015 (11)     | 33 weeks        | Submassive | Pre-eclampsia    | Through delivery        |
| Krishnamurthy et al., 1999 (9) | 26 weeks     | Submassive | None             | Through delivery        |
| Bechtel et al., 2005 (12)  | 30 weeks        | Massive    | None             | Through delivery        |

*Source of bleeding was not identified, but the patient became hypotensive and anemic (drop in hemoglobin by 2 g/dl) 24 h after the procedure.

CDT = catheter-directed thrombolysis; GA = gestational age; PE = pulmonary embolus; PTB = preterm birth.
expeditious thrombolysis and associated resolution right ventricular strain.

**AUTHOR RELATIONSHIP WITH INDUSTRY**

The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

**REFERENCES**

1. American College of Obstetricians and Gynecologists. Guidelines for diagnostic imaging during pregnancy and lactation. ACOG committee opinion No. 723. Obstet Gynecol 2017;130:e210.

2. U.S. Centers for Disease Control and Prevention. Enhancing Reviews and Surveillance to Eliminate Maternal Mortality. Available at: https://www.cdc.gov/reproductivehealth/maternal-mortality/erase-mm/index.html. Accessed November 11, 2019.

3. Greer IA. Pregnancy complicated by venous thrombosis. N Engl J Med 2015;373:540-7.

4. American College of Obstetricians and Gynecologists. Inherited thrombophilias in pregnancy. ACOG practice bulletin No. 197. Obstet Gynecol 2018;132:e18.

5. Sista AK, Kuo WT, Schiebler M, Madoff DC. Stratification, imaging, and management of acute massive and submassive pulmonary embolism. Radiology 2017;284:5-24.

6. Keanon C, Akl EA, Ornelas J, et al. Antithrombotic therapy for VTE disease: CHEST guideline and expert panel report. Chest 2016;149:315-22.

7. Heavner MS, Zhang M, Bast CE, Parker L, Eyer RF. Thrombolysis for massive pulmonary embolism in pregnancy. Pharmacother J Hum Pharmacol Drug Ther 2017;37:1449-57.

8. Gowda N, Nwabuobi CK, Louis JM. Catheter-directed thrombolytic therapy in the management of massive pulmonary embolism in pregnancy. Obstet Gynecol 2019;134:1002-4.

9. Krishnamurthy P, Martin CB, Kay HH, et al. Catheter-directed thrombolysis for thromboembolic disease during pregnancy: a viable option. J Matern Fetal Med 1999;8:24-7.

10. Sofocleous CT, Hinrichs C, Bahramipour P, Baron A, Abujudeh H, Contractor D. Percutaneous management of life-threatening pulmonary embolism complicating early pregnancy. J Vasc Interv Radiol 2001;12:1355-6.

11. Pick J, Berlin D, Horowitz J, Winokur R, Sista AK, Lichtman AD. Massive pulmonary embolism in pregnancy treated with catheter-directed tissue plasminogen activator. Case Rep 2015;4:91-4.

12. Bechtel J, Mountford M, Ellinwood W. Massive pulmonary embolism in pregnancy treated with catheter fragmentation and local thrombolysis. Obstet Gynecol 2005;105:1158-60.

**KEYWORDS** catheter-directed thrombolysis, pregnancy, thromboembolism

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MINI-FOCUS ISSUE: INTERVENTIONAL CARDIOLOGY

IMAGING VIGNETTE: CLINICAL VIGNETTE

Left Main Coronary Artery Stent Misadventure

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ABSTRACT

Coronary artery bypass grafting has long been the standard of care for patients with left main coronary artery (LMCA) disease. Lately, percutaneous coronary intervention (PCI) has become a suitable alternative for these patients, but the procedure may be challenging. We describe 2 cases of LMCA PCI failure requiring surgical intervention. (Level of Difficulty: Advanced.) (J Am Coll Cardiol Case Rep 2020;2:1905–6) © 2020 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

CASE DESCRIPTIONS

A 69-year-old woman underwent a primary percutaneous coronary intervention (PCI) with left main coronary artery (LMCA) and left anterior descending (LAD) coronary artery stenting. This procedure was followed by staged treatment of the left circumflex artery and further LAD stenting for severe in-stent restenosis with an LMCA stent post-dilatation as a result of suboptimal expansion. After 6 months she presented with unstable angina. Diagnostic imaging showed the coronary stent protruding through the LMCA origin into the aortic root (Figure 1A), and a repeat coronary angiogram showed in-stent thrombosis. The patient was then referred for surgery and underwent on-pump coronary artery bypass grafting to the LAD and left circumflex artery. Once the aorta was opened, the LMCA stent was found protruding approximately 1 cm into the left sinus of Valsalva, in direct contact with the aortic valve, which was not damaged (Figure 1B). The stent was then cut at the origin of the LMCA, and the operation was completed successfully.

A second patient, a 76-year-old woman, 2 months following a primary PCI with LMCA and LAD stenting for an anterior ST-segment elevation myocardial infarction, presented with exertional angina. Echocardiographic examination showed a stent protruding through the left coronary ostium. At coronary angiography, the protruding stent was unexpanded and fractured (Figures 1C and 1D). In this case, open heart surgery was necessary to cut the fractured stent protruding into the aorta with few clots for approximately 7 mm (Figures 1E and 1F) and to perform intraoperative balloon dilation through the LMCA, under direct vision, to achieve full stent expansion. The operation was then completed uneventfully.

Both patients were discharged home, and at 6 months follow-up they were both free from angina, with no signs of myocardial ischemia during exercise electrocardiogram testing.

LMCA PCI may be challenging because of certain anatomic and structural factors: the length and angle of bifurcation and its specific histological characteristics could make stent positioning difficult or even
impossible. The most frequent complications are in-stent restenosis, stent fracture, thrombosis, and malposition, which can increase the risk of early and late coronary events and/or damage to the aortic valve. A malpositioned LMCA stent may be treated surgically (1) or conservatively (2). These 2 patients underwent surgery. The malpositioned stents were cut in both cases to avoid aortic damage and to prevent thromboembolic events and/or endocarditis, in addition to coronary artery bypass grafting and intraoperative balloon stent dilatation, respectively, to treat coronary ischemia.

**FIGURE 1** LMCA PCI Failure and Repair

(A and B) Patient 1. Echocardiographic and surgical views of the stent protruding through the left main coronary ostium in direct contact with the left cusp of the aortic valve. (C and D) Patient 2. Angiographic images of the malpositioned and fractured left main stent. (E) Patient 2. Surgical view after cut of the protruding stent. (F) Patient 2. The trimmed portion of the stent. LMCA = left main coronary artery; PCI = percutaneous coronary intervention.

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**REFERENCES**

1. Nakamura M, Minakata K, Yamazaki K, et al. Aortic valve replacement in patients with protruding coronary artery stents. J Cardiol Cases 2014;10:213-5.

2. Kim JH, Kim KW, Choe WJ. Suspected coronary ostium calcification identified as a protruding stent by epiaortic echography. J Clin Ultrasound 2015; 43:135-7.

**KEY WORDS** complication, coronary artery bypass, stents
MINI-FOCUS ISSUE: INTERVENTIONAL CARDIOLOGY

CASE REPORT: CLINICAL CASE

Functional Recovery of a Failed Radial Artery Graft After Progression of Native Coronary Stenosis

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ABSTRACT

Competitive flow from the native vessel can lead to coronary graft failure. However, restoration of graft patency can occasionally occur. We present the case of subtotal occlusion of a radial artery graft bypassing a lesion with moderate stenosis, with subsequent late functional recovery once the native vessel disease had progressed. (Level of Difficulty: Intermediate.) (J Am Coll Cardiol Case Rep 2020;2:1907-10) © 2020 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

PRESENTATION

A 47-year-old female patient, former smoker, presented to the emergency department of the authors’ hospital due to an episode of syncope in the standing position, which was preceded by a brief episode of chest discomfort.

At presentation, the patient was asymptomatic and hemodynamically stable. Systolic and diastolic blood pressure values were 132/75 and 122/71 mm Hg in the supine position and on standing, respectively. Heart rate was 72 beats/min. Physical examination was unremarkable.

Electrocardiography (ECG) revealed normal sinus rhythm without atrioventricular or intraventricular conduction delay or specific repolarization abnormalities, and initial cardiac biomarker and d-dimer levels proved to be normal.

MEDICAL HISTORY

The patient had a medical history of arterial hypertension and 3-vessel coronary artery disease treated with coronary artery bypass grafting (CABG) 1 year previously. Pre-CABG coronary angiography was indicated by limiting angina pectoris (Canadian Cardiovascular Society Class III) and had revealed extensive atherosclerosis of left anterior descending artery (LAD) with consecutive stenotic lesions 90% to 95%, borderline stenosis (50%) of the proximal left circumflex artery, 80% stenosis of the first obtuse marginal branch (OM1), and 50% stenosis of the mid right coronary artery (RCA) right dominance. The

LEARNING OBJECTIVES

- To emphasize the fact that restoration of patency of subtotally occluded radial arterial grafts can occur in the long-term, even after more than 5 years.
- To become familiar with the pathophysiology of coronary graft failure and key properties of radial arterial grafts.

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LAD was grafted by the left interior thoracic artery (LITA), OM1 by a saphenous vein graft (SVG), and the posterior descending artery (PDA) by a left radial artery graft.

Long-term medical therapy included oral low-dose aspirin; metoprolol, 25 mg twice daily, atorvastatin, 40 mg daily, and ramipril, 5 mg daily.

**DIFFERENTIAL DIAGNOSIS**

Initial differential diagnosis included: 1) non-ST-segment elevation acute coronary syndrome; 2) an arrhythmic event; and 3) neurally mediated syncope precipitated by noncardiac chest discomfort or emotional stress.

**INVESTIGATIONS**

The patient was admitted to the cardiology clinic for further investigation and management. Serial testing of cardiac biomarkers and repeated ECGs did not yield results compatible with acute myocardial injury. Transthoracic echocardiography showed preserved left ventricular systolic function without any other remarkable findings. Twenty-four-hour ECG monitoring did not reveal any significant heart rhythm disturbances.

ECG exercise testing was positive for ischemia, and thus, exclusion of graft failure or progression of native vessel coronary artery disease was deemed mandatory.

Coronary angiography did not reveal significant progression of native vessel disease. LITA graft to LAD and SVG to OM were functioning well, whereas the RA graft to RCA was found diffusely narrowed and subtotally occluded (“string sign”) (Figure 1B, Video 1). As the bypassed stenotic lesion of the right coronary artery was of borderline severity (50% diameter) (Figure 1A, Video 2), the RA graft failure was presumed to be due to competitive flow from the native vessel. Subsequently, further noninvasive testing with single-photon emission computed tomography (SPECT) was performed, which did not reveal myocardial ischemia at any territory.

**DISCUSSION**

According to current guidelines (1), the decision to repeat revascularization in CABG patients with angiographic evidence of graft failure must be based on the presence of either a large area of inducible ischemia on noninvasive testing, usually defined as at least 10% of left ventricular myocardium, or severe symptoms despite optimal medical therapy. If revascularization is deemed appropriate, percutaneous
coronary intervention of the native vessel is the preferred approach in most cases.

In the present case, the constellation of symptoms, clinical picture, and laboratory and angiographic findings was not suggestive of an acute coronary syndrome, whereas the patient had not experienced typical angina post-CABG.

**MANAGEMENT**

Due to the lack of inducible ischemia on SPECT, conservative therapy was chosen. The patient remained asymptomatic throughout hospitalization and was discharged 4 days after admission. Neuromediating syncope was considered the most probable cause of transient loss of consciousness. Medical therapy remained the same, and a follow-up visit was scheduled.

**FOLLOW-UP**

Eight years later, the patient once again underwent coronary angiography due to an atypical chest pain syndrome with concomitant nonspecific repolarization abnormalities on ECG. LITA graft to LAD and SVG to OM were shown to be patent and functioning well, whereas no clinically significant disease progression in native branches of the left coronary artery was noted. On the other hand, significant atherosclerosis progression was now observed in mid-RCA (90%), and the PDA was totally occluded at its origin (**Figure 2A**, Video 3). Importantly, however, selective angiography of the radial artery graft, which demonstrated “string sign” on previous catheterization, was now shown to be fully patent and functional with satisfactory run-off to the PDA (**Figure 2B**, Video 4).

**CONCLUSIONS**

RA grafts have been shown to carry superior long-term patency rates compared to SVG and have been associated with a lower risk of mid-term major adverse events when used to supplement single or bilateral interior thoracic artery grafts (2). Currently, radial artery grafts comprise the preferred approach in grafting native vessels other than the LAD, in cases where right interior thoracic artery grafts cannot be used (1). However, the hemodynamic significance of native vessel lesions should be established prior to surgery by functional assessment because competitive flow from the native vessel is a leading cause of early and late graft failure. The radial artery, particularly, is characterized by a thicker wall and higher myocyte density in the media compared to the interior thoracic artery, which may account for the well-established predisposition of radial artery grafts for early postoperative spasm, leading sometimes to
graft failure (3). In addition, placement of a graft to bypass a lesion of moderate angiographic severity has been associated with significantly greater incidence of native vessel disease progression. Interestingly, the latter phenomenon occurs more frequently at the right coronary circulation (4).

There is evidence that late functional recovery and restoration of patency can occur in a large proportion of radial artery grafts that appear subtotally or totally occluded, with the presence of a native vessel stenosis of at least 90% constituting an independent predictive factor of graft recovery. This phenomenon has been observed 6 to 12 months post-CABG, but to the best of the authors’ knowledge, the present case is the first very late (8 years) string sign reversal to be reported (5,6).

In this patient’s original CABG procedure, the radial artery should have probably been used to graft the more severely stenosed OM1, although it is doubtful if grafting the RCA was indicated at all. Nevertheless, the configuration of grafts used, although inappropriate, provided a valuable insight into the physiology of radial artery grafts.

AUTHOR RELATIONSHIP WITH INDUSTRY

The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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REFERENCES

1. Neumann F-J, Sousa-Uva M, Ahlsson A, et al., for the ESC Scientific Document Group. 2018 ESC/EACTS guidelines on myocardial revascularization. Eur Heart J 2019;40:87-165.
2. Gaudino M, Benedetto U, Fremes S, et al. Radial-artery or saphenous-vein grafts in coronary-artery bypass surgery. N Engl J Med 2018;379:2069-77.
3. Acar C, Jebara VA, Portoghese M, et al. Comparative anatomy and histology of the radial artery and the internal thoracic artery. Implication for coronary artery bypass. Surg Radiol Anat 1991;13:283-8.
4. Hayward PA, Zhu YY, Nguyen TT, Hare DL, Buxton BF. Should all moderate coronary lesions be grafted during primary coronary bypass surgery? An analysis of progression of native vessel disease during a randomized trial of conduits. J Thorac Cardiovasc Surg 2013;145:140-8; discussion 148-9.
5. Kim JB, Kang JW, Song H, et al. Late improvement in graft patency after coronary artery bypass grafting: serial assessment with multidetector computed tomography in the early and late postoperative settings. J Thorac Cardiovasc Surg 2011;142:793-9.
6. Merlo M, Terzi A, Tespili M, Ferrazzi P. Reversal of radial artery ‘string sign’ at 6 months follow-up. Eur J Cardiothorac Surg 2003;23:432-4.

KEY WORDS CABG, coronary graft failure, radial arterial graft

APPENDIX For supplemental videos, please see the online version of this paper.
An azygos vein varix was incidentally discovered in a 26-year-old man. Owing to the potential risk of pulmonary emboli, we implanted a covered stent in the superior vena cava, effectively excluding the varix. Eighth months later, the varix was thrombosed and involuted. (Level of Difficulty: Advanced.) (J Am Coll Cardiol Case Rep 2020;2:1911–6) © 2020 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).
MANAGEMENT

At catheterization, the large azygos vein varix was confirmed by angiography with a size estimated at 5 cm x 2.5 cm x 2.5 cm (Figures 3A and 3B, Videos 1, 2, 3, and 4). The diameter of the azygos vein, as it entered the superior vena cava, was 16 mm. The superior vena cava diameter was 19 to 22 mm. Hemodynamics were normal, including normal pulmonary arterial pressure, and no evidence of right-to-left or left-to-right shunts. Right pulmonary angiography showed no pulmonary arterial or venous connections with the varix. The azygos vein, proximal to the varix, did not fill during varix angiography and could not be entered with a Wholey wire (Medtronic, Minneapolis, Minnesota). A 4.5 mm Cheatham Platinum covered stent (NuMed, Hopkinton, New York) was deployed in the superior vena cava with a 24-mm Balloon in Balloon catheter (B. Braun, Melsungen, Germany). After the intervention, superior vena cava angiography showed no further flow into the varix (Figures 3C and 3D, Videos 5 and 6); additionally, pulmonary angiography showed no compression of the right pulmonary artery or the right upper pulmonary veins. The patient was discharged on daily warfarin with an international normalized ratio goal of 2.0 and daily aspirin 325 mg, until the therapeutic international normalized ratio was achieved.

FOLLOW-UP

Six months later, the warfarin was discontinued, and he was maintained on a daily aspirin 325 mg. Eight
months after catheterization, a chest CTA showed thrombosis and partial involution of the varix (Figure 4), a wide-open superior vena cava, and no other venous abnormalities.

**DISCUSSION**

Galen was the first to name the “azygos” vein, which in Greek means unpaired (1). The azygos system is a venous network responsible for draining the thoracic wall and upper lumbar region and supplies collateral circulation between the superior vena cava and the inferior vena cava (Figure 5). The H-shaped configuration consists of the azygos, hemiazygos, accessory hemiazygos veins, and the left superior intercostal vein (2).

Anomalies of the azygos vein are rare and often incidentally identified on thoracic imaging (2). Congenital azygos vein abnormalities include absence of the azygos vein, lateral azygos vein associated with an azygos lobe of the right lung, interrupted inferior vena cava with azygos continuity to the superior vena cava, and partial anomalous pulmonary venous return of 1 of more veins to the azygos vein. Among acquired azygos vein abnormalities are enlargement due to right atrial hypertension, inferior vena cava obstruction or portal hypertension, abnormal size or direction of flow from a superior vena cava obstruction, and extrinsic displacement from neoplasms, mediastinal lymph node enlargement, or aortic aneurysm with or without dissection (2).

Marked enlargement of a portion of the azygos vein has been referred to as a varix (3,4) or an aneurysm (5–10). Some authors suggest that a venous varix and a venous aneurysm have different vessel wall histology (5), with varices having increased fibrous tissue and medial thickening and aneurysms showing reduced number and size of muscle and elastic fibers, intimal hyalinization, fragmentation of the internal elastic lamella, and excessive fibrous connective tissue. In the absence of pathologic confirmation, we have chosen varix. Varices can be congenital or acquired. The acquired form is most often due to high central venous pressure, cardiac decompensation, portal hypertension, arteriovenous fistula, pregnancy, external compression, or trauma (5). Our
patient had no evidence of the acquired etiologies; thus, we deemed it a probable congenital azygos vein varix.

Because of their rarity, management of azygos vein varices is controversial (5). Some recommend conservative management (6); nevertheless, patients have presented with intraluminal thrombus formation or severe pulmonary embolism, likely originating from the varix (5–7). Azygos vein varix rupture is another possible adverse outcome; however, there are no reports of rupture, likely secondary to low-pressure venous environment. There are reports of surgical treatment of azygos vein varices with good results and without recurrence.

![Angiographic Images Before and After Stent Placement](image)

Baseline angiogram in the varix (V): (A) anteroposterior view and (B) lateral view. Images after delivery of the covered stent in the superior vena cava (SVC): (C) anteroposterior view and (D) lateral view. S = stent.
Cardiac catheter intervention has also been described. Techniques include coil occlusion of the varix (9), Amplatzer device placement in the azygous vein on both sides of the varix (4,10), and covered stent implantation within the varix (7).

In our patient, the varix was considered to be too large for intracavitary coil or device implantation. The proximal azygous was very small and could not be entered. Therefore, the decision was made to place a covered stent in the superior vena cava with the aim...
FIGURE 5 Diagrammatic Representation of Systemic Venous Return

of completely occluding the connection of the azygous vein and the superior vena cava. Technically, implantation was straightforward utilizing common techniques used by congenital cardiac interventionists. Warfarin anticoagulation was given for 6 months to allow for stent endothelialization. Eight months later the patient remained asymptomatic, and follow-up CTA showed oblitative thrombosis, partial involution of the varix, and no other venous abnormalities.

CONCLUSIONS

We describe successful covered stent exclusion of an azygos vein varix in a young man with reassuring findings on CTA imaging 8 months later. This technique offers an additional method of preventing potential embolic events from the varix to the pulmonary circulation.

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REFERENCES

1. Paraskevas GK, Koutraslianotis KN, Pantikas M, Nourisios G. What is the history of the term “azygos vein” in the anatomical terminology? Surg Radiol Anatomy 2019;41:1155–62.

2. Dudiak CM, Olson MC, Posniak HV. CT evaluation of congenital and acquired abnormalities of the azygos system. Radiographics 1991;11:233–46.

3. Podbielski FJ, Sam AD, Halladorson AO, Iash-Sznajder J, Vigneswaran WT. Giant azygos vein varix. Ann Thorac Surg 1997;63:1167–9.

4. Davis BS, Cretcher MR, Gover DD, Thoresen AA. Arch of the azygos vein varix: A source of pulmonary emboli excluded with Amplatzer plug occlusion. J Vasc Interv Radiol 2017;28:186–7.

5. Kreibich M, Siepe M, Grohmann J, Pache G, Beyersdorf F. Aneurysms of the azygous vein. J Vasc Surg Venous Lymphat Disord 2017;5:576–86.

6. Yang JY, Kim DH, Lee JH, Suk EH. Evaluating a thrombosed azygous vein aneurysm combined with pulmonary arterial thromboembolism by ECG-gated multidetector CT: a case report. Korean J Radiol 2011;12:754–6.

7. Favelier S, Estivale S, Pottcheper P, Loffroy R. Successful endovascular treatment of a large azygous vein aneurysm with stent-graft implantation. Ann Thorac Surg 2015;99:1453.

8. Ko SF, Huang CC, Lin JW, et al. Imaging features and outcomes in 10 cases of idiopathic azygos vein aneurysm. Ann Thorac Surg 2014;97:873–8.

9. Irurzun J, de España F, Areñas J, García-Sevilla R, Gil S. Successful endovascular treatment of a large idiopathic azygos arch aneurysm. J Vasc Interv Radiol 2008;19:1251–4.

10. Weber HS. Transcatheter occlusion of an azygos vein aneurysm. Catheter Cardiovasc Interv 2011;77:99–102.

KEY WORDS azygos vein varix, covered stent

APPENDIX For supplemental videos, please see the online version of this paper.
MINI-FOCUS ISSUE: CARDIOMYOPATHIES

CASE REPORT: CLINICAL CASE

Percutaneous Transluminal Septal Myocardial Ablation for Hypertrophic Obstructive Cardiomyopathy Under Extracorporeal Membrane Oxygenation Support

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ABSTRACT

We report the case of a 70-year-old woman with hypertrophic obstructive cardiomyopathy, who was admitted because of severe heart failure and cardiogenic shock and mechanical support requiring extracorporeal membrane oxygenation. She recovered well by percutaneous transluminal septal myocardial ablation under the extracorporeal membrane oxygenation support and was discharged without complications. (Level of Difficulty: Advanced.) (J Am Coll Cardiol Case Rep 2020;2:1917–22) © 2020 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

HISTORY OF PRESENTATION

A 70-year-old woman with hypertrophic obstructive cardiomyopathy required extracorporeal membrane oxygenation (ECMO) support due to cardiogenic shock and acute heart failure and showed dramatic improvement after a percutaneous transluminal septal myocardial ablation (PTSMA) (Figure 1).

The patient became aware of exertion-related chest symptoms almost 9 years ago and presented to another hospital. Transthoracic echocardiography (TTE) revealed a diffuse left ventricular (LV) hypertrophy, except in the posterior wall, and the maximum wall thickness of the LV was 20 mm. The maximum velocity of the left ventricular outflow tract (LVOT) was 503.2 cm/s on Doppler echocardiography, and the pressure gradient of the LVOT was estimated as 101.3 mm Hg. The patient was diagnosed with hypertrophic obstructive cardiomyopathy (HOCM). She was treated with β-blockers and disopyramide. The pressure gradient in the LVOT decreased to 30 mm Hg, and she was well managed without significant cardiac events, except for syncope, which occurred several times over 8 years. Thereafter, she

LEARNING OBJECTIVES

- To learn how to manage patients with severe heart failure caused by HOCM under ECMO.
- To understand the effects of PTSMA in patients experiencing cardiogenic shock due to HOCM.
was diagnosed with traumatic subarachnoid hemorrhage caused by syncope, but no remarkable changes on TTE or arrhythmia were detected after the event; she recovered well without neurological sequelae. Two weeks after the event, she was brought to the emergency room due to nausea, dizziness, and chest oppression resulting from intensive work in a hot room. Her blood pressure and maximum LVOT velocity were 67/48 mm Hg and 4.3 m/s on TTE, respectively; therefore, she was diagnosed with cardiogenic shock with hypovolemia and admitted to the hospital. Intravenous volume load was started, and the dosage of the β-blocker was increased because hypovolemic shock was considered to exacerbate LVOT stenosis. Several hours later, she developed hypoxemia due to pulmonary edema and cardiopulmonary arrest caused by pulseless ventricular tachycardia (VT). After recovery from cardiac arrest by defibrillation, injection of epinephrine, and mechanical ventilation, continuous injection of nifekalant was started to prevent VT. VT was well suppressed and her condition had been stable for almost 2 days. However, immediately after the injection of 4-mg midazolam to suppress unnecessary body movement, her carotid artery pulse could not be palpated and her systolic blood pressure suddenly dropped to nearly 30 mm Hg, without measurable diastolic pressure. Therefore, 0.15 mg of norepinephrine was infused 3 times but was ineffective; hence, 0.5 μg/kg/min of norepinephrine was continuously administered. However, her systolic blood pressure remained low, and venoarterial extracorporeal membrane oxygenation (ECMO) was started on the fourth day. On the fifth day, she was transferred to our hospital for more intensive treatment. A venous cannula was placed in the right common femoral vein for extraction, an arterial cannula was placed into the right or left femoral artery for infusion, and the blood flow of ECMO was regulated at 2.1 l/min (the number of rotations was 2,910/min).

The patient did not have any other medical history, except hypertrophic cardiomyopathy (HCM).

DIFFERENTIAL DIAGNOSIS

Two days after starting ECMO, she was transferred to our hospital. Almost 1 month before the admission, TTE revealed diffuse LV wall thickness of ≥15 mm excluding the posterior segment, with significant LVOT stenosis and a pressure gradient of approximately 60 mm Hg at rest (Figures 2A and 2B), a typical abnormality observed in HCM (Maron type III) (1). Her grandchild had been diagnosed with HCM.

She did not have other cardiac or systemic disease that could account for the magnitude of hypertrophy; therefore, she was finally diagnosed with HCM (2,3).

INVESTIGATIONS

Results of medical examinations performed after the transfer to our hospital were as follows: blood pressure 108/74 mm Hg, heart rate 122 beats/min, body temperature 35.5°C, and B-type natriuretic peptide level 1,246.4 pg/ml.

Chest x-ray film showed bilateral pulmonary congestion and pleural effusion, and the cardiothoracic ratio was 60% (Figure 3A). Her electrocardiogram revealed normal sinus rhythm and ST-segment depression in leads V3 to V6, aVL, and I (Figure 4). TTE revealed preserved LV contraction and accelerated blood flow through the LVOT at approximately 1.3 m/s. When ECMO flow was reduced from 1.8 l/min to 0.7 l/min, the blood flow through the LVOT increased to 2.3 m/s. The size of the left atrium was 39 mm on TTE.

**ABBREVIATIONS AND ACRONYMS**

AF = atrial fibrillation
ECMO = extracorporeal membrane oxygenation
HCM = hypertrophic cardiomyopathy
HOCM = hypertrophic obstructive cardiomyopathy
LV = left ventricular
LVOT = left ventricular outflow tract
PTSMA = percutaneous transluminal septal myocardial ablation
TTE = transthoracic echocardiography
VT = ventricular tachycardia

**FIGURE 1** Treatment Timeline

Timeline of the treatment

Hypertrophic cardiomyopathy with left ventricular outflow obstruction was initially suspected on transthoracic echocardiography.

Eight years had passed without significant cardiac events under the treatment of β-blockers and disopyramide.

She was admitted because of hypovolemia and subsequent cardiogenic shock.

Several hours had passed

Intravenous volume load and increased β-blocker dosage were started. However, she developed hypoxemia due to pulmonary edema and finally CPA caused by VT.

Two days had passed

VT was well managed by nifekalant, but ECMO was started because her blood pressure decreased after the injection of midazolam and norepinephrine was not effective.

Two days had passed

She was transferred to our hospital. PTSMA was successfully performed under ECMO support on the 10th day of admission. She recovered well and was finally re-transferred to the previous hospital on the 45th day.

**PAST MEDICAL HISTORY**

The patient did not have any other medical history, except hypertrophic cardiomyopathy (HCM).

**DIFFERENTIAL DIAGNOSIS**

Two days after starting ECMO, she was transferred to our hospital. Almost 1 month before the admission, TTE revealed diffuse LV wall thickness of ≥15 mm excluding the posterior segment, with significant LVOT stenosis and a pressure gradient of approximately 60 mm Hg at rest (Figures 2A and 2B), a typical abnormality observed in HCM (Maron type III) (1). Her grandchild had been diagnosed with HCM.

She did not have other cardiac or systemic disease that could account for the magnitude of hypertrophy; therefore, she was finally diagnosed with HCM (2,3).

**INVESTIGATIONS**

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Continuous intravenous injection of landiolol was started from 3 μg/kg/min and increased to 10 μg/kg/min; oral administration of 300-mg cibenzoline per day was also started (4). After the onset of atrial fibrillation (AF), cardiogenic shock occurred, and the systolic blood pressure decreased to 80 mm Hg; amiodarone was started, which effectively prevented AF.

Invasive coronary angiography revealed no significant stenosis of the coronary arteries on the eighth day. PTSMA was planned because of the risk of cardiogenic shock caused by the recurrent AF or...

**FIGURE 2** Transthoracic Echocardiography Findings Almost 1 Month Before Admission

(A) Left ventricular (LV) ejection fraction is approximately 70%, and diffuse severe LV hypertrophy excluding the basal posterior wall is observed. The maximum LV wall thickness was 20 mm. (B) Systolic anterior motion of the mitral valve is also observed, and the accelerated blood flow of the LV outflow tract was approximately 3.85 m/s.

**FIGURE 3** Chest X-Ray Films Before and After Percutaneous Transluminal Septal Myocardial Ablation

(A) Chest x-ray film showing bilateral pulmonary congestion and pleural effusion. The cardiothoracic ratio is approximately 60%. (B) Bilateral pulmonary congestion and pleural effusion are no longer observed after percutaneous septal myocardial ablation.
hypovolemia. On the 10th day, PTSMA was performed, and 1.5 ml of absolute ethanol was injected into the first major septal branch. Her LVOT pressure gradient decreased to 4.5 mm Hg (Figure 5) after the procedure, ECMO support was terminated on the 11th day, and she was extubated next day. Cardiac magnetic resonance imaging was performed on the 22nd day, and late gadolinium enhancement was clearly detected in the interventricular septum (Figure 6). Pulmonary congestion finally disappeared on her chest x-ray film on the 25th day (Figure 3B). An implantable cardioverter-defibrillator was implanted for secondary prevention of VT on the 30th day, and she was finally transferred to the previous hospital for rehabilitation on the 45th day of admission.
DISCUSSION

Patients with symptomatic LVOT obstruction in HCM should be treated initially with nonvasodilating β-blockers titrated to the maximum tolerated dose (2). Class Ia and Class II antiarrhythmic drugs are also recommended to decrease LVOT obstruction and improve symptom (1).

Septal reduction therapy should be considered for patients with drug-resistant HOCM (2), with septal myectomy and PTSMA. They are effective for LVOT obstruction, with similar clinical outcomes (5). This case was regarded as drug-resistant HOCM because the pressure gradient to the LVOT was 30 mmHg, even with the administration of 2 medicines, and ECMO support was necessary when AF or hypovolemia occurred; therefore, she was considered an appropriate candidate for septal reduction therapy. Minimally invasive treatment was finally selected, considering her age and ECMO outcomes. We obtained written informed consent from the patient for the publication of this report.

FOLLOW-UP

Post-treatment, she was discharged and periodically followed up. Based on our literature review, no other case report described a patient undergoing PTSMA while under ECMO support.

CONCLUSIONS

PTSMA is useful for patients with HOCM, even in those with deteriorated hemodynamic situation under ECMO support.

AUTHOR RELATIONSHIP WITH INDUSTRY

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3. Olivotto I, Maron BJ, Tomberli B, et al. Obesity and its association to phenotype and clinical course in hypertrophic cardiomyopathy. J Am Coll Cardiol 2013;62:449–57.

4. Hamada M, Shigematsu Y, Inaba S, et al. Anti-arrhythmic drug cibenzoline attenuates left ventricular pressure gradient and improves trans-mitral Doppler flow pattern in patients with hypertrophic obstructive cardiomyopathy caused by midventricular obstruction. Circ J 2005;69:940–5.

5. Agarwal S, Tuzcu EM, Desai MY, et al. Updated meta-analysis of septal alcohol ablation versus myectomy for hypertrophic cardiomyopathy. J Am Coll Cardiol 2010;55:823–34.

**KEY WORDS** ablation, acute heart failure, cardiomyopathy
**Dynamic Takotsubo Syndrome**

When SCAD Hides in a Pot

Siddharth Jogani, MD, Philippe Timmermans, Sr, MD, Walter Desmet, MD PhD, Pieter Koopman, MD, Philippe Timmermans, Jr, MD, MSc

**ABSTRACT**

Both Takotsubo cardiomyopathy and spontaneous coronary artery dissection (SCAD) of the distal portion of the left anterior descending artery affect the apical myocardium. It is important to distinguish between both diseases, because therapy and follow-up differ. Revascularization may be lifesaving in SCAD, whereas heart failure management is vital in Takotsubo cardiomyopathy. (Level of Difficulty: Intermediate.) (J Am Coll Cardiol Case Rep 2020;2:1923-31) © 2020 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

**PATIENT #1**

**PRESENTATION.** A 50-year old woman was transferred to the hospital with acute onset of chest pain. At presentation, she was hemodynamically stable. Electrocardiography (ECG) showed nonspecific ST-T alterations in the inferolateral leads.

**MEDICAL HISTORY.** The patient had a medical history of Sudeck atrophy leading to amputation of her left forearm.

**DIFFERENTIAL DIAGNOSIS.** Differential diagnosis included acute coronary syndrome and pulmonary embolism (PE).

**INVESTIGATIONS.** Due to subtle ECG changes, an urgent transthoracic echocardiography (TTE) was performed, which showed akinesia of the apicolateral segment with suspicion of an apical thrombus (Video 1A). This structure, however, was not visualized in other fragments (Video 1B). Coronary angiography revealed a moderate stenosis in the distal portion of the left circumflex artery (LCX) (Figure 1). The right coronary artery (RCA) (Figure 2) and the left anterior descending artery (LAD) (Figure 3) did not show any apparent stenosis. Ventriculograms showed akinesia of the apex without evidence of an apical thrombus (Video 2). ECGs obtained on day 3, showed a typical evolution with negative T waves in the precordial leads. Takotsubo cardiomyopathy (TC) was diagnosed. The patient was treated with angiotensin-
converting enzyme (ACE) inhibitors and a beta-blocker.

During admission, the patient suffered repeated mild attacks of angina, despite declining troponin levels. TTE on the third day showed dyskinesia in the basal and mid portions of the inferolateral and inferior walls. On day 5, Q-waves formed in the inferior leads, suggesting ischemia in the LCX or RCA territory. Due to these evolving signs of ischemia on ECG and TTE, angiography was repeated on the seventh day, revealing type I spontaneous coronary artery dissection (SCAD) of the LCX (Figure 4) with subsequent occlusion and type IIb SCAD of the RCA (Figure 5) with partial occlusion of the distal portion. The caliber of the distal portion of the LAD (Figure 6) was normal. Optical coherence tomography and intravascular ultrasonography were not attempted because of the risk that dissection would worsen with subsequent occlusion. Computed tomography angiography of the cerebral blood vessels showed no signs of fibromuscular dysplasia (FMD). Computed tomography angiography of the renal blood vessels was not performed.

**MANAGEMENT.** The patient was treated medically with low-dose aspirin, an ACE inhibitor, spironolactone, and beta-blockers. TTE on the day of discharge (day 18) showed a nearly full recovery of the global and regional left ventricular functions. The patient was discharged in good health.

**FOLLOW-UP.** TTE 6 weeks after discharge showed persistent full recovery of left ventricular function. Angiography at 2 months after discharge showed complete resolution of the lesions (Figures 7 to 9). Medical treatment with ACE inhibitors, beta-blockers, and low-dose aspirin was continued. Because of this unusual clinical picture, all angiographies were reviewed, and expert opinion was sought. On review, the first angiography showed evidence of coronary dissection of the distal portion of the LCX (Figure 1) and the LAD (Figure 3). This explains why wall motion abnormalities differed between the echocardiography and ventriculography on day 1 and also explains the negative T waves in the precordial leads on day 3.

**PATIENT 2**

**PRESENTATION.** A 59-year-old woman presented to the emergency ward with symptoms of angina and dyspnea. At presentation, she was pain free and...
The first angiogram in Patient 1 shows right coronary artery without stenosis. RCA = right coronary artery; SCAD = spontaneous coronary artery dissection.

The first angiogram of Patient 1 shows a narrow lumen in the distal part of the LAD (white arrows), suspected for spontaneous coronary artery dissection after review. D1 = first diagonal branch; other abbreviations as in Figure 1.
The second angiogram of Patient 1 shows type I SCAD of the distal portion of the LCX (white arrow) with subsequent occlusion (white arrowheads). Abbreviations as in Figure 1.

The second angiogram of Patient 1 shows type IIb SCAD of the distal portion of the RCA with partial occlusion. (white arrowheads) Abbreviations as in Figures 1 and 2.
FIGURE 6 Second Angiogram of Patient 1: No SCAD of LAD

The second angiogram of Patient 1 shows normal caliber of the distal part of the LAD (white arrows). Abbreviations as in Figure 1.

FIGURE 7 Third Angiogram of Patient 1: No SCAD of LCX

The third angiogram of Patient 1 shows complete resolution of lesion in the LCX (white arrows). Abbreviations as in Figure 1.
The third angiogram of Patient 1 shows complete resolution of the lesion in the RCA. Abbreviations as in Figures 1 and 2.

The third angiogram of Patient 1 shows normal caliber of the distal part of the LAD (white arrows). Abbreviations as in Figure 1.
hemodynamically stable. ECG showed nonspecific ST-T alterations in the inferolateral leads.

**MEDICAL HISTORY.** The patient had a medical history of arterial hypertension, hypercholesterolemia, and TC diagnosed 3 months earlier, based on akinesia of the apex seen on ventriculography.

**DIFFERENTIAL DIAGNOSIS.** Differential diagnosis included acute coronary syndrome, TC, SCAD, and pulmonary embolism.

**INVESTIGATIONS.** Because of the atypical presentation, mild ECG changes and troponin concentrations of 267 ng/l (<14 ng/l), urgent angiography was not performed. On the second day, however, troponin concentration had risen 4-fold. Coronary angiography revealed type IIb SCAD of the first diagonal branch of the LAD (Figure 10). Reviewing the first angiography, performed in a nearby heart center, showed evidence of coronary dissection of the distal portion of the LAD and a diagonal branch (Figure 11). TC should not have been diagnosed exclusively by ventriculography.

**MANAGEMENT.** The patient was treated medically with low-dose aspirin. She was already taking ACE inhibitors, spironolactone, and beta-blockers.

**DISCUSSION**

SCAD is a noniatrogenic separation of the coronary arterial wall. The underlying mechanism has yet to be elucidated, but an intimal tear or bleeding of the vasa vasorum could be the driving force (1), leading to a false lumen with intramural hematoma (2).

Until recently, SCAD was considered a rare disease, primarily seen in young women during the peripartum period and in patients with connective tissue disorders. The emergence of high sensitivity biomarkers and the use of intracoronary imaging have...
changed our mindset. A recent multicenter prospective observational study (3) showed that SCAD predominantly affects young to middle-aged women (mean age: 52 years old). FMD was seen in one-third of the patients, and peripartum SCAD or association with other connective diseases was rare. Emotional stress was reported in 50.3% and physical stress in 28.9% of patients. The association between SCAD (4) and FMD has recently been confirmed at a genetic level (4,5). A common variant of chromosome 6 at the PHACTR1 locus could be a risk locus for SCAD and FMD.

Because shear stress may be the driving force for SCAD, medical therapy with beta-blockers and single-antiplatelet therapy is the treatment of choice. Revascularization is needed in some cases of SCAD patients who have ongoing ischemia (6), in contrast to TC, where treatment is based on the acute presentation of the disease, management of heart failure or in some cases shock. The role of long-term therapy with ACE inhibitors and beta-blockers is not well established.

CONCLUSIONS

This paper describes 2 cases of SCAD which were initially misdiagnosed as TC. These cases underscore the need for interventionists to familiarize themselves with the often subtle and sometimes hard to recognize angiographic appearance of SCAD. These cases also emphasize the fact that one should at all times be prepared to challenge an initial diagnosis and use additional imaging if deemed necessary. We clinicians should be aware of dynamic coronary pathology in SCAD.

AUTHOR RELATIONSHIP WITH INDUSTRY

All authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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REFERENCES

1. Alfonso F. Spontaneous coronary artery dissection: new insights from the tip of the iceberg? Circulation 2012;126:667–70.

2. Alfonso F, Bastante T. Spontaneous coronary artery dissection: novel diagnostic insights from large series of patients. Circ Cardiovasc Interv 2014;7:638–41.

3. Saw J, Starovoitov A, Humphries K, et al. Canadian spontaneous coronary artery dissection cohort study: in-hospital and 30-day outcomes. Eur Heart J 2019;40:1188–97.

4. Adlam D, Olson TM, Combaret N, et al. Association of the PHACTR1/EDN1 genetic locus with spontaneous coronary artery dissection. J Am Coll Cardiol 2019;73:58–66.

5. Kiando SR, Tucker NR, Castro-Vega LJ, et al. PHACTR1 is a genetic susceptibility locus for fibromuscular dysplasia supporting its complex genetic pattern of inheritance. PLoS Genet 2016;12:e1006367.

6. Hayes SN, Kim ESH, Saw J, et al. Spontaneous coronary artery dissection: current state of the science: a scientific statement from the American Heart Association. Circulation 2018;137:e523–57.

KEY WORDS acute coronary syndrome, case series, coronary angiography, spontaneous coronary artery dissection, takotsubo cardiomyopathy

APPENDIX For supplemental videos, please see the online version of this paper.
A 70-year-old male with prior orthotopic heart transplant developed left bundle branch block followed by new-onset left ventricular systolic dysfunction. He underwent His bundle pacing for cardiac resynchronization therapy with complete normalization of his ejection fraction. This is the first reported case of left bundle branch block–induced cardiomyopathy in a transplanted heart. (Level of Difficulty: Advanced.) (J Am Coll Cardiol Case Rep 2020;2:1932–6) © 2020 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).
presentation. He had undergone annual dobutamine stress echocardiograms with normal left ventricular systolic function and no inducible ischemia. The patient had a baseline narrow QRS on prior routine ECGs.

**DIFFERENTIAL DIAGNOSIS**

The differential diagnoses for left ventricular systolic dysfunction (LVSD) in a patient with a remote history of OHT include allograft rejection and cardiac allograft vasculopathy. Other causes of cardiomyopathy, such as infiltrative, hypertensive, tachycardia-mediated, idiopathic dilated cardiomyopathy, and LBBB-induced cardiomyopathy must be considered as well.

**INVESTIGATION**

Transthoracic echocardiogram (TTE) revealed new-onset severely reduced left ventricular ejection fraction (LVEF) of 10% to 15% (Figure 2A, Video 1). There was significant intraventricular dyssynchrony with a posterior-to-septal wall delay (PSWD) of 324 ms (Figure 3A).

Coronary angiogram showed normal coronary arteries with no transplant vasculopathy. Endomyocardial biopsy revealed mild cellular rejection (1R) with no antibody-mediated rejection. Etiologies of LVSD such as alcohol abuse, illicit drug use, uncontrolled hypertension, and thyroid

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**FIGURE 1** Electrocardiogram

(A) At time of presentation: sinus tachycardia and typical left bundle branch block (LBBB) with a QRS duration of 170 ms. (B) After His bundle pacing: nonselective His bundle recruitment of underlying LBBB with a QRS duration of 110 ms.
dysfunction were excluded in this patient. He also had no evidence of atrial tachyarrhythmias on prior ECGs and subsequent device interrogations. Biopsy specimens were negative for infiltrative disease in the donor heart.

**MANAGEMENT**

The patient was treated with diuretics as well as high-dose steroids and thymoglobulin for 1R acute cellular rejection in the setting of new-onset LVSD. Repeat endomyocardial biopsy 3 weeks later was negative for cellular rejection (0R). Guideline-directed medical therapy was titrated to maximally tolerated doses. However, repeat TTEs over the following 9 months showed no improvement in LVEF.

The patient was referred to electrophysiology for cardiac resynchronization therapy and defibrillator placement (CRT-D). A review of the patient’s serial ECGs showed new-onset persistent typical LBBB 6 months before his presentation with heart failure. Because of the operator’s significant experience with His-bundle pacing (HBP), the patient underwent HBP for CRT-D with the SelectSecure pacing lead (model 3830, Medtronic Inc., Minneapolis, Minnesota). The lead was placed in the proximal portion of the His bundle based on HV interval measurements. The His lead was plugged into the left ventricular port of the CRT-D device. Subsequent ECG showed nonselective HBP with recruitment of underlying left bundle branch fibers with a QRS of 110 ms (Figure 1B). The pacing threshold for the His lead was 2.25 V at 1 ms and remained stable over time.

**DISCUSSION**

The most common conduction abnormality after OHT is a right bundle branch block. However, the development of LBBB after OHT has not been readily reported in the literature. Our patient developed LVSD 6 months after the onset of persistent LBBB. Common etiologies of LVSD were reasonably excluded in this patient and follow-up device interrogation excluded the possibility of subclinical tachyarrhythmias.
Although mild cellular rejection cannot be entirely excluded as the cause of late graft failure, the lack of improvement in LVEF with immunosuppression and super-response to His bundle pacing points against this as a cause for his LVSD.

To our knowledge, this is the first reported case of LVSD with LBBB in a transplanted heart treated successfully with HBP with normalization of LVEF. We believe the temporal relationship of new-onset persistent typical LBBB with the development of LVSD, followed by super-response to HBP to be demonstrative of LBBB-induced cardiomyopathy. HBP corrected the underlying LBBB, thereby directly overcoming LBBB-induced electrical dyssynchrony.

The concept of LBBB-induced cardiomyopathy has been supported by several studies (3–6). A retrospective study by Valliant et al. (4) defined it as the presence of a typical LBBB for >5 years with normal sinus rhythm and LVEF >50% at the time of diagnosis, with decrease in LVEF to ≤40%, heart failure symptoms, no alternative causes of cardiomyopathy, presence of major left heart mechanical dyssynchrony, and super-response to CRT (10). In this study of 375 patients, 1.6% receiving CRT met these predefined criteria for LBBB-induced cardiomyopathy. While our patient meets most of these criteria, he only developed persistent LBBB 6 months before clinical presentation.

The decision to pursue HBP over conventional biventricular pacing (BVP) for CRT in this patient was based on the operator’s experience and positive outcomes with HBP. BVP for CRT has a nonresponse rate of 30% to 40%, which is partially related to unfavorable coronary sinus anatomy (7). Therefore, alternative strategies, such as HBP, have emerged. A previous study has shown the safety and feasibility of
HBP as a bail-out strategy for failed BVP or as an initial strategy for CRT (8). In this study, 75% of nonresponders to BVP had improvement in LVEF after HBP (8). Additionally, the His-SYNC pilot trial was a prospective, randomized controlled trial comparing HBP to BVP as an initial strategy for CRT. While the intention-to-treat study did not show a benefit in HBP compared to BVP, there was considerable crossover. A secondary analysis of the as-treated cohort showed statistically greater electrical resynchronization and a trend toward superior echocardiographic response with HBP compared to BVP (9). Longer trails are required to adequately compare outcomes of these 2 CRT strategies.

FOLLOW-UP

TTE 1-month post-device implantation revealed an improvement in LVEF to 42%. By 4 months, the patient had normalization of LVEF to 75% (Figure 2B, Video 2), reduction in PSWD to 95 ms (Figure 3B), and significant improvement in exercise capacity and New York Heart Association functional class.

CONCLUSIONS

We demonstrate a case of the development of persistent typical LBBB in a transplanted heart with resultant LVSD, treated successfully with HBP with complete normalization of LVEF. Although LBBB-induced cardiomyopathy is not widely recognized, we believe this case is a unique example of this entity due to the direct correction of LBBB with HBP.

AUTHOR RELATIONSHIP WITH INDUSTRY

Dr. Dandamudi is on the advisory boards of Biotronik, Abbott, and Medtronic; and serves as a consultant for Abbott and Medtronic. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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REFERENCES

1. Golshayan D, Seydoux C, Berguer DG, et al. Incidence and prognostic value of electrocardiographic abnormalities after heart transplantation. Clin Cardiol 1998;21:680–4.

2. Ferretto S, Tafciu E, Giuliani I, et al. Interventricular conduction disorders after orthotopic heart transplantation: risk factors and clinical relevance. Ann Noninvasive Electrocardiol 2017;22:e12402.

3. Wang NC, Singh M, Adelstein EC, et al. New-onset left bundle branch block-associated idiopathic nonischemic cardiomyopathy and left ventricular ejection fraction response to guideline-directed therapies: the NEOLITH study. Heart Rhythm 2016;13:933–42.

4. Vaillant C, Martins RP, Donal E, et al. Resolution of left bundle branch block-induced cardiomyopathy by cardiac resynchronization therapy. J Am Coll Cardiol 2013;61:1089–95.

5. Sze E, Dunning A, Loring Z, et al. Comparison of incidence of left ventricular systolic dysfunction among patients with left bundle branch block versus those with normal QRS duration. Am J Cardiol 2017;120:1900–97.

6. Blanc JJ, Faterni M, Bertault V, Baraket F, Etienne Y. Evaluation of left bundle branch block as a reversible cause of non-ischemic dilated cardiomyopathy with severe heart failure: a new concept of left ventricular dyssynchrony-induced cardiomyopathy. Europace 2005;7:604–10.

7. Daubert C, Behar N, Martins RP, Mabo P, Leclercq C. Avoiding non-responders to cardiac resynchronization therapy: a practical guide. Eur Heart J 2017;38:1463–72.

8. Sharma PS, Dandamudi G, Herweg B, et al. Permanent His-bundle pacing as an alternative to biventricular pacing for cardiac resynchronization therapy: a multicenter experience. Heart Rhythm 2018;15:413–20.

9. Udadhyay GA, Vijayaraman P, Nayak HM, et al. On-treatment comparison between corrective His bundle pacing and biventricular pacing for cardiac resynchronization: a secondary analysis of the His-SYNC pilot trial. Heart Rhythm 2019;16:1797–807.

KEY WORDS cardiac resynchronization therapy, cardiac transplant, cardiomyopathy

APPENDIX For supplemental videos, please see the online version of this paper.
Myocardial Vasculitis Associated With the Immune Checkpoint Inhibitor Pembrolizumab

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ABSTRACT
Recent developments in immune checkpoint inhibitors (ICIs) have provided new treatment strategies for advanced cancer. However, ICIs lead to an imbalance between T cell–mediated inflammatory responses and immune tolerance in the myocardium. Here we report the first case that implicates the contribution of ICI-induced vasculitis to myocardial injury. (Level of Difficulty: Intermediate.) (J Am Coll Cardiol Case Rep 2020;2:1937–41) © 2020 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

HISTORY OF PRESENTATION
A 79-year-old female patient underwent surgery for malignant melanoma of the right jaw. Upon identification of cervical lymph node metastases, immunotherapy with a programmed cell death protein-1 (PD-1) inhibitor, pembrolizumab, was initiated at a dose of 200 mg every 3 weeks. After 10 cycles of pembrolizumab, the treatment was discontinued because of exanthema on her limbs and trunk (Figure 1A). A femoral skin biopsy was performed, and the patient was treated with oral prednisolone 30 mg/day. Histopathologically, the biopsy specimen showed infiltration of lymphocytes, neutrophils, and eosinophils surrounding the small blood vessels (Figure 1B). After 1 month on prednisolone, the patient’s skin condition deteriorated, and she was hospitalized for treatment with intravenous immunoglobulin therapy at 17.5 g/day (0.4 g/kg/day). As no improvement was observed after 5 days of intravenous immunoglobulin treatment, 3-day steroid pulse therapy (methylprednisolone 1,000 mg/day) was added to her drug regimen, followed by oral administration of prednisolone 45 mg/day. Her condition improved, and the dose of prednisolone was tapered to 5 mg/day for 2 weeks. At this time, the patient experienced acute onset of aphasia and right homonymous hemianopsia.

LEARNING OBJECTIVES
• To review ICI-induced vasculitis.
• To propose a new adverse event, ICI-induced myocardial vasculitis.

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Computed tomography revealed a cerebral hemorrhage in the left parietal and occipital lobe, followed by sudden onset of chest pain 3 days later. Electrocardiography showed no specific ST-segment changes, and transthoracic echocardiography revealed a left ventricular ejection fraction of 80% without reduced local wall motion. C-reactive protein was 2.02 mg/dl, and serum levels of creatinine kinase (CK) and CK-MB were within their normal ranges at 40 IU/l and 9 IU/l, respectively, although serum troponin T was measured at 0.077 ng/ml, which was somewhat higher than the normal value (<0.014 ng/ml). Electrocardiography performed on the following day revealed slight ST-segment elevation in leads II, III, and aVF (Figure 2) and increases in serum CK, CK-MB, and troponin T levels to 391 IU/l, 54 IU/l, and 1.340 ng/ml, respectively.

**DIFFERENTIAL DIAGNOSIS**

In this patient, acute coronary syndrome was most suspected, followed by myocarditis, pericarditis, and stress cardiomyopathy.

**INVESTIGATIONS**

To exclude acute myocardial infarction, emergency left heart catheterization was performed. Coronary angiography showed normal coronary arteries, and left ventriculography detected focal reduced motion of the inferior wall (Video 1). On subsequent pathological evaluation, endomyocardial biopsy was performed at the right ventricular septum. We collected more than 2 myocardial samples to minimize sampling errors. There were no inflammatory infiltrates within the myocardium in any sample (Figure 3A), and many neutrophils and a few eosinophils and lymphocytes negative for PD-1 were detected in the regions surrounding the small blood vessels, in association with obstruction of the vascular lumina (Figures 3B and 3C). Furthermore, we also detected prominent expression of immunoreactive PD-1.
ligand 1 (PD-L1) in association with the infiltrates at the small vessels (Figure 3D), a finding we attributed to pembrolizumab-mediated oversuppression of PD-1. These results strongly suggested that the myocardial injury in this case was not related to myocarditis but due to myocardial vasculitis associated with pembrolizumab treatment.

MANAGEMENT

Although repeat steroid pulse therapy was considered, we decided to continue the existing steroid treatment because on the day after endomyocardial biopsy, the patient’s chest pain disappeared, and CK, CK-MB, and troponin T levels improved to 105 U/L, 8 IU/L, and 0.700 ng/ml, respectively. CRP reached its peak value of 19.14 mg/dl at 5 days after the onset of chest pain, then tended to improve, decreasing to 1.07 mg/dl 25 days later.

DISCUSSION

Immune checkpoint inhibitors (ICIs) have provided a paradigm shift in cancer treatments, extending survival particularly in patients with cancer at advanced stages who could not overcome their incurable conditions (1). One critical disadvantage of ICI treatment is the possibility of immune-related adverse events (irAEs) (2). Untoward activation of the immune system may contribute to adverse events associated with ICI therapy (3). In recent years, cardiovascular complications of ICI therapy, especially ICI-associated myocarditis, with an incidence of fatality of 30% to 50%, have attracted attention (4,5). In addition to ICI-associated myocarditis, ICI-associated vasculitis is also an important irAE (4). An observational, retrospective pharmacovigilance study identified 82 cases of vasculitis among 31,321 adverse events (0.26%) reported in patients receiving ICIs, with a mortality rate of 6.1% (6). Although vasculitis associated with ICI therapy could affect any size blood vessel, a systematic review of case reports (7) indicated that large-vessel vasculitis (giant-cell arteritis and aortitis) and vasculitis of the nervous system (primary angiitis of the central nervous system and isolated vasculitis of the peripheral nervous system) were among the most common types associated with ICI therapy. Here, we report a case of myocardial injury due to myocardial vasculitis in a patient undergoing treatment for malignant melanoma with pembrolizumab. To the best of our
knowledge, this is the first report of myocardial vasculitis associated with ICI therapy. Although the mechanisms underlying the development of vasculitis in this setting are not clearly understood, PD-1 inhibition enhances the activation of CD4\(^+\) T cells and can result in the release of proinflammatory cytokines and cytotoxic mediators within the arterial tissue. A significant point to be emphasized is that these factors can also promote remodeling processes that ultimately lead to intimal proliferation and vascular occlusion (8). Grabie et al. (9) reported that although the initiation of cardiac injury is dependent on T cells, secondary inflammatory events involving polymorphonuclear leukocytes play an essential role in myocardial damage in a mouse model. Furthermore, PD-L1 is up-regulated in the myocardium during drug-induced cardiac injury. This expression of PD-L1 was dependent on interferon gamma produced by infiltrating T cells and performing an important role in protecting the myocardium from immune-mediated excessive inflammation (9).

Our findings, which include PD-1-negative neutrophil infiltration together with PD-L1 up-regulation in the periarterial region, may reflect cytokine-induced inflammatory processes. Likewise, myocardial vasculitis with neutrophils dominant, rather than lymphocyte infiltration into the myocardium, may explain the limited efficacy of prednisolone in this case. As such, during prednisolone tapering, one should consider the possibility that additional irAEs such as vasculitis may develop.

**FOLLOW-UP**

One month later, transthoracic echocardiography showed a left ventricular ejection fraction of 62%
without reduced local wall motion, and CK, CK-MB, and troponin T levels were further improved to 16 IU/l, 3 IU/l, and 0.050 ng/ml, respectively. No signs of worsening myocardial vasculitis were detected.

CONCLUSIONS

ICIs including pembrolizumab may cause myocardial injury due not only to myocarditis but also to myocardial vasculitis.

AUTHOR RELATIONSHIP WITH INDUSTRY

The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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REFERENCES

1. Ribas A, Wolchok JD. Cancer immunotherapy using checkpoint blockade. Science 2018;359:1350-5.
2. Abdel-Wahab N, Shah M, Suarez-Almazor ME. Adverse events associated with immune checkpoint blockade in patients with cancer: a systematic review of case reports. PLoS ONE 2016;11:e0160221.
3. Postow MA, Sidlow R, Hellmann MD. Immune-related adverse events associated with immune checkpoint blockade. N Engl J Med 2018;378:158-68.
4. Bali S, Ghosh RK, Wongsaengpak S, et al. Cardiovascular toxicities of immune checkpoint inhibitors: JACC review topic of the week. J Am Coll Cardiol 2019;74:1714-27.
5. Zhang L, Awadalla M, Mahmood SS, et al. Cardiovascular magnetic resonance in immune checkpoint inhibitor-associated myocarditis. Eur Hear J 2020;41:1733-43.
6. Salem JE, Manouchehri A, Moey M, et al. Cardiovascular toxicities associated with immune checkpoint inhibitors: an observational, retrospective, pharmacovigilance study. Lancet Oncol 2018;19:1579-89.
7. Daxini A, Cronin K, Sreih AG. Vasculitis associated with immune checkpoint inhibitors—a systematic review. Clin Rheumatol 2018;37:2579-84.
8. Cadena RH, Abdulahad WH, Hospers GAP, et al. Checks and balances in autoimmune vasculitis. Front Immunol 2018;9:1-11.
9. Grabie N, Gotsman I, DaCosta R, et al. Endothelial programmed death-1 ligand 1 (PD-L1) regulates CD8⁺ T-cell-mediated injury in the heart. Circulation 2007;116:2062-71.

KEY WORDS myocardial injury, pembrolizumab, vasculitis

APPENDIX For a supplemental video, please see the online version of this paper.
A 40-year-old woman presented to her internist with 2 weeks of dyspnea on exertion, lower extremity edema, headaches, and peripheral neuropathy. N-terminal pro-brain natriuretic peptide was 3,126 pg/ml. Furosemide was initiated, and she was referred for outpatient cardiology evaluation. Due to progressive dyspnea, she instead presented to the emergency department. On examination, she was afebrile, with blood pressure 122/88 mm Hg, pulse 96 beats/min, respirations 16 breaths/min, pulse oximetry 96% on room air. Her examination showed no jugular venous distension, clear lungs bilaterally, and a soft systolic murmur was heard at the right upper sternal border along with a split S2. No peripheral edema was noted. Dermatologic and neurologic examinations were unremarkable.
syndrome (HES), eosinophilic granulomatosis with polyangiitis (EGPA), drug-induced eosinophilia, and leukemia/myeloproliferative disorder (Table 1).

**INVESTIGATIONS**

Laboratory testing showed N-terminal pro-brain natriuretic peptide 478 pg/ml, troponin 0.10 ng/ml, D-dimer 1,600 ng/ml, complete blood count showed 37% eosinophils: 2,700 absolute, serum creatinine 1.43 mg/dl. Urinalysis was unrevealing. Serum immunoglobulin E 309 kU/l. Chest computed tomography showed no pulmonary embolism. Trans-thoracic echocardiogram displayed left ventricular function test. Reduced LV longitudinal shortening, and diffuse LV apical thrombus and smaller RV apical thrombus, right atrial dilation (Video 1). Cardiac magnetic resonance imaging (CMR) demonstrated a large layering right ventricular thrombus and smaller RV apical thrombus, reduced LV longitudinal shortening, and diffuse subendocardial late gadolinium enhancement (LGE) consistent with endomyocardial fibrosis (Video 2, Figures 1 and 2).

Evaluation for hematologic causes of peripheral eosinophilia, including Epstein-Barr virus, human immunodeficiency virus, hepatitis C virus, serum protein electrophoresis, serum free light chains, tryptase, genetic abnormalities (BCR-ABL, JAK2 protein electrophoresis, serum free light chains, syndrome was negative. Computed tomography of situs hybridization analysis was without rearrangement.

**DISCUSSION**

Eosinophilic myocarditis, or Loeffler’s syndrome, is a hypereosinophilic syndrome defined by organ damage with 20% of cases having cardiac involvement and persistent eosinophilia (1). Although endomyocardial biopsy is the gold standard for diagnosis of eosinophilic myocarditis, the sensitivity is only 54% (2).

The most likely etiology of this patient’s peripheral eosinophilia is primary HES, but the differential diagnosis includes EGPA, malignancy/lymphoproliferative disorder, and drug-induced eosinophilia (Table 1). A diagnosis of HES requires the presence of

**MANAGEMENT**

After consultation with hematology, rheumatology, and allergy/immunology services, the patient was started on high-dose methylprednisolone, then transitioned to oral prednisone at 1 mg/kg/day and tapered by 10 mg/day each week. She demonstrated good clinical response to high-dose steroids, and her eosinophil count remained undetectable with steroid taper. As an outpatient, treatment was initiated with anti-interleukin (IL)-5 therapy (mepolizumab). She was anti-coagulated with heparin and transitioned to warfarin. She was diuresed with bumetanide and spironolactone given inadequate response to furosemide.
1,500 peripheral eosinophils/microliter, no alternative etiologies, and organ damage due to hyper-eosinophilia (3). On presentation, our patient had an elevated serum creatinine of 1.3 to 1.5 mg/dl without proteinuria. Her renal function improved with diuresis, arguing against renal involvement. Cardiac and neurologic involvement hinted at EGPA, but without asthma or sinusitis (despite a positive c-ANCA), this was not diagnostic of vasculitis. EGPA is a small vessel vasculitis and is not associated with development of thrombi. Because she remained symptomatic despite discontinuation of sulfasalazine, drug-induced eosinophilia is unlikely.

Eosinophilic myocarditis is a major cause of morbidity and mortality among patients with HES and should be considered even in patients who lack peripheral eosinophilia (4–7). Eosinophil-mediated heart damage evolves through 3 stages: an acute necrotic stage, an intermediate stage characterized by thrombus formation along the damaged endocardium, and a fibrotic stage characterized by altered cardiac function due to restrictive cardiomyopathy and/or entrapment of the chordae tendineae leading to mitral and tricuspid regurgitation (7). Interestingly, it appears these are not discrete stages but rather an overlapping syndrome. CMR in eosinophilic myocarditis most often demonstrates subendocardial LGE (57.1%) (8), and in the acute setting, as in this case, can present with diffuse subendocardial LGE (Figure 1) (9). Our patient also developed biventricular apical thrombi (Figure 2).

In HES, eosinophil-based granules contain cytotoxic proteins that act as platelet agonists and increase vascular permeability while activating factor XII, a procoagulant that predisposes to thrombosis (8). There are no guidelines for treatment of eosinophilic myocarditis and the mortality rate approaches >20% if eosinophil count does not normalize (8). In a 2017 review, corticosteroids were frequently used (77.7%) in systemic conditions with primary indications such as EGPA (87.0%) or HES (86.7%). Thus, treatment revolves around reducing cardiac function due to restrictive cardiomyopathy and/or entrapment of the chordae tendineae leading to mitral and tricuspid regurgitation (7). Interestingly, it appears these are not discrete stages but rather an overlapping syndrome. CMR in eosinophilic myocarditis most often demonstrates subendocardial LGE (57.1%) (8), and in the acute setting, as in this case, can present with diffuse subendocardial LGE (Figure 1) (9). Our patient also developed biventricular apical thrombi (Figure 2).

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involvement by reducing peripheral eosinophilia. In some cases, a second immunosuppressive agent (8), such as mepolizumab, an anti-IL-5 receptor monoclonal antibody, can be used to block IL-5-mediated eosinophil differentiation and survival. By blocking IL-5, mepolizumab reduces the number of circulating and tissue eosinophils. Mepolizumab is approved by the Food and Drug Administration for the treatment of EPGA and has a well-tolerated side-effect profile. Previous case reports have shown that in eosinophilic myocarditis, anti-IL-5 therapy resulted in improved LVEF and stabilized cardiac function (10). There are no current guidelines for type or duration of therapy, but because of the high risk of progression and worsening fibrosis should tissue eosinophilia recur, we continued mepolizumab indefinitely.

**FOLLOW-UP**

Our patient continued a steroid taper and initiated mepolizumab 300 mg subcutaneously every 4 weeks. Her absolute eosinophil count remained zero despite tapering prednisone to 5 mg daily. She remains on bumetanide and spironolactone with normalization of her renal function and improvement in her lower extremity edema. Dyspnea improved, and her diuretic requirement decreased. Because of ease of use, the patient elected to switch her anticoagulation to apixaban 5 mg twice daily following a comprehensive discussion of the off-label use of direct oral anticoagulants for management of ventricular thrombus, with the understanding of the inherent equipoise in the literature. Transthoracic echocardiogram at 6 and 14 weeks showed persistent but smaller LV apical thrombus, and preserved LVEF. CMR performed 3 months after treatment initiation showed LVEF 52%, persistent LV thrombus with resolution of RV thrombus, and improving but persistent myocardial edema indicative of resolving inflammation. Following resolution of RV thrombus, RV biopsy was performed and showed moderate subendocardial fibrosis on trichrome stain (Figure 3) without a significant number of inflammatory cells, concerning for progression to the fibrotic stage of eosinophilic myocarditis. The patient has mild peripheral neuropathy without further systemic symptoms.

**CONCLUSIONS**

In patients with a history of atopy and hyper-eosinophilia presenting with heart failure, the diagnosis of eosinophilic myocarditis should be considered, particularly in the presence of cardiac dysfunction or ventricular thrombi. A thorough clinical investigation for the etiology of eosinophilia should be undertaken. In the case of eosinophilic myocarditis and/or HES, initiation of immunosuppression with high-dose steroids in conjunction with anticoagulation and guideline-directed medical therapies for heart failure is the treatment strategy of choice. A steroid-sparing regimen including anti-IL-5 therapy can be considered. We recommend...
co-management by a multidisciplinary team including cardiology and allergy/immunology specialists.

**AUTHOR RELATIONSHIP WITH INDUSTRY**

The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

**REFERENCES**

1. Kuchynka P, Palecek T, Masek M, et al. Current diagnostic and therapeutic aspects of eosinophilic myocarditis. BioMed Res Int 2016;2016:2829583.
2. Rizkallah J, Desautels A, Malik A, et al. Eosinophilic myocarditis: two case reports and review of the literature. BMC Res Notes 2013;6:538.
3. Kahn JE, Groh M, Lefevre G. (A critical appraisal of) classification of hypereosinophilic disorders. Front Med (Lausanne) 2017;4:216.
4. Chusid MJ, Dale DC, West BC, Wolff SM. The hypereosinophilic syndrome: analysis of fourteen cases with review of the literature. Medicine (Baltimore) 1975;54:1-27.
5. Ogbovu PU, Rosing DR, Horne MK 3rd. Cardiovascular manifestations of hypereosinophilic syndromes. Immunol Allergy Clin North Am 2007;27:457-75.
6. Take M, Sekiguchi M, Hiroe M, et al. Clinical spectrum and endomyocardial biopsy findings in eosinophilic heart disease. Heart Vessels Suppl 1985;1:243-9.
7. Weller PF, Bubley GJ. The idiopathic hypereosinophilic syndrome. Blood 1994;83:2759-79.
8. Brambatti M, Matassini MV, Adler ED, Klingel K, Camici PG, Ammirati E. Eosinophilic myocarditis: characteristics, treatment, and outcomes. J Am Coll Cardiol 2017;70:2363-75.
9. Mavrogeni SI, Symakis PP, Koutrougoagopoulos L, et al. Cardiac tissue characterization and imaging in autoimmune rheumatic diseases. J Am Coll Cardiol Img 2017;10:1387-96.
10. Song T, Jones DM, Homsi Y. Therapeutic effect of anti-IL-5 on eosinophilic myocarditis with large pericardial effusion. BMJ Case Rep 2017;2017. bcr-2016-218992.

**KEY WORDS** cardiac MRI, cardiomyopathies, eosinophilic myocarditis, Loeffler’s endocarditis

**APPENDIX** For supplemental videos, please see the online version of this paper.
A 72-year-old man on rivaroxaban developed effusive constrictive pericarditis secondary to hemopericardium. His condition improved with anti-inflammatory therapy supporting a diagnosis of transient constrictive pericarditis. On follow-up, residual constriction developed requiring surgical pericardiectomy. Although many cases with transient constrictive pericarditis resolve with medical management, some may progress and require pericardiectomy. (Level of Difficulty: Advanced.) (J Am Coll Cardiol Case Rep 2020;2:1947–50) © 2020 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).
PAST MEDICAL HISTORY

His past medical history was significant for hypertension and hyperlipidemia. He was a non-smoker. He had no family or personal history of autoimmune diseases.

INVESTIGATIONS, MANAGEMENT, AND FOLLOW-UP

His cardiac magnetic resonance imaging (MRI) showed residual trace pericardial effusion, thick pericardium (4 mm), pericardial edema, prominent diastolic septal bounce, respirophasic septal shift, and pericardial enhancement on delayed gadolinium imaging, suggestive of acute pericardial inflammation (Figures 1B1 to 1C1, Video 1). Review of the outside hospital records showed that the pericardial fluid analysis was negative for neoplastic cells and infectious disease work-up, and that he had elevated right atrial pressures even after draining the hemopericardium (most likely secondary to rivaroxaban use). These findings were suggestive of effusive inflammatory constriction. He was treated with furosemide 80 mg intravenous daily and started on triple anti-inflammatory therapy with colchicine 0.6 mg twice-a-day, prednisone 50 mg once-a-day, and aspirin 650 mg once-a-day. His chest pain and shortness of breath improved (from NYHA functional class III to NYHA functional class I to II) and he was discharged 1 week later. On follow-up after 4 months (March 2014), a repeat cardiac MRI showed a decrease in pericardial thickness (4 to 3 mm), edema, inflammation, and the associated constrictive physiology (Figures 1B2 to 1C2). The colchicine dose was reduced to 0.6 mg once-a-day, and prednisone was tapered very slowly every 2 weeks as per European Society of Cardiology guidelines (1). His condition continued to improve and prednisone was stopped July 2014 (total 7 months of therapy).

RECURRENT TRANSIENT CONstriction. He returned 2 months later (September 2014) with generalized malaise. A cardiac MRI showed a significant increase in pericardial thickening (3 to 5 mm), edema, inflammation, and respirophasic septal shift consistent with returning inflammatory constriction. He was restarted on prednisone 5 mg once-a-day, in addition to colchicine 0.6 mg twice-a-day and aspirin 650 mg once-a-day (Figures 1B3 to 1C3). On follow-up, constrictive physiology improved on imaging, and prednisone was again stopped in April 2015. All anti-inflammatory medications were stopped in April 2018.

FIGURE 1

Multimodality Imaging-Guided Therapy for Recurrent Pericarditis

Baseline echocardiogram using pulsed-wave Doppler (PWD) demonstrating significant (A) respiratory variation of peak E-wave velocity (26%), (B) annulus reversus, and (C) increased hepatic vein diastolic flow reversal with expiration. Baseline magnetic resonance imaging showing pericardial edema on short-axis view on T2 short tau recovery sequence (D, arrow) and pericardial inflammation on delayed hyper-enhancement sequence (E, arrow). Follow-up imaging after initiation of anti-inflammatory therapy demonstrating (F) improvement of respiratory variation of peak E-wave velocity (13%) on PWD, (G) resolution of pericardial edema on T2 STIR sequence and persistent pericardial delayed hyperenhancement (H, arrow). Once tapering of medication began, subsequent worsening of (I) respiratory variation of peak E-wave velocity (20%), reoccurrence of pericardial edema on T2 STIR (J, arrow) and inflammation on delayed hyperenhancement (DHE) sequences (K, arrow). With re-escalation of therapy there was, once again, improvement of the mitral inflow pattern (15%) (L), resolution of pericardial edema on both T2 STIR (M) and inflammation on DHE (N, arrow) sequences.

ABBREVIATIONS AND ACRONYMS

CP = constrictive pericarditis
DHE = delayed hyper-enhancement
ECP = effusive constrictive pericarditis
MRI = magnetic resonance imaging
NYHA = New York Heart Association
PWD = pulsed-wave Doppler
TCP = transient constrictive pericarditis

REFERENCES

1. Jain et al. JACC: CASE REPORTS, VOL. 2, NO. 12, 2020
Atypical Case of Transient Constriction Pericarditis
OCTOBER 2020:1947–50
In December 2019, he presented with a 2-week history of 25-lb weight gain and exertional dyspnea. He was diagnosed with NYHA functional class III heart failure. Cardiac MRI findings showed evidence of constrictive pericarditis (Figures 1B4 to 1C4). He underwent surgical radical pericardiectomy for symptomatic heart failure and his symptoms resolved. Pathological examination of the pericardium showed organized fibrous pericarditis without granulomas. On follow-up until March 2020, he continues to remain asymptomatic.

**DISCUSSION**

This case was initially diagnosed as effusive constrictive pericarditis (ECP) secondary to an inflammatory reaction induced by an episode of hemopericardium due to rivaroxaban. ECP has been previously described as a clinical condition where constrictive physiology persists after treatment of pericardial effusion (2). However, improvement on initiation of anti-inflammatory therapy supported a diagnosis of transient constrictive pericarditis (TCP), which is described as a reversible form of constriction with spontaneous recovery on medical treatment, without progression to irreversible fibrosis and calcification (1). Our case was unique in the recurrent nature of the TCP findings, and the patient eventually experienced decompensated heart failure needing surgical pericardiectomy. Our case also shows that the inflammation can be treated with improvement of NYHA functional class; however, residual constriction can persist, and in some cases progress.

TCP was first described in a case series of 16 patients who were initially diagnosed with ECP but the objective finding of constrictive physiology resolved with anti-inflammatory therapy over a mean duration of 2.7 months (3). However, no patient in this case series had recurrent constriction. The study suggests that TCP may be an advanced stage in the spectrum of ECP, and that many cases may resolve on medical therapy. Another case series by Haley et al. (4) reported spontaneous resolution of constriction in TCP in 22 patients over a mean duration of 8.3 weeks.

The underlying pathophysiology of constriction is a transient loss of pericardial elasticity caused by inflammation, edema, and fibrin deposition (3,4). The clinical findings represent impaired diastolic ventricular filling, including an elevated jugular venous pressure with a steep “y” descent, increased inspiratory venous pressure (Kussmaul’s sign), and exaggerated respiratory variation in systolic blood pressure (pulsus paradoxus) (4). Common known etiologies are post-viral, post-cardiac injury, radiation-induced, and infectious (5). Our case had a unique presentation with TCP secondary to an inflammatory response triggered by a hemopericardium. Current guidelines support the role of multimodality imaging to help establish diagnosis (1,6). The characteristic echocardiographic findings of constriction include prominent diastolic septal bounce, plethoric and noncollapsible inferior vena cava, and respiratory variation of mitral and tricuspid inflows. Tissue Doppler imaging of the mitral annulus may show a characteristic reduction of the lateral early diastolic velocity relative to the septal velocity (e’), a phenomenon known as annulus reversus. There is also an increase in diastolic transmural flow velocity (E), leading to abnormally normal to increased E/e’, a phenomenon known as annulus paradoxus (1). Cardiac MRI can demonstrate abnormal physiology and anatomy: pericardial thickness (>3 mm); pericardial edema; and pericardial inflammation on delayed gadolinium hyperenhancement, with or without fat-suppression, consistent with TCP (1).

TCP may resolve spontaneously resolve or require anti-inflammatory therapy. Severe cases warrant a triple therapy with colchicine, nonsteroidal anti-inflammatory drugs, and corticosteroids (7). Refractory cases may treated with biological agents, such as anakinra, but there is limited evidence (8). Our case was unique because the patient had decompensated heart failure with worsening of underlying constrictive physiology and inflammation, needing surgical pericardiectomy.

**CONCLUSIONS**

TCP is a reversible form of inflammatory constrictive pericarditis, which may present after an episode of ECP (3). Early recognition and treatment with anti-inflammatory agents may prevent chronic constriction and need of surgical pericardiectomy.

**AUTHOR RELATIONSHIP WITH INDUSTRY**

The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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REFERENCES

1. Adler Y, Charron P, Imazio M, et al. 2015 ESC Guidelines for the diagnosis and management of pericardial diseases: the Task Force for the Diagnosis and Management of Pericardial Diseases of the European Society of Cardiology (ESC) Endorsed by: the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J 2015;36:2921-64.

2. Sagristà-Sauleda J, Angel J, Sánchez A, Permanyer-Miralda G, Soler-Soler J. Effusive-constrictive pericarditis. N Engl J Med 2004;350:469-75.

3. SagristÀ-Sauleda J, Permanyer-Miralda G, Candell-Riera J, Angel J, Soler-Soler J. Transient cardiac constriction: an unrecognized pattern of evolution in effusive acute idiopathic pericarditis. Am J Cardiol 1987;59:961-6.

4. Haley JH, Tajik AJ, Danielson GK, Schaff HV, Mulvagh SL, Oh JK. Transient constrictive pericarditis: causes and natural history. J Am Coll Cardiol 2004;43:271-5.

5. Gentry J, Klein AL, Jellis CL. Transient constrictive pericarditis: current diagnostic and therapeutic strategies. Curr Cardiol Rep 2016;18:41.

6. Klein AL, Abbara S, Agler DA, et al. American Society of Echocardiography clinical recommendations for multimodality cardiovascular imaging of patients with pericardial disease: endorsed by the Society for Cardiovascular Magnetic Resonance and Society of Cardiovascular Computed Tomography. J Am Soc Echocardiogr 2013;26:965-1012.

7. Imazio M, Brucato A, Cumetti D, et al. Corticosteroids for recurrent pericarditis: high versus low doses: a nonrandomized observation. Circulation 2008;118:667-71.

8. Jain S, Thongprayoon C, Espinosa RE, et al. Effectiveness and safety of anakinra for management of refractory pericarditis. Am J Cardiol 2015;116:1277-9.

KEY WORDS cardiac magnetic resonance imaging, effusive constrictive pericarditis, hemopericardium, pericarditis, recurrence, transient constrictive pericarditis

APPENDIX For supplemental videos, please see the online version of this paper.
A 38-year-old African American woman with no medical history presented to cardiology office for syncope and palpitations. Twelve-lead electrocardiography revealed sinus rhythm with right bundle branch block and left posterior hemiblock. A 30-day event monitor showed no significant arrhythmia. Echocardiography revealed reduced left ventricular ejection fraction at 34%. A $^{201}$Tc sestamibi nuclear myocardial perfusion study using a cadmium-zinc-telluride camera was then pursued for the etiology of cardiomyopathy, which demonstrated severe, multifocal, predominantly fixed and distinct perfusion defects involving different parts of myocardium (apex, apical lateral, basal septal, mid inferior, and mid anteroseptal) (Figure 1). The perfusion defects did not correlate with any specific coronary distribution and are characteristic of cardiac sarcoidosis. The quantitative analysis of myocardial perfusion study showed a summed stress score of 24, a summed differential score of 8, and a summed rest score of 16. Left ventricular ejection fraction was 33%, end-diastolic volume was 65 ml, and end-systolic volume was 44 ml. The patient was subsequently fitted with a LifeVest (ZOLL Cardiac Diagnostics, Chelmsford, Massachusetts), and coronary angiography revealed normal coronary artery anatomy. Cardiac magnetic resonance imaging (MRI) detected multifocal areas of globular delayed enhancement and T2 hyperintensity confirming cardiac sarcoidosis (Figure 2). Additionally, splenic nodules and mediastinal and hilar lymphadenopathy were evident on MRI, supporting a diagnosis of
systemic sarcoidosis. Steroid treatment was subsequently started, and repeat cardiac MRI is planned in 3 months for evaluation of treatment efficacy and permanent implantable cardioverter-defibrillator candidacy.

Distinct defects on myocardial perfusion studies that do not correlate with coronary anatomic distributions should raise suspicion, and further work-up for cardiac sarcoidosis should be pursued even if findings on coronary angiography are normal.

A $^{99m}$Tc sestamibi myocardial perfusion study demonstrated severe, multifocal, predominantly fixed and distinct perfusion defects involving different parts of myocardium, which did not correlate with any specific coronary distribution. The quantitative analysis showed a summed stress score of 24, a summed differential score of 8, and a summed rest score of 16. Left ventricular ejection fraction was 36%, end-diastolic volume was 65 ml, and end-systolic volume was 42 ml.
Cardiac magnetic resonance imaging demonstrating multifocal areas of globular delayed enhancement (red arrows) and T2 hyperintensity (yellow arrows), confirming cardiac sarcoidosis.

**AUTHOR RELATIONSHIP WITH INDUSTRY**

Both authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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**KEY WORDS** cardiac magnetic resonance, cardiomyopathy, nuclear medicine
We describe a 54-year-old male in whom eosinophilic myocarditis secondary to T-cell lymphoma complicated by bilateral ischemic stroke was diagnosed. The source, identified as an apical tear with thrombus formation, was revealed by transthoracic echocardiography. (Level of Difficulty: Advanced.) (J Am Coll Cardiol Case Rep 2020;2:1954–8) © 2020 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

PRESENTATION

A 54-year-old man initially presented to the hospital with pre-syncpe, which progressed to syncope lasting <5 min. This was coupled with symptoms of sudden onset and left-sided chest tightness which self-resolved after 2 min. He had been under review by his general practitioner for 4 months due to generalized fatigue and weight loss.

Physical examination revealed a weight of 41 kg, a blood pressure of 96/60 mm Hg, and unremarkable cardiac and respiratory examinations. There was a diffuse erythematous rash in the left lower limb. Electrocardiography demonstrated normal sinus rhythm. Biochemistry tests revealed a raised troponin concentration of 1,268 ng/l (reference, 0 to 14 ng/l) and an eosinophil count of $7.6 \times 10^9$/l (reference 0 to $0.5 \times 10^9$ cells/l). He was referred to cardiology.

On review at the cardiac center, believed the diagnosis was myocarditis. Cardiac magnetic resonance (CMR) imaging showed appearances consistent with a diagnosis of eosinophilic myocarditis (EM). Coronary angiography revealed no evidence of coronary artery disease.

Given the working diagnosis of EM, secondary causes were sought. The decision was made to perform a skin biopsy, and a cardiac biopsy was considered. The patient improved clinically and was discharged with prescriptions for edoxaban, 30 mg once daily, and prednisolone, 40 mg once daily, and scheduled for follow-up in the rheumatology clinic in 2 weeks. Unfortunately, he missed that...
appointment and presented to cardiology clinic 2 months later with neck swelling, when he was urgently admitted to hospital. Biochemistry tests revealed a rise in his eosinophil count to $19.7 \times 10^9$ cells/l (reference, 0 to $0.5 \times 10^9$ cells/l), and it was decided to increase the dose of prednisolone to 100 mg once daily. Computed tomography (CT) of his neck demonstrated lymphadenopathy, which was promptly confirmed as T-cell lymphoma on biopsy. The decision was for a course of chemotherapy with cyclophosphamide.

During this admission, the patient deteriorated from sepsis secondary to cholecystitis and later experienced new onset of seizures with a reduction in his consciousness using a Glasgow Coma Scale (GCS) of 9/15. Head CT demonstrated multiple bilateral acute infarctions. The infarct areas were not amenable to thrombectomy. The GCS score continued to deteriorate, and he was transferred to the intensive care unit. Investigations were undertaken to identify the source for the bilateral cerebral infarcts.

**MEDICAL HISTORY**

He had a history of hepatitis B, asthma, intravenous drug use, and excessive use of alcohol.

**DIFFERENTIAL DIAGNOSIS**

The most probable diagnosis in this case was ischemic stroke secondary to EM, given its ability to develop left ventricular (LV) thrombus and neurological

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**FIGURE 1** Cardiac Magnetic Resonance 4-Chamber View

(A) Four-chamber steady state free precession sequence. (B) Corresponding T2-weighted STIR sequence shows increased signal in the apical and lateral segments. (C) T2-weighted map sequence demonstrates edema in the apical and lateral segments. (D) Late gadolinium-enhanced sequence shows subendocardial late gadolinium enhancement in the apical and lateral segments (yellow arrows).
complications (1). Further differential diagnoses included reduced GCS score, seizures and intracranial bleeding, and malignancy or intracerebral infection.

**INVESTIGATIONS**

CMR demonstrated diffuse subendocardial late gadolinium enhancement matching increased signal on short-T1 inversion recovery (STIR) images, with mild LV systolic impairment (ejection fraction, 50%) (Figures 1 and 2). A skin biopsy revealed eczematous changes. A bone marrow biopsy revealed no increase in eosinophils. An axillary lymph node biopsy confirmed T-cell lymphoma. Following the reduced consciousness and seizures, head CT revealed infarcts involving the frontal, parietal, and left temporo-occipital regions.

Critical care echocardiography demonstrated an apical tear with preserved apical architecture suggestive of intramural myocardial tear resulting in a small apical cavity in continuity with the main LV cavity (Video 1A). Small mobile structures were attached to dissected myocardium and believed to be the source of embolism (Video 1B). Color flow Doppler interrogation revealed diastolic flow in the apical cavity (Video 1C). Pulse wave Doppler demonstrated diastolic flow into the apical cavity and systolic flow out of it (Figure 3). A differential diagnosis based on
the images would have been a cardiac thrombus alone. However, the systolic flow and evidence of disruption of the muscular layer favored an LV tear.

**MANAGEMENT**

Cyclophosphamide therapy was begun, which resulted in a partial response, with a reduction of the eosinophil count to a range of 20 to 30 \( \times 10^9 \) cells/l from 70 \( \times 10^9 \) cells/l (reference, 0 to 0.5 \( \times 10^9 \) cells/l).

**DISCUSSION**

To the authors’ knowledge, there are no other published reports that describe secondary EM due to T-cell lymphoma resulting in LV apical intramural tear. There have been documented cases of T-cell lymphoma causing ventricular wall rupture, but those were due to the tumor itself (2,3). Although it was not possible to perform a cardiac biopsy, given his deterioration, his clinical presentation in addition to his biochemistry markers and CMR favored a diagnosis of EM. A possible explanation for the tear could be related to activated eosinophils and eosinophil granule proteins in the necrotic and thrombotic tissue, leading to muscle damage (4).

Hypereosinophilic syndrome (HES) is hypereosinophilia with evidence of organ damage or dysfunction related solely to hypereosinophilia and not secondary to another condition. HES can be primary, secondary, or idiopathic (5). This patient’s presentation was consistent with secondary HES due to the overproduction of eosinophilopoietic factors by malignancy.

Cardiac complications of HES occur in 3 stages: an acute necrotic stage, a thrombotic stage, and a fibrotic stage (5). EM presents in stage 1 with chest pain, mimicking an acute myocardial infarction possibly related to myocardial necrosis (6). Typically the electrocardiogram would demonstrate ST-segment changes of ischemia, which were absent in this case (1). The patient experienced an embolic brain event (stage two) prior to detection of the intracardiac thrombus.

Advances in echocardiography have yielded a higher level of sensitivity of 93% for cardiac masses (7). It remains a challenge to differentiate between EM with endomyocardial thickening and apical mural thrombus based on echocardiography alone (8). The increasing number of intensive care clinicians partaking in echocardiography has been shown to help therapeutic management (9). For cardiac masses, CMR yields a respective sensitivity and specificity of 67% and 91%. EM is typically characterized as extensive myocardial hyperintensity on T2-weighted imaging along with subendocardial late enhancement (10). Endomyocardial biopsy is the gold standard for the diagnosis of EM with a sensitivity of 54% (1). Unfortunately, this patient deteriorated, and it was not appropriate to perform a biopsy.

EM has been successfully treated, in the medical literature, with corticosteroids with partial or complete response in 85% with monotherapy (10). The present patient was treated with both anticoagulation pre-emptively and with corticosteroids, and despite these treatments, the condition progressed.

**OUTCOME.** Following a multidisciplinary team meeting, it was decided, given his deterioration and poor prognosis, palliation was appropriate.

**CONCLUSIONS**

LV wall tear is a rare complication of EM. EM is difficult to treat due to its indolent course, which can lead to a delay in diagnosis. In this case, the complication was found by noncardiology specialists performing transthoracic echocardiography.

**AUTHOR RELATIONSHIP WITH INDUSTRY**

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REFERENCES

1. Kassem KM, Souka A, Harris DM, Parajuli S, Cook JL. Eosinophilic myocarditis: classic presentation of elusive disease. Circ Cardiovasc Imaging 2019;12:e009487.

2. Armstrong EJ, Bhave P, Wong D, et al. Left ventricular rupture due to HIV-associated T-cell lymphoma. Tex Heart Inst J 2010;37:457–60.

3. Molajo AO, McWilliam L, Ward C, Rahman A. Cardiac lymphoma: an unusual case of myocardial perforation—clinical, echocardiographic, haemodynamic and pathological features. Eur Heart J 1987;8:549–52.

4. Tai P-C, Spry CF, Olsen EJ, Ackerman S, Dunnette S, Gleich G. Deposits of eosinophil granule proteins in cardiac tissues of patients with eosinophilic endomyocardial disease. Lancet 1987;329:643–7.

5. Mankad R, Bonnichsen C, Mankad S. Hypereosinophilic syndrome. cardiac diagnosis and management. Heart 2016;102:100–6.

6. Thambidorai SK, Koralakunta HL, Arouni AJ, Hunter WJ, Holmberg MJ. Acute eosinophilic myocarditis mimicking myocardial infarction. Texas Heart Inst J 2009;36:355–7.

7. Kirkpatrick JN, Wong T, Bednarz JE, et al. Differential diagnosis of cardiac masses using contrast echocardiographic perfusion imaging. J Am Coll Cardiol 2004;43:1412–9.

8. Koh TW, Coghlan JG, Davarashvilli J, Lipkin DP. Biventricular thrombus mimicking eosinophilic endomyocardial disease. Eur J Heart J 1996;1770–1.

9. Beaulieu Y. Specific skill set and goals of focused echocardiography for critical care clinicians. Crit Care Med 2007;35 Suppl:S144–9.

10. Rizkallah J, Desautels A, Malik A, et al. Eosinophilic myocarditis: two case reports and review of the literature. BMC Res Notes 2013;6:538.

KEY WORDS echocardiography, eosinophilic myocarditis, thrombus

APPENDIX For supplemental videos, please see the online version of this paper.
Erdheim-Chester Disease
A Case of Right Atrial Involvement and Superior Vena Cava Stenosis

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ABSTRACT
We describe the case of a 79-year-old woman with a history of Erdheim-Chester disease who presented with bradycardia and infiltration of the superior vena cava and right atrium. This case highlights an important consideration in type of pacemaker placement given the frequency of right atrial involvement in Erdheim-Chester disease. (Level of Difficulty: Advanced.) (J Am Coll Cardiol Case Rep 2020;2:1959–65) © 2020 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

HISTORY OF PRESENTATION
A 79-year-old woman was referred from her endocrinologist’s office to the hospital for a persistent heart rate in the 30s (beats/min). She has carried a presumed diagnosis of Erdheim-Chester disease (ECD) for 6 years, after incidental imaging demonstrated mass-like infiltration of the right atrium and asymptomatic thickening of the ascending and descending thoracic aorta, right kidney, and right adrenal gland (Figure 1). Invasive work-up with biopsy was recommended at that time; however, the patient deferred further testing and monitoring. On current admission, she denied any chest pain, fatigue, syncope, or presyncope. Her home medications included amlo- dipine, losartan, metoprolol, furosemide, and rosuvastatin. Physical examination demonstrated a pulse of 38 beats/min, blood pressure of 128/64 mm Hg, respiratory rate of 17 breaths/min, and oxygen saturation of 98% on room air. Lungs were clear to auscultation, and cardiac examination demonstrated bradycardia with regular rhythm, without other significant findings.

LEARNING OBJECTIVES
- To consider use of leadless pacemakers in management of arrhythmias for patients with ECD who have right atrial involvement.
- To understand common structural and electrophysiological cardiac manifestations of ECD.

PAST MEDICAL HISTORY
The patient had a history of hypertension and hyperlipidemia.
Differential Diagnosis

The most likely cause of bradycardia in this patient was thought to be progressive infiltration of the conduction system from ECD. Other differential diagnoses included medication-induced bradycardia, myocardial ischemia or infarction, and alternate infiltrate disorders including amyloidosis and lymphoma.

Investigation

The patient’s admission troponin was negative, and the electrocardiogram demonstrated a new junctional escape rhythm (Figure 2). The patient underwent cardiac magnetic resonance imaging that demonstrated infiltrative lesions involving the superior vena cava (SVC), aorta, proximal pulmonary artery, and right atrium (Figures 3A to 3C). There was evidence of

Figure 1 Chest Cardiac Magnetic Resonance, 6 Years Earlier

Chest cardiac magnetic resonance demonstrates a mass-like infiltrative lesion involving the right atrium that is most pronounced along the lateral free wall (A and B, arrowheads), with milder involvement of the interatrial septum (A, open arrow) on (A) T1 and (B) T2 fat-suppressed imaging. A small pericardial effusion is also present (B, red arrows). There is periaortic infiltration (C and D, white arrows) of the ascending and descending aorta on (C) T1 and (D) T2 fat-suppressed imaging.
significant cardiac disease progression when compared with imaging 6 years earlier (Figures 4A and 4B). There was evidence of flow acceleration across the SVC and at the sinoatrial junction, indicating severe stenosis; however, the patient did not clinically present with signs or symptoms of SVC syndrome (Figures 5A to 5F). Right-sided heart catheterization was performed through right femoral vein access without an attempt to cross the SVC stenosis. There were minimally elevated pressures, with a right atrial pressure of 10 mm Hg and normal cardiac output and cardiac index. Intracardiac echocardiography-guided endomyocardial biopsy specimens were obtained of the right atrial septum during the procedure, and examination confirmed the diagnosis of ECD, with histological sections demonstrating fibrotic tissue, abundant histiocytes with xanthomatous cytoplasm, and mixed inflammatory cells (Figure 6). Immunostaining identified cells with CD163, BRAF V600E, and factor XIIIa positivity and CD1a and S100 negativity, a typical expression pattern in ECD (1).

**MANAGEMENT**

The patient’s home metoprolol use was discontinued. After several days of inpatient monitoring, her cardiac rhythm continued to fluctuate among a junctional escape rhythm, ectopic atrial bradycardia, and atrial fibrillation with slow ventricular response. At this point, a decision was made for the patient to undergo pacemaker placement. Given the concern that standard lead placement could worsen SVC stenosis and result in SVC syndrome, a Medtronic Micra leadless pacemaker (Medtronic, Minneapolis, Minnesota) was placed under fluoroscopy through right femoral vein access without complications.
Four-chamber phase sensitive inversion recovery images demonstrate (A) extensive late gadolinium enhancement of the infiltrative lesion along the right atrium (RA) and atrioventricular sulcus. (B) Superior extension of the late gadolinium enhancement, with circumferential encasement of the superior vena cava (white arrowhead) and further extension of the infiltrative lesion along the aortic root (Ao), proximal pulmonary artery (PA), and aortopulmonary window (black arrowhead). Late gadolinium enhancement is also visible along the descending thoracic aorta (white arrow). (C) The structural relationship of the late gadolinium enhancement is better depicted in a short-axis phase sensitive inversion recovery image. Extension of late gadolinium enhancement along the left atrioventricular sulcus is also shown in this image (red arrow). LA = left atrium, rpa = right pulmonary artery.
DISCUSSION

Although ECD most commonly manifests as non-Langerhans histiocytic infiltration of bones, extraskeletal involvement has been reported to occur in >50% of all cases and is associated with poor clinical prognosis (2,3). Common sites of extraskeletal involvement include the cardiovascular system, retro-orbital tissue, lung, liver, spleen, retroperitoneum, and skin (4). Cardiovascular involvement in ECD has been reported to occur in up to 75% of all patients (4). This most commonly manifests as infiltration of the pericardium and myocardium with a tendency to involve the right atrial myocardium, often with a pseudotumor appearance (5,6). Extensive vascular involvement of the thoracic aorta and SVC has also been reported (7). Typical electrocardiographic abnormalities that have been reported include shortening of the PR interval, sinoatrial block, sinus bradycardia, Q-wave abnormalities, and ST-T wave abnormalities (6). Identifying cardiac involvement is crucial because cardiovascular complications, including hemodynamically significant arrhythmias, cardiomyopathy, myocardial infarction, and severe valvular insufficiency, are frequent causes of death in patients with ECD (2). Cardiac magnetic resonance is an accurate tool for localizing lesions and for assessing the extent of disease involvement (4). This report presents a case of ECD in which cardiac infiltration has extended from the right atrium to involve surrounding vasculature, including the SVC, proximal pulmonary artery, and multiple segments of the aorta. The severity of stenosis at the cavoatrial junction in this case resulted in a decision to place a leadless pacemaker to avoid exacerbating SVC stenosis and inducing SVC syndrome.
FIGURE 5  Evaluation of SVC Stenosis

(A) Selected image from a cine steady-state free precession stacked 4-chamber sequence at the level of the superior cavoatrial junction demonstrates circumferential stenosis of the superior vena cava (SVC) by the infiltrative mass. The degree of SVC stenosis can be best appreciated from a frontal view (B). Magnitude and velocity images from through-plane (C and D) and in-plane (E and F) phase contrast velocity mapping demonstrate flow acceleration along the stenosed segment of the superior vena cava and superior cavoatrial junction (red circles).
CONCLUSIONS

Although this case illustrates a common presentation of ECD with cardiac involvement, it highlights a unique case in which the severity of SVC stenosis affected decision making in the management of bradyarrhythmia. Given that both conduction abnormalities and right atrial involvement are common cardiac manifestations of ECD, careful consideration should be taken when deciding on the approach and type of pacemaker placement for significant arrhythmias in these patients.

AUTHOR RELATIONSHIP WITH INDUSTRY

The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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REFERENCES

1. Ivan D, Neto A, Lemos L, Gupta A. Erdheim-Chester disease: a unique presentation with liver involvement and vertebral osteolytic lesions. Arch Pathol Lab Med 2003;127:e337–9.
2. Antunes C, Graça B, Donato P. Thoracic, abdominal and musculoskeletal involvement in Erdheim-Chester disease: CT, MR and PET imaging findings. Insights Imaging 2014;5:473–82.
3. Cavalli G, Guglielmi B, Berti A, Campochiaro C, Sabbadini MG, Dagna L. The multifaceted clinical presentations and manifestations of Erdheim-Chester disease: comprehensive review of the literature and of 10 new cases. Ann Rheum Dis 2013;72:1691–5.
4. Ponsiglione A, Puglia M, Barbuto L, et al. Cardiac involvement in Erdheim-Chester disease: MRI findings and literature revision. Acta Radiol Open 2015;4:2058460115592273.
5. Gupta A, Kelly B, McGuigan JE. Erdheim-Chester disease with prominent pericardial involvement: clinical, radiologic, and histologic findings. Am J Med Sci 2002;324:96–100.
6. Haroche J, Cluzel P, Toledano D, et al. Images in cardiovascular medicine. Cardiac involvement in Erdheim-Chester disease: magnetic resonance and computed tomographic scan imaging in a monocentric series of 37 patients. Circulation 2009;119: e597–8.
7. Sánchez-Nadales A, Wang TK, Anampa-Guzmán A, Xu B. Multisystem Erdheim-Chester disease with extensive pericardial and vascular involvement. Circ Cardiovasc Imaging 2020;13: e010123.

KEY WORDS cardiac magnetic resonance, cardiac pacemaker, stenosis
What Looks Like a Clot But Is Not a Clot?
Cardiac Leiomyosarcoma Mimicking Pulmonary Embolism

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ABSTRACT

Primary cardiac tumors in the right ventricular outflow tract are often misdiagnosed as pulmonary embolism due to rarity and inadequate imaging characterization. Multimodality imaging offers advantages and facilitates subsequent diagnostics and management. We present a case of a woman with suspected submassive pulmonary embolism who was found to have pleomorphic leiomyosarcoma. (Level of Difficulty: Intermediate.) (J Am Coll Cardiol Case Rep 2020;2:1966–8)

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A woman in her 70s with a history of 2 primary lung cancers and nonhuman immunodeficiency virus-related cutaneous Kaposi’s sarcoma presented with increasing dyspnea and was transferred for advanced management of a large filling defect in the main pulmonary artery. Vital signs at the time of transfer were notable for a heart rate of 82 beats/min, blood pressure 118/84 mm Hg, and oxygen saturation at rest on room air was 98%. Examination was notable for regular rhythm with a soft systolic ejection murmur at the cardiac base, jugular venous pulsation was noted at the ear while the patient was seated at 90 degrees, lungs were clear bilaterally, and bilateral pitting edema was present to the mid-shins.

She had 2 primary lung cancers for which she underwent a resection without adjuvant therapy for an adenocarcinoma in the 1980s and a right lower lobectomy for adenocarcinoma with adjuvant chemotherapy in 2015. She has never smoked and was considered to be in remission before admission. She also had a history of Kaposi’s sarcoma of her right posterior lower leg which had been excised.

A repeat chest tomography (CT) showed a lobulated lesion in the right ventricular outflow tract (RVOT) (Figure 1A) extending into the proximal main pulmonary artery (PA) with right ventricular (RV) and right atrial enlargement. Positron-emission tomography performed 2 months prior for cancer surveillance showed a fludeoxyglucose-avid soft tissue lesion in the main PA corresponding to the mass seen on the CT scan (Figure 1B). A transthoracic echocardiogram showed a severely dilated RV with moderate-to-severe systolic dysfunction and RV free wall hypokinesis with sparing of the RV apex. There was also evidence of mild-to-moderate supravalvular pulmonic stenosis. Cardiac magnetic resonance imaging showed a 30 × 25-mm lobulated mass with late gadolinium enhancement in the RVOT and PA (Figure 1C, Video 1) consistent with a tumor. Given possible intercurrent thrombus, she received systemic parenteral anticoagulation. She underwent surgical resection of RV and PA mass with reconstruction of RVOT and proximal main PA along with a
pulmonic valve replacement. Pathology of the mass showed high-grade pleomorphic leiomyosarcoma involving the endocardium (Figures 1D and 1E).

This patient presented with acute cardiopulmonary symptoms and was found to have a primary cardiac sarcoma. Acute thrombus was initially suspected; however, gross pathology ultimately showed no thrombus present (Figure 1F). Primary cardiac malignancies are rare with an incidence rate of ~0.02% based on autopsy studies (1). Conventional CT imaging is often not sensitive enough to distinguish tumor from thrombus, therefore multimodal imaging is helpful to better characterize RVOT lesions. Cardiac magnetic resonance imaging is particularly useful in distinguishing tumor from thrombus and malignant tumors from benign (2,3). Positron-emission tomography can be useful in further delineating intracardiac masses as thrombi tend to not be fludeoxyglucose avid. This patient did well in the post-operative period and was discharged to rehabilitation. This case highlights the utility of multimodal imaging in characterizing intracardiac masses and in guiding therapeutic and further diagnostic strategies.

AUTHOR RELATIONSHIP WITH INDUSTRY

Dr. Vaduganathan has received the KL2/Catalyst Medical Research Investigator Training award from Harvard Catalyst (NIH/NCATS Award UI 1TR002541); serves on advisory boards for Amgen, AstraZeneca, Bayer AG, Baxter Healthcare, Boehringer Ingelheim, Cytokinetics, and Relypsa; and participates on clinical endpoint committees for studies sponsored by Novartis and the NIH. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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![Figure 1](image-url)
REFERENCES

1. Maleszewski JJ, Bois MC, Bois JP, Young PM, Stulak JM, Klairich KW. Neoplasia and the heart: pathological review of effects with clinical and radiological correlation. J Am Coll Cardiol 2018;72:202-27.

2. Araoz PA, Eklund HE, Welch TJ, Breen JF. CT and MR imaging of primary cardiac malignancies. Radiographics 1999;19:1421-34.

3. Kassi M, Polsani V, Schutt RC, et al. Differentiating benign from malignant cardiac tumors with cardiac magnetic resonance imaging. J Thorac Cardiovasc Surg 2019;157:1912-1922 e1912.

KEY WORDS cardiac magnetic resonance, echocardiography, right ventricle

APPENDIX For a supplemental video, please see the online version of this paper.
A 70-year-old right-handed woman presented to our emergency department with acute aphasia that started a few hours before presentation. On examination, she had global aphasia and right hemiplegia. Her vital signs were normal, and she was in sinus rhythm. Cardiac auscultation revealed normal heart sounds and no cardiac murmurs/rubs. She did not have fever, weight loss, myalgias, or arthralgias.

PAST MEDICAL HISTORY

The past medical history included essential hypertension managed on metoprolol 25 mg twice daily, type 2 diabetes mellitus on metformin 500 mg twice daily, prior transient ischemic attack without any residual neurological deficits on clopidogrel 75 mg, and hyperlipidemia on simvastatin 5 mg daily. She had breast cancer in 1996 and underwent a right mastectomy with reconstruction followed by radiation therapy and remained in complete remission on anastrozole.

LEARNING OBJECTIVES

- To understand the importance of echocardiographic imaging in the work-up of cardiogenic stroke in the older adult population.
- To comprehend the pathophysiology of left atrial appendage masses.
- To recognize the pathogenesis of intravascular papillary endothelial hyperplasia.
- To understand that Masson tumor is curative but residual tumor can recur after resection; therefore, careful follow-up with echocardiography should be paramount.
DIFFERENTIAL DIAGNOSIS

Because of the acute nature of her symptoms, an acute cerebrovascular accident secondary to hypertension, type 2 diabetes mellitus, or cardiogenic causes due to paroxysmal atrial fibrillation (AF) or patent foramen ovale with deep venous thrombosis, vegetations caused by infectious endocarditis, or tumors were considered.

INVESTIGATIONS

Immediate head computed tomography without intravenous contrast revealed patchy acute infarcts in anterior part of left middle cerebral artery territory with hemorrhagic transformation in lateral left parietal cortex, which was stable on repeat imaging (Figure 1). Brain MR angiography revealed normal carotid arteries and normal intracranial circulation.

She was monitored on telemetry without documented episodes of any arrhythmias during the hospitalization for 5 days and 14 days in inpatient rehabilitation. She underwent transthoracic and transesophageal echocardiograms (TEE) that showed normal valvular function, preserved left ventricular ejection fraction with diastolic dysfunction, and a negative bubble study. However, a mobile mass with a stalk was seen in the left atrial appendage (LAA) (Figure 2A).

MANAGEMENT

With a provisional diagnosis of a LAA thrombus, she was anticoagulated with heparin and then switched to apixaban on discharge. A follow-up TEE 2 months later showed an interval increase in the size of the mass to 15 mm (Figure 2B, Video 1).

Given the increase in mass size, a decision was made to proceed with mass resection during cardiopulmonary bypass surgery. Intraoperatively, the mass was noted to be in the LAA, pedunculated, ovoid, and matched the description noted in the TEE.

Pathological evaluation showed that the lesion was composed of multiple papillae lined by bland endothelial cells suggestive of papillary endothelial hyperplasia on hematoxylin and eosin stain (Figure 3). Careful histopathological evaluation was performed to distinguish Masson tumor from angiosarcomas and other common masses including papillary fibroelastoma. The tumor was positive for CD31, CD34, factor VIII–related antigen, and smooth muscle actin, which is commonly seen in Masson tumors (Figure 4), and CD105 negative, which excluded angiosarcomas. Moreover, the mass did not show any pleomorphism, increased mitotic activity, or necrosis. Papillary fibroelastomas are very similar to Masson tumors but have distinctive clusters of yellow-white hair like projections. They can be CD31 and CD34 positive; however, are typically smooth muscle actin negative.
DISCUSSION

Masson tumor was first described in 1923 by the French pathologist Pierre Masson and later termed intravascular papillary endothelial hyperplasia (IPEH) (1). In 1983, Hashimoto et al. (2) described 3 forms of Masson tumor: 1) a primary form arising in a dilated vascular space; 2) a secondary or mixed mass arising from a pre-existing vascular lesion; and 3) an extravascular mass that appears within hematomas. IPEH is a rare vascular growth that may occur in any location in the body, with a predilection for the skin of the head, neck, fingers, and trunk (3). To the best of our knowledge, this is one of the very few case reports of Masson tumor located in the LAA. Therefore, it is extremely rare for it to be located in the LAA (4).

Although Masson tumors rarely occur in the LAA, it is very logical for endothelial lesions to occur in this location, because the LAA is the only cardiac structure in the left atrium (LA) derived from the primitive atrium (5). Thus, the LAA has a more trabecular lining, whereas the rest of the LA cavity has a smooth endocardium. The LAA functions as a contractile reservoir and decompression chamber as it undergoes suction during ventricular systole and acts like a vessel during diastole (6). It has been postulated that cardiomyopathy or AF leading to decreased function, increased filling pressures, and remodeling of the LAA are major risk factors for blood stasis and thrombi formation (7). However, limited data suggests that patients with isolated elevated end-diastolic pressures without LA or LAA enlargement, can lead to LAA thrombus formation in the absence of AF (8). In our patient’s case, she did not have any history of AF, left ventricular dysfunction, or LA enlargement, which makes this case of Masson tumor much more difficult to explain. Risk factors for Masson tumor are still unknown; they can occur

FIGURE 3 Pathology of Left Atrial Appendage Mass

Multiple papillae lined by bland endothelial cells suggestive of papillary endothelial hyperplasia on hematoxylin and eosin stain. Original magnification × 100.
sporadically, or in situations of vascular stasis. Therefore, we can speculate that Masson tumor may have formed in an organized thrombus during undetected episodes of paroxysmal AF.

The pathogenesis of IPEH is still unclear. Inflammation and vascular stasis related to thrombus formation, typically within a vein or artery, stimulate histiocytic release of endothelial basic fibroblast growth factor and support the formation of endothelial hyperplasia (9). In contrast to thrombi, Masson tumors develop in patients on anticoagulation therapy. In our patient’s case, the differentiation of IPEH from other vascular malignant tumors, such as angiosarcoma, was essential, especially in light of its apparent growth over a short period of time. Masson tumors are cured by surgical excision, whereas angiosarcoma, for example, is a malignant tumor that is capable of metastasis and may require surgery with adjuvant chemotherapy.

Several criteria are important in differentiating IPEH from malignant angiosarcoma including intraluminal lesion origin, minimal necrosis, similarity to organized thrombus, and lack of pleomorphic and mitotic activity in cells, such as in our patient (10). In addition, Masson tumor is typically positive for CD31, CD34, smooth muscle actin, and factor VIII-related antigen (10).

Because the LA appendage is structurally complex and varies morphologically among individuals, it can be challenging to diagnose LAA pathology using imaging (5). Three-dimensional echocardiography with Doppler and contrast agents enable analysis of the vascular patterns of cardiac tumors: malignant tumors exhibit higher vascularity than benign tumors, whereas thrombi are avascular. TEE is currently used as the gold standard modality to diagnose and exclude LAA masses. It has a sensitivity of 92% in comparison to intraoperative observation, which is

Papillary cores of hyaline tissue (original magnification ×400) with hematoxylin and eosin stain (A), CD34 (B), factor VIII-related antigen (C), and smooth muscle actin (D) stains.

**FIGURE 4** Immunohistochemistry Stains of Left Atrial Appendage Mass
98% sensitive with positive and negative predictive values of 100% and 86%, respectively (11).

FOLLOW-UP

The patient tolerated the surgical procedure well and was discharged 7 days after cardiac surgery on long-term apixaban. On her 3-month follow-up, her TEE did not show mass recurrence.

CONCLUSIONS

This case highlights a rare case of Masson tumor, and the importance of performing multimodality imaging for appropriate diagnosis and treatment. LAA is a common site for thrombi because of its complex anatomic, histological, and functional characteristics. Blood stasis is one of the hallmark reasons for increased thrombi formation, which can result in endothelial hyperplasia or IPEH. Histological examination provides the mainstay in achieving a definitive diagnosis. Complete resection of Masson tumor is curative but tumor can recur. Therefore, careful follow-up with echocardiography in the process of investigating the etiology for cardiogenic cerebral infarction is paramount.

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AUTHOR RELATIONSHIP WITH INDUSTRY

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REFERENCES

1. Masson P. Hemangioendotheliome vegetant intravasculaire. Bull Soc Anat (Paris) 1923;93:517.
2. Hashimoto H, Daimaru Y, Enjoji M. Intravascular papillary endothelial hyperplasia. A clinicopathologic study of 91 cases. Am J Dermatopathol 1983; 5:539–46.
3. Clearkin KP, Enzinger FM. Intravascular papillary endothelial hyperplasia. Arch Pathol Lab Med 1976;100:441–4.
4. Modi A, Moorjani N, Pontefract D, Livesey S. Isolated papillary endothelial hyperplasia in the left atrial appendage. Interact Cardiovasc Thorac Surg 2008;7:1204–6.
5. Naksuk N, Padmanabhan D, Yogeswaran V, Asirvatham SJ. Left atrial appendage. J Am Coll Cardiol EP 2016;2:403.
6. Tabata T, Oki T, Yamada H, et al. Role of left atrial appendage in left atrial reservoir function as evaluated by left atrial appendage clamping during cardiac surgery. J Am Coll Cardiol 1998;81:327–32.
7. Beigel R, Wunderlich NC, Ho SY, Arsanjani R, Siegel RJ. The left atrial appendage: anatomy, function, and noninvasive evaluation. J Am Coll Cardiol Imag 2014;7:1251.
8. Vigna C, Russo A, De Rito V, et al. Frequency of left atrial thrombi by transesophageal echocardiography in idiopathic and in ischemic dilated cardiomyopathy. J Am Coll Cardiol 1992;70:1500–1.
9. Levere SM, Barsky SH, Meals RA. Intravascular papillary endothelial hyperplasia: a neoplastic “actor” representing an exaggerated attempt at recanalization mediated by basic fibroblast growth factor. J Hand Surg 1994;19:509–64.
10. Akdur NC, Donmez M, Gozel S, Ustun H, Hucumenoglu S. Intravascular papillary endothelial hyperplasia: histomorphological and immunohistochemical features. Diagn Pathol 2013;8:167.
11. Manning WJ, Weintraub RM, Waksmonski CA, et al. Accuracy of transesophageal echocardiography for identifying left atrial thrombi. A prospective, intraoperative study. Ann Intern Med 1995;123:817–22.

KEY WORDS cardio-oncology, cardioembolic disease, echocardiography, left atrial appendage, Masson tumor, multimodality imaging, stroke, vascular stasis

APPENDIX For supplemental videos, please see the online version of this paper.
"Catch Me If You Can"
Recurrent ST-Segment Elevation Myocardial Infarction Due to Aortic Thrombus

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ABSTRACT

A 42-year-old male patient presented with recurrent inferior ST-segment elevation myocardial infarction with minimal atherosclerotic disease on intracoronary imaging. Transesophageal echocardiogram and computed tomography aortogram revealed the underlying cause to be a mobile aortic thrombus in the right coronary cusp, prolapsing into and out of the right coronary ostium. (Level of Difficulty: Beginner.) (J Am Coll Cardiol Case Rep 2020;2:1974–8)

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HISTORY OF PRESENTATION

A 42-year-old Indian gentleman with no past medical history presented to the emergency department with chest discomfort associated with diaphoresis. He had smoked 5 cigarettes a day for the past 10 years and drank 2 U of alcohol per week.

His blood pressure was 108/74 mm Hg, pulse rate 70 beats/min and oxygen saturation 98% on room air. Examination revealed dual heart sounds without murmurs, and lungs were clear on auscultation. There was no elevated jugular venous pressure or pedal edema. Electrocardiography (ECG) showed Q waves with mild ST-segment elevation in the inferior leads and reciprocal ST-segment depression in the lateral leads (Figure 1). Troponin T was elevated (1,854 ng/l) and chest radiography was normal.

An inferior ST-segment elevation myocardial infarction (STEMI) was diagnosed. Emergency coronary angiography revealed normal left anterior

LEARNING OBJECTIVES

- In patients with STEMI without any culprit lesion or significant atherosclerotic disease, coronary artery embolization should be considered.
- Coronary artery embolization can be due to cardiac diseases (atrial fibrillation, dilated cardiomyopathy, endocarditis, and intracardiac tumor), systemic diseases (malignancy, systemic autoimmune diseases, and antiphospholipid syndrome) or aortic thrombus.
- Interventional cardiologists, besides focusing on the coronary vessel, need to pay attention to other details such as reflux of contrast into the aorta, as an aortic thrombus may be visualized. Additionally, if an aortic thrombus obstructs the coronary ostium, a catheter can be manipulated to force the thrombus away from the ostium to allow proper engagement and intervention.
descending and circumflex arteries but filling defects in the whole right coronary artery (RCA) (Video 1). Using a 6-F Ikari Left 3.5 guide catheter (Terumo, Tokyo, Japan), multiple large thrombi were aspirated (Figure 2) and Thrombolysis In Myocardial Infarction flow grade 3 was restored (Video 2). As no lesion was noted, balloon dilatation or stent implantation was not performed. A single dose of intravenous eptifibatide followed by 24-h infusion was administered in view of the heavy thrombus burden.

Post-primary percutaneous coronary intervention (PCI), there was complete resolution of the ST-segment elevations on ECG (Figure 3). However, he redeveloped chest discomfort 9 h later with recurrence of ST-segment elevation in the inferior leads (Figure 4).

Repeat emergency PCI was performed, and despite multiple attempts using the same catheter as the first PCI attempt, we could not engage the RCA ostium. We changed to a 6-F Judkins Right 4 guide catheter (Cordis, Santa Clara, California) and eventually, by prolapsing the tip of the catheter in the right coronary cusp, managed to successfully engage the RCA ostium from below (Video 3). The proximal RCA was found to be occluded again. After aspirating large thrombi, a filling defect in the right posterior atrioventricular artery (RPAV) was noted (Video 4). Differentials included thrombus, dissection, or plaque rupture. However, no balloon dilatation had been performed in the RPAV up to this point, and it would have been unusual for the proximal RCA to be occluded if the culprit lesion was in the RPAV. Intravascular ultrasound (IVUS) demonstrated layered thrombus in the RPAV and minor atherosclerotic disease in the rest of the RCA. The filling defect persisted despite repeat aspiration thrombectomy; hence, a 2.25 × 28 mm drug-eluting stent was implanted in the distal RCA to RPAV with good angiographic result and TIMI flow grade 3 (Video 5).

The patient returned to the coronary care unit with complete resolution of ST-segment elevations on ECG and was administered a total of 24 h of intravenous eptifibatide. He improved symptomatically with no further complications.

**DIFFERENTIAL DIAGNOSES**

The patient presents with recurrent inferior STEMI without any clear etiology—there was no culprit lesion or significant atherosclerotic disease on coronary angiography or IVUS.

The differential diagnoses at this point were either a plaque rupture not well seen on angiography or IVUS, or an embolic phenomenon in a patient with a hypercoagulable state (e.g., antiphospholipid syndrome, malignancy, inherited thrombophilia), intracardiac or aortic thrombus, atrial fibrillation, or a paradoxical embolus from the venous circulation.

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**FIGURE 1** Electrocardiogram on Presentation With Inferior ST-Segment Elevation
INVESTIGATIONS

Transthoracic echocardiogram showed a severely impaired left ventricular ejection fraction of 25% and no intracardiac thrombus or shunt. Telemetry throughout admission did not detect atrial fibrillation.

A computed tomography aortogram looking for embolic sources revealed an irregular filling defect in the right coronary cusp close to the RCA ostium (Figures 5 to 8).

Transesophageal echocardiography confirmed a 6 × 9 mm thrombus, arising from the sinus of Valsalva of the right coronary cusp, prolapsing into and out of the RCA ostium (Figure 9, Video 6).

Cardiac magnetic resonance imaging demonstrated a 7 × 5 mm filling defect near the RCA ostium that did not have contrast enhancement in the delayed phase after gadolinium administration, suggesting thrombus rather than tumor (Video 7).

Further history revealed that the patient did not consume regular or traditional medications, had no prolonged immobility or recent overseas travel, and had no signs and symptoms suggestive of malignancy or autoimmune conditions. A thrombophilia screen (anticardiolipin IgM and IgG, lupus anticoagulant, antithrombin III, factor V Leiden and JAK2 mutation) was negative.

MANAGEMENT

In addition to a beta-blocker and high-intensity statin, triple antithrombotic therapy (vitamin K antagonist, aspirin, and clopidogrel) was prescribed. An angiotensin-converting enzyme inhibitor or aldosterone antagonist was not prescribed because of borderline low-normal blood pressure. A repeat transesophageal echocardiogram 2 months later documented resolution of the aortic root thrombus, and vitamin K antagonist therapy was stopped. He completed a total of 12 months of dual antiplatelet therapy and has remained asymptomatic and free from hospitalization for more than a year.

DISCUSSION

Coronary artery embolism can be caused by cardiac diseases (atrial fibrillation, dilated cardiomyopathy, endocarditis, and intracardiac tumor) or systemic
diseases (malignancy, systemic autoimmune diseases, and antiphospholipid syndrome) (1). The most common cause is atrial fibrillation.

However, coronary artery embolism due to aortic thrombus is rare and has been reported in only a few case reports (2,3). To the best of our knowledge, this is the first case report of recurrent STEMI secondary to an aortic thrombus.

There are no guidelines on the optimal management of such patients. Medical therapy with anticoagulation and surgical management with percutaneous or open surgery have been described (4,5). In a meta-analysis of 200 patients, medical therapy has been associated with an increased risk of recurrence of aortic thrombus and peripheral embolization (5).

On retrospective review of the coronary angiograms, reflux into the aorta during contrast injection shows a filling defect just outside the RCA ostium with contrast flowing around this defect (Video 8). First, this can be compared with a different patient with normal backflow into the aorta (Video 9). Second, the reason we had difficulty engaging the RCA during the second procedure was likely because the aortic thrombus was obstructing the RCA ostium. By prolapsing the catheter and engaging the ostium from below, the thrombus was likely shifted away allowing for
proper engagement and successful completion of the PCI.

**CONCLUSIONS**

Coronary artery embolization is a rare cause of STEMI, and aortic thrombus is a differential diagnosis.

**AUTHOR RELATIONSHIP WITH INDUSTRY**

The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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**REFERENCES**

1. Popovic B, Agrinier N, Bouchahda N, et al. Coronary embolism among ST-segment-elevation myocardial infarction patients. Circ Cardiovasc Interv 2018;11:e005587.
2. Amabile N, Quilici J, Bonnet J-L, Habib G. Right coronary artery embolism from a thrombus of the ascending aorta. Heart 2006;92:89.
3. Eguchi K, Ohtaki E, Misu K, et al. Acute myocardial infarction caused by embolism of thrombus in the right coronary sinus of Valsalva: a case report and review of the literature. J Am Soc Echocardiogr 2004;17:173-7.
4. Verma H, Meda N, Vora S, George RK, Tripathi RK. Contemporary management of symptomatic primary aortic mural thrombus. J Vasc Surg 2014;60:1524–34.
5. Fayad ZY, Semaan E, Fahoum B, Briggs M, Tortolani A, D’Ayala M. Aortic mural thrombus in the normal or minimally atherosclerotic aorta. Ann Vasc Surg 2013;27:282-90.

**KEY WORDS** acute coronary syndrome, aorta, thrombus

**APPENDIX** For supplemental videos, please see the online version of this paper.
MINI-FOCUS ISSUE: CLINICAL CARDIOLOGY

CASE REPORT: CLINICAL CASE

Vacuuming in Crowded Dangerous Spaces
Aspiration of Large Ascending Aortic Thrombus

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ABSTRACT

A patient had a stroke caused by a large, pedunculated aortic ascending mass and was deemed at high risk for near-term recurrent stroke. This case illustrates percutaneous aspiration thrombectomy of ascending aortic thrombus with the AngioVac system (Angiodynamics, Latham, New York), with conscious sedation for early stroke detection and with endovascular cerebral embolic protection. (Level of Difficulty: Intermediate.) (J Am Coll Cardiol Case Rep 2020;2:1979–83) © 2020 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

HISTORY OF PRESENTATION

A 48-year-old man presented to the emergency department roughly 23 h after acute-onset dysarthria and persistent right upper and lower extremity weakness, which led to a fall. He thought his symptoms would resolve spontaneously, but they did not. Presenting vital signs were blood pressure 142/76 mm Hg, heart rate 84 beats/min, and O2 saturation 98%.

PAST MEDICAL HISTORY

The patient had a history of popliteal arterial thrombosis of unclear origin and had been noncompliant with recommended anticoagulation.

DIFFERENTIAL DIAGNOSIS

The patient’s symptoms were highly consistent with an acute cerebrovascular event, the differential diagnosis for which included hemorrhagic event, embolic ischemic event originating from a cardiac structure (e.g., thrombus in the left atrial appendage or left ventricle, myxoma, fibroelastoma), embolic event originating from the aorta (i.e., aortic arch atheroma), and intrinsic atherosclerotic cerebrovascular disease.

LEARNING OBJECTIVES

- To understand that aortic thrombus is one of the causes of embolic acute stroke.
- To understand potential treatment options for ascending aortic thrombus.
- To better understand the technical and practical or clinical implications of percutaneous aspiration thrombectomy in the ascending aorta.
INVESTIGATIONS

Computed tomography (CT) and computed tomography angiography (CTA) of the brain showed an infarct in the middle cerebral artery territory without major branch vessel occlusion or hemodynamically significant stenosis. Magnetic resonance imaging of the brain confirmed a left middle cerebral artery–territory acute ischemic stroke with a tiny focus of hemorrhagic transformation. Transesophageal echocardiography and CTA of head and neck revealed a large, pedunculated ascending aortic mass (Figures 1A to 1C, Video 1), consistent with thrombus. CTA extended far enough into the abdomen also to detect incidentally an adherent, infrarenal abdominal aortic thrombus.

MANAGEMENT

The patient was started on dual platelet inhibition therapy with aspirin and clopidogrel. Blood pressure goals of <220/110 mm Hg were defined, and medical therapy was initiated to that effect. Vascular and cardiothoracic surgical services were involved in his care but deferred surgical intervention in favor of conservative medical therapies. However, after multidisciplinary discussion involving the primary neurological service and surgical and structural heart disease services, it was decided that the location, size, and morphology of the ascending aortic thrombus put the patient at high risk for short-term recurrent stroke or other embolism and that catheter-based aspiration, although off-label, was reasonable. The patient and his family were counseled in detail about the potential risks and benefits of medical therapy versus off-label aspiration thrombectomy. The decision was made to attempt endovascular thrombectomy with the AngioVac system (Angiodynamics, Latham, New York).

Transesophageal echocardiography was used to guide positioning of the AngioVac system, to visualize thrombus extraction, and for detection of thrombus embolization, which would prompt an early cerebral angiogram and, if needed, catheter-based cerebrovascular rescue. The patient was not intubated, and he was sedated only moderately, to allow for early detection of neurological changes. Sentinel cerebral embolic protection (Boston Scientific, Marlborough, Massachusetts) was planned by CT and was used: a 0.014-inch wire was delivered through the right radial approach into the right brachiocephalic artery and directly into the left common carotid artery with the aid of a diagnostic Judkins right-4 catheter (Figures 2A to 2C, Video 2), to minimize the risk of wire or device interaction with the thrombus and possible dislodgement and embolization, because the thrombus was located only 1 cm inferior to the great vessels (Video 3). The left vertebral artery was protected within flow of a balloon in the ostial left subclavian artery (Figure 2B).

The AngioVac system inflow cannula was inserted through the right femoral artery and outflow cannula in the left femoral vein. The inflow cannula was advanced to the descending abdominal aorta, and the circuit flows slowly increased to 3.5 l/min to ensure stable hemodynamics. The inflow cannula was advanced to the proximal descending aorta, and then the tip was flexed while slowly advancing around the...
aortic arch toward the thrombus (Video 4). After the inflow cannula was positioned in close proximity to the thrombus (Video 5), circuit flows were increased to 4 l/min. After approximately 3 min of aspiration, the thrombus finally separated from the aortic wall (Video 6). The large aspirated thrombus became trapped inside the tip of the inflow cannula, thus leaving a small piece still adherent to the aorta (Figures 2D to 2F, Video 7). The thrombus and inflow cannula were removed from the body (Figure 3); histopathologic examination confirmed organized thrombus. Cerebral angiography before terminating the intervention showed normal head and neck cerebral circulation without stenosis or occlusion.

**DISCUSSION**

This case illustrates clinical and technical considerations related to safe and effective aspiration thrombectomy of thrombus from the ascending aorta.

The AngioVac Generation 3 cannula has a self-expanding nitinol funnel-shaped tip (20-degree and 180-degree angled tips) that enabled safe navigation across the aortic arch. It is important to emphasize the following: 1) this is off-label use of the device; and 2) this use is not without risk, especially with thrombus located so precariously close to the great cerebral vessels. Careful consideration therefore should be given to risk and benefit of such aspiration attempts on a case-by-case basis.

Potential complications of using the AngioVac system in arterial circulation include systemic distal embolization and vascular complications related to the large-bore access. There are few reports of off-label use of this system in arterial circulation (1,2) and 1 in the ascending aorta (3). Our case importantly included embolic protection using the Sentinel device (filters in brachiocephalic and left common carotid arteries) and an occlusive balloon positioned at the ostium of the left subclavian artery (to protect the left vertebral artery).
Treatment options for thoracic aortic mural thrombus include medical therapy with anticoagulation with or without fibrinolysis, open surgical thrombectomy, endovascular thrombectomy, or endovascular stent placement (location of thrombus in this case makes the last option unfavorable) (4). A systematic review comparing surgical treatment with conservative medical treatment demonstrated that open repair was superior to medical treatment in terms of rate of systemic embolism or persistent thrombus (5). Another review showed that medically treated patients were more likely to have persistent thrombus compared with patients treated with open or endovascular aortic intervention (6). For our patient, cardiothoracic and vascular surgical services deferred open surgical interventions in favor of medical therapy. Medical therapy was considered, but the patient had demonstrated poor adherence in the past, and the thrombus size, location, and morphology were believed to represent a high short-term stroke risk. Thrombolytic therapy was contraindicated given the size of the embolic stroke with small hemorrhagic transformation. AngioVac thrombectomy was chosen only after extensive and multidisciplinary discussion with neurology, neurointerventional, and structural heart disease services, and with the patient, and after multidisciplinary procedure planning among the radiology, neurointerventional, and structural heart disease services.

**FOLLOW-UP**

The patient awoke. He was discharged without new neurological deficits and had anticoagulant therapy using rivaroxaban. The presumed mechanism for this large thrombus, along with the infrarenal aortic thrombus and a history of popliteal arterial thrombus, is a hypercoagulable state. However, on work-up that included testing for the MTHFR (methylenetetrahydrofolate reductase) variants, the factor V (Leiden) variant, and the 20210G>A variant of the prothrombin gene, no diagnosis was found.

**CONCLUSIONS**

In the carefully selected patient, percutaneous aspiration thrombectomy of ascending aortic thrombus can be effectively and safely performed with the AngioVac system, in this case with conscious sedation for early stroke prevention and with endovascular cerebral embolic protection.

**AUTHOR RELATIONSHIP WITH INDUSTRY**

The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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REFERENCES

1. So CY, Wang DD, Kang G, Villablanca PA, Frisoli T, O’Neill WW. Vacuuming the LAA: left atrial appendage thrombectomy using AngioVac to facilitate percutaneous mitral balloon valvuloplasty. Structural Heart 2020;4:243-4.

2. Monastiriotis S, Gonzales C, Kokkosis A. The use of AngioVac for symptomatic aortic thrombus complicated by mesenteric ischemia. Ann Vasc Surg 2016;32:129.e1-6.

3. Tsilimparis N, Spanos K, Debus ES, Rohlf F, Kölbl T. Technical aspects of using the AngioVac system for thrombus aspiration from the ascending aorta. J Endovasc Ther 2018;25:550-3.

4. Riambau V, Böckler D, Brunkwall J, et al. Editor’s choice - management of descending thoracic aorta diseases: clinical practice guidelines of the European Society for Vascular Surgery (ESVS). Eur J Vasc Endovasc Surg 2017;53:4-52.

5. Fayad ZY, Semaan E, Fahoum B. Aortic mural thrombus in the normal or minimally atherosclerotic aorta. Ann Vasc Surg 2013;27:282-90.

6. Meyer mann K, Trani J, Caputo FJ. Descending thoracic aortic mural thrombus presentation and treatment strategies. J Vasc Surg 2017;66:931-6.

KEY WORDS AngioVac, ascending aortic thrombus, aspiration thrombectomy, cerebral embolic protection

APPENDIX For supplemental videos, please see the online version of this paper.
A 68-year-old man presented following a cardiac arrest. Cardiopulmonary resuscitation was performed by the Lund University Cardiopulmonary Assist System (LUCAS), a mechanical chest compression device. Investigations revealed an aortic dissection, which was likely an iatrogenic injury from mechanical cardiopulmonary resuscitation by LUCAS. This case highlights this potential complication. (Level of Difficulty: Beginner.) (J Am Coll Cardiol Case Rep 2020;2:1984–7) © 2020 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

HISTORY OF PRESENTATION

A 68-year-old man presented to the emergency department following a witnessed cardiac arrest. He had been experiencing intermittent chest discomfort all day and became unresponsive at home. No bystander cardiopulmonary resuscitation (CPR) was performed. Paramedics arrived within 5 min, and CPR was initiated using the Lund University Cardiopulmonary Assist System (LUCAS). Initial rhythm resembled coarse ventricular fibrillation (VF), for which 2 shocks were given, with return of spontaneous circulation within 12 min of paramedics’ arrival.

When the patient arrived in the emergency department, he was sedated and intubated. Blood pressure was 130/93 mm Hg and 138/88 mm Hg in the right and left arms, respectively. Primary survey did not reveal any signs of trauma. He had normal heart and lung sounds.

PAST MEDICAL HISTORY

Past medical history includes hypertension and depression.

DIFFERENTIAL DIAGNOSIS

Differential diagnosis included intracranial hemorrhage, pulmonary embolism, myocardial infarction, aortic dissection, seizure, arrhythmia syndromes (e.g., Brugada syndrome, long QT syndrome), and cardiomyopathies (e.g., dilated cardiomyopathy, hypertrophic cardiomyopathy).
INVESTIGATIONS

Electrocardiogram (ECG) showed a normal sinus rhythm with no ST-segment elevations or Q waves. Initial troponin was 41 ng/l (normal < 30 ng/l). There was evidence of lactic acidosis with a pH of 7.15 (normal 7.35 to 7.45), partial pressure of carbon dioxide of 42 mm Hg (normal 35 to 45 mm Hg), and a lactate of 6.4 mmol/l (normal 1 to 1.8 mmol/l).

Initial imaging included head computed tomography (CT), which did not reveal any infarction or hemorrhage. CT pulmonary angiography ruled out pulmonary embolism, though a Stanford type B aortic dissection was incidentally found (Figure 1). There was involvement of aortic branches down to the common iliac arteries and signs of visceral hypoperfusion, with the right kidney completely infarcted, and the left kidney 50% infarcted. In addition, 2 rib fractures were noted.

MANAGEMENT

The patient was taken immediately to the angiography suite for placement of an aortic endograft, which successfully sealed the origin of the dissection flap just distal to the left subclavian artery. During the procedure, the patient developed runs of ventricular tachycardia. Owing to concerns regarding an underlying acute coronary syndrome, the patient was then taken to the cardiac catheterization lab. A ruptured plaque was found in the proximal circumflex artery, with corresponding wall motion abnormality in the inferolateral wall. A 2.5 × 16 mm drug-eluting stent was deployed, with excellent flow at the end of the procedure. Post-procedure ECG showed ST-segment elevations in the inferior leads, with reciprocal changes in the lateral leads. These findings of ischemia resolved in subsequent ECGs. Troponin peaked at 1,205 ng/l.

DISCUSSION

This case report illustrates a potential complication from the use of a mechanical CPR device. A likely sequence of events was that the patient suffered a cardiac arrest from a myocardial infarction (MI), with subsequent CPR by LUCAS resulting in an aortic dissection. Although a causal relation cannot be definitively established, a number of symptoms and signs support this theory. First, the patient complained of chest pain, and not back pain, throughout the day. Second, angiography revealed a ruptured plaque with corresponding wall motion abnormality, supporting the diagnosis of an MI. ST-segment elevations in the post-catheterization ECG adds to the evidence. Third, a type B aortic dissection should not cause VF, which makes an MI-induced cardiac arrest more likely. Therefore, the aortic dissection was likely the result, and not the cause, of the initial collapse and the need for CPR.

A number of imaging modalities and techniques could have helped establish the chronology of this case. A transthoracic echocardiogram could have identified wall motion abnormality earlier in the management course and should be performed after return of spontaneous circulation, particularly given the history of chest pain and VF. Intraluminal techniques including fractional flow reserve, intravascular ultrasound, and optical coherence tomography, which were unfortunately not performed in this case, could help establish the presence of a ruptured plaque. Cardiac magnetic resonance is another imaging modality to confirm the myocardial territory affected by the MI post-event.

Although acute coronary syndrome was suspected given the initial rhythm of VF, the patient was first taken to the angiography suite for management of the aortic dissection. A point of discussion is whether the patient should have undergone coronary revascularization first. However, given the absence of ST-segment elevations on the initial ECG and the patient’s profound lactic acidosis secondary to visceral malperfusion, a clinical decision was made between the vascular surgery and cardiology team to...
intervene on the dissection flap first. If the patient had presented initially with ST-segment elevations or ongoing arrhythmias, then management might have been different.

CPR is not only a life-sustaining maneuver, but also a maneuver that has the potential for significant injuries. The most common injuries include rib and sternal fractures, with reported rates of 31.2% and 15.1%, respectively (1). Injuries to the lungs, stomach, liver, spleen, and blood vessels have also been reported (2). Injuries to the aorta are rare, with a rate of 1.5% for aortic ruptures and lacerations (1) and only a number of case reports of aortic dissections following manual CPR (3–5). The proximal descending aorta is often implicated, owing to the shear force between a mobile aortic arch and a fixed descending aorta (3).

The use of mechanical CPR devices such as LUCAS in out-of-hospital cardiac arrests has gained popularity in recent years. The 2015 American Heart Association Guidelines specify that chest compressions should be delivered at a rate of 100 to 120 per minute, with a depth of 5 to 6 cm (6). Mechanical CPR devices have the theoretical advantage of providing higher-quality and more consistent chest compressions, though they have not been found to improve survival in randomized controlled trials (7,8). The 2015 American Heart Association Guidelines for Resuscitation consider mechanical chest compression devices acceptable in settings in which the delivery of high-quality manual compressions may be challenging or dangerous for the provider (e.g., during transportation or coronary intervention) (6).

There are also concerns regarding potential injuries from the more powerful compressions delivered. Observational studies found that LUCAS CPR resulted in a higher incidence of skeletal and soft tissue injury than manual CPR (9,10). Conversely, a recent randomized controlled trial did not find that the LUCAS caused any more serious or life-threatening visceral damage than manual CPR did (11). In this case, a hypothesized mechanism of injury is that cephalad displacement of the LUCAS may increase the risk of aortic injuries. LUCAS is positioned by aligning the lower edge of the suction cup immediately above the distal end of the sternum (12), focusing compressive forces centrally over the heart (Figure 2). However, if the device were to migrate cephalad, unintended shear forces between a mobile aortic arch and a fixed descending aorta may result in an aortic dissection.

In a recent scientific letter, routine imaging within the first hours of admission revealed traumatic complications in 10 of the 11 patients who received mechanical chest compressions (10). Given the potential for serious traumatic complications from mechanical CPR, systematic use of imaging post-resuscitation should be considered. A chest roentgenogram should be performed in all patients after receiving chest compressions to rule out common injuries, including rib and sternal fractures. If there are signs of ongoing blood loss or hemodynamic instability, then CT of the chest and abdomen should be pursued.

FOLLOW-UP

The remainder of patient’s recovery was complicated by an acute kidney injury and transient ischemic encephalopathy. Nonetheless, 2 months later, he was discharged to a long-term care facility with a cerebral performance category score of 2, which corresponds to moderate cerebral disability.

CONCLUSIONS

This is one of the first case reports of a patient experiencing an aortic dissection after receiving mechanical CPR. Care providers must be vigilant in ensuring the proper positioning of LUCAS during the resuscitation process. A key to this patient’s survival was the serendipitous early recognition of the aortic dissection, which allowed for immediate intervention. Aortic dissections should be recognized as a potential complication of CPR, particularly when performed by a mechanical chest compression device.
Investigations for intrathoracic and aortic injuries should be considered in survivors of mechanical CPR, as early diagnosis and management can significantly impact clinical outcomes. Nonetheless, it is important to emphasize that early and high-quality CPR, whether provided mechanically or manually, improves survival and neurological outcomes in out-of-hospital cardiac arrests, and should not be delayed because of concerns regarding potential complications.

REFERENCES

1. Miller AC, Rosati SF, Suffredini AF, Schrump DS. A systematic review and pooled analysis of CPR-associated cardiovascular and thoracic injuries. Resuscitation 2014;85:724-31.
2. Buschmann CT, Tsokos M. Frequent and rare complications of resuscitation attempts. Intensive Care Med 2009;35:397-404.
3. Lee J, Hong S. Aortic dissection in a survivor after cardiopulmonary resuscitation. Korean J Crit Care Med 2016;32:218-22.
4. Oren-Grinberg A, Shahul S, Sarge T. Dissection of the thoracic aorta following cardiopulmonary resuscitation. Crit Ultrasound J 2011;3:25-7.
5. Chiang M, Huang Y, Wu M. Incidental finding of aortic dissection following cardiopulmonary resuscitation. Br J Hosp Med (Lond) 2019;80:i.
6. Kleinman ME, Brennan EE, Goldberger ZD, et al. Part S: adult basic life support and cardiopulmonary resuscitation quality: 2015 American Heart Association guidelines update for cardiopulmonary resuscitation and emergency cardiovascular care. Circulation 2015;132:5414-35.
7. Robertsson S, Lindgren E, Smekal D, et al. Mechanical chest compressions and simultaneous defibrillation vs conventional cardiopulmonary resuscitation in out-of-hospital cardiac arrest: the LINC randomized trial. JAMA 2014;311:53-61.
8. Perkins GD, Lall R, Quinn T, et al. Mechanical versus manual chest compression for out-of-hospital cardiac arrest (PARAMEDIC): a pragmatic, cluster randomised controlled trial. Lancet 2015;385:947-55.
9. Friberg N, Schmidbauer S, Walther C, Englund E. Skeletal and soft tissue injuries after manual and mechanical chest compressions. Eur Heart J Qual Care Clin Outcomes 2019;5:259-65.
10. Iglesies J, Loma-Osorio P, Aboal J, Núñez M, Brugada R. Mechanical chest compressions and traumatic complications in out-of-hospital cardiac arrest. Is there a price to pay? Rev Esp Cardiol (Engl Ed) 2019;72:259-61.
11. Koster RW, Beenen LF, van der Boom EB, et al. Safety of mechanical chest compression devices AutoPulse and LUCAS in cardiac arrest: a randomized clinical trial for non-inferiority. Eur Heart J 2017;38:3006-13.
12. Jolife AB. Lucas™ 2 Chest Compression System – Instructions for Use [Internet]. Available at: https://www.lucas-cpr.com/files/9398026,100901-00_Rev_B,LUCAS2,JFU_US_LowRes.pdf. Accessed November 1, 2019.

KEY WORDS aorta, complication, dissection, myocardial infarction, ventricular fibrillation

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Cardiogenic Shock and Mitral Valve Chord Rupture
A Rare Presentation of Libman-Sacks Endocarditis

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ABSTRACT

Distinguishing Libman-Sacks endocarditis from other valvular heart disease etiologies has important implications for management. We present a case of a 23-year-old man who presented in extremis with fever and cardiogenic shock caused by Libman-Sacks endocarditis with associated mitral valve chord rupture. (Level of Difficulty: Beginner) (J Am Coll Cardiol Case Rep 2020;2:1988–91) © 2020 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

HISTORY OF PRESENTATION

A 23-year-old undomiciled man presented to the emergency department with 3 h of acute-onset dyspnea. Over the past 6 weeks he reported subjective fever, diaphoresis, weight loss, arthralgias, pleuritic chest pain, and frothy urine. Two months ago he completed treatment with amoxicillin-clavulanate for streptococcal pharyngitis and denied injected drug use.

On physical examination, the patient was tachypneic, using accessory muscles of respiration. The heart rate was 143 beats/min, blood pressure was 109/57 mm Hg, the oxygen saturation was 95% on 4 l/min oxygen by nasal cannula, and the temperature was 39.4°C. Jugular venous distention, a II/VI decrescendo systolic murmur at the left lower sternal border, a blowing III/VI holosystolic murmur at the apex radiating to the axilla, and S3 were noted. A Janeway lesion was present on the plantar surface of the left second toe. The extremities were cold, with trace pretibial edema. The lungs had bilateral rales and pulses were intact. There was no hepatosplenomegaly.

LEARNING OBJECTIVES

- To highlight how Libman-Sacks endocarditis can mimic infective endocarditis.
- To describe a severe, rare presentation of this uncommon clinical entity.

PAST MEDICAL HISTORY

The patient had no known medical or surgical history.
INVESTIGATIONS

Chest radiography revealed diffuse pulmonary edema. An electrocardiogram showed sinus tachycardia. The white blood cell count was $11.7 \times 10^3/\mu l$ with 81% neutrophil predominance. The hemoglobin was 8.9 g/dl and the platelet count was $226 \times 10^3/\mu l$. Serum creatinine peaked at 2.18 mg/dl with subnephrotic proteinuria and hematuria on urinalysis. A serum arterial lactate level peaked at 3.7 mmol/l. A ferritin level and transferrins at urination were elevated at 1,718 ng/ml and 64%, respectively. Troponin levels were normal. The erythrocyte sedimentation rate was elevated at 139 mm/HR and C-reactive protein was elevated (7 mg/l). Testing for acquired immunodeficiency, tick-borne illnesses, tuberculosis, and cultures for bacteria, fungi, and HACEK organisms were negative. A rheumatologic work-up revealed a positive antinuclear antibody, positive double-stranded DNA titer (>1:10), positive Smith antibodies (>8.0 antibody index), and negative antineutrophil cytoplasmic antibody serologies. Complement levels were low, including C3 (35 mg/dl), C4 (6 mg/dl), and complement CH50 (<10). An antiphospholipid syndrome (APLS) evaluation was negative.

Transthoracic echocardiography (Figure 1, Video 1) obtained the day of presentation revealed normal biventricular function and posterior mitral valve leaflet thickening with severe mitral regurgitation and mild to moderate aortic insufficiency. Transesophageal echocardiography (Figure 2, Video 2) obtained 5 days later demonstrated restricted mitral valve leaflets with poor leaflet coaptation. Mitral valve chord rupture was noted.

DIFFERENTIAL DIAGNOSIS

The constellation of heart failure, fever, murmur, and echo findings raised concern for infective endocarditis (IE). Despite meeting modified Duke criteria for definite IE, the patient did not develope on empiric antibiotics and cultures remained negative. Myocarditis or myopericarditis were considered as was subvalvular apparatus pathology. Systemic lupus erythematosus (SLE) with nephritis and Libman-Sacks endocarditis (LSE) were likewise considered in context of fever, arthralgia, and foamy urine. Recent streptococcal pharyngitis raised consideration of rheumatic fever and rheumatic valvular disease.

MANAGEMENT

Noninvasive positive pressure ventilation was started concomitantly with intravenous furosemide. Cultures were obtained and empiric vancomycin and ceftriaxone were started. Three days after transesophageal echocardiography, the patient underwent mitral valve replacement for cardiogenic shock (size 27-mm Epic biological valve), aortic valve repair (left coronary cusp-noncoronary cusp commissural closure), and tricuspid valve repair (posterior DeVega annuloplasty). Intraoperatively, there was an inflamed mitral valve with a retracted posterior leaflet, mitral valve chord rupture, and subvalvular destruction. The aortic valve demonstrated diffuse thickening and loss of integrity of the left coronary cusp and noncoronary cusp. Pericardial adhesions were noted.
Renal biopsy demonstrated diffuse proliferative lupus nephritis and thrombotic microangiopathy. Antibiotics were discontinued because cultures and tissue were negative for infectious organisms. Aspirin and immunosuppression were initiated, followed by coumadin on discharge.

**DISCUSSION**

This case demonstrates a dramatic presentation of LSE manifesting as cardiogenic shock because of acute valvular insufficiency from mitral valve chord rupture with poor leaflet coaptation in the context of concomitant aortic valve destruction. LSE is a form of non-IE, also known as marantic, verrucous, or nonbacterial thrombotic endocarditis, and is the result of sterile fibrin and platelet accumulation involving the cardiac valves, chordae tendineae, or endocardium. Endothelial injury is thought to be the inciting pathophysiologic insult resulting in platelet deposition and migration of inflammatory cells to exposed subendothelial connective tissue (1). LSE must be differentiated from IE. This patient met criteria for “definite” IE by modified Duke criteria, which is approximately 80% sensitive and specific (2). The persistent fever, negative cultures, and failure to improve with appropriate empiric antibiotics favored a noninfective etiology. Antibiotics were discontinued on clinical improvement after surgery.

LSE is associated with SLE and APLS, yet has been described in APLS without SLE and with malignancies (3). LSE is most often found postmortem, with incident autopsy series findings ranging from 0.9% to 1.6%. Rates are estimated to be higher in patients with underlying malignancy, particularly with adenocarcinomas. LSE most frequently involves the aortic and mitral valves (4,5).

LSE frequently presents with thromboembolism, and up to 43% of patients with SLE demonstrate valvular vegetations on initial echocardiographic evaluation. Vegetations are associated with increased mortality and may involve isolated basal, middle, or tip portions of leaflets on both valve surfaces (Figure 3); however, diffuse thickening of the aortic valve cusps or mitral valve leaflets is a distinctive finding in these patients (1,6). Valvular disease does not relate temporally to the clinical features of lupus, and coexisting infective and Libman-Sacks...
vegetations have been described. Valvular regurgitation is not usually progressive and valve stenosis is unlikely to develop (7).

Management of LSE focuses on treatment of the underlying disease and anticoagulation for thromboembolic events. Surgery is reserved for patients with symptomatic disease or recurrent thromboembolism (8). Guideline recommendations for antithrombotic therapy in patients with LSE without evidence of thromboembolism or concomitant APLS are limited, with a Class IIc recommendation in patients with signs of systemic or pulmonary emboli (9). This patient had evidence of thrombotic microangiopathy and was therefore anticoagulated in the absence of APLS. A bioprosthetic valve was chosen over a mechanical mitral valve because of concern regarding compliance with anticoagulation.

FOLLOW-UP

The patient was maintained on coumadin, prednisone, mycophenolate mofetil, and hydroxychloroquine. Cardiovascular symptoms resolved after surgery. The blood pressure on discharge was 140/96 mm Hg and heart rate was 62 beats/min.

CONCLUSIONS

LSE presenting as acute heart failure and hemodynamic decompensation with mitral valve chord rupture is rare. LSE can mimic IE and diagnosing this noninfectious etiology is paramount to guiding further management.

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REFERENCES

1. Reisner SA, Brenner B, Haim N, Edoute Y, Markiewicz W. Echocardiography in nonbacterial thrombotic endocarditis: from autopsy to clinical entity. J Am Soc Echocardiogr 2000;13:876-81.
2. Gomes A, Glaudemans AIWJM, Touw DJ, et al. Diagnostic value of imaging in infective endocarditis: a systematic review. Lancet Infect Dis 2017;17:e1-14.
3. Liu J, Frishman WH. Nonbacterial thrombotic endocarditis: pathogenesis, diagnosis, and management. Cardiol Rev 2016;24:244-7.
4. Deppisch LM, Fayemi AO. Non-bacterial thrombotic endocarditis: clinicopathologic correlations. Am Heart J 1976;92:723-9.

APPENDIX

For supplemental videos, please see the online version of this paper.
Disseminated Actinomycosis Presenting as Chronic Right-Heart Failure Due to Right Ventricular and Pericardial Infiltration

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ABSTRACT

Actinomycosis is an indolent, slowly progressive bacterial infection prevalent in tropical countries, commonly affecting cervicofacial, thoracic, abdominal, or pelvic regions. With early diagnosis and appropriate therapy, the prognosis is excellent. However, late presentation and widespread dissemination can be fatal. This paper reports a rare case of disseminated actinomycosis with fatal cardiac involvement. (Level of Difficulty: Intermediate.)

PRESENTATION

A 53 year-old male, a farmer, with no comorbidities or habits presented with symptoms of multiple discharging sinuses over the chest and below-knee (BK) stump resulting from an amputated left lower limb 1 year ago. The patient experienced gradual onset of breathlessness (New York Heart Association [NYHA] functional class II), fatigue, right lower limb swelling, a vague abdominal bloating sensation, decreased appetite, weight loss, and malaise for the previous 6 months. His pulse was 70 beats/min, blood pressure was 90/70 mm Hg, and his arterial oxygen saturation was 95%. Physical examination revealed right lower limb pedal edema with an elevated jugular venous pulse (9 cm H2O from the sternal angle). The patient’s chest (Figure 1) and left lower limb stump from a previous amputation (Figure 2) showed multiple, indurated, nontender sinuses with scanty pale yellow putty-like discharge.

LEARNING OBJECTIVES

- Widespread dissemination and extensive cardiac involvement can occur with actinomycosis.
- Appropriate diagnosis through meticulous evaluation is a must to cure and prevent dissemination and fatalities.

MEDICAL HISTORY

He had undergone left lower limb BK amputation 10 years ago for nonhealing wounds and swelling. The exact diagnosis and treatment received at that time were not known due to a lack of records and the inability of the patient to recollect.
DIFFERENTIAL DIAGNOSIS

Given the significant history, chronicity, indolent nature, and peripheral discharging sinuses, the following differential diagnoses were made: 1) actinomycosis from the previous actinomycetoma; 2) eumycotic mycetoma with dissemination; or 3) tuberculosis with right heart failure of uncertain cause.

INVESTIGATIONS

Electrocardiography showed normal axis, asymmetrical ST-segment depression in leads II, III, and aVF, and monophasic R-wave in the anterior chest leads with asymmetrical T-wave inversions. Complete blood counts showed hemoglobin of 10.3 gm/dl, a microcytic hypochromic blood picture and, an erythrocyte sedimentation rate of 110 mm/h. A Mantoux test result was intermediate with a reading of 13 mm after 48 h, and a cartridge-based nucleic acid amplification test results for tuberculosis was negative. C-reactive protein concentration was elevated (19.5 mg/l). Serology for human immune deficiency virus and hepatitis B and C infections were negative. Cardiac biomarkers, B-type natriuretic peptides, renal, liver, thyroid function tests parathormone, lipids, and coagulation parameters were normal.

Radiographs of the stump showed well-defined lytic lesions in the lower and upper ends of the femur and tibia (Figure 3A). Three-dimensional (3D) reconstruction of the 128 multislice computed tomography scan (MSCT) of the thorax showed lytic lesions in the anterior ends of the lower ribs (Figure 3B). Posteroanterior (Figure 3C) and lateral (Figure 3D) radiographs of the chest showed mild cardiomegaly with features of right atrial (RA) enlargement, and the lower ribs showed well-defined lytic lesions in the anterior ends.

Two-dimensional echocardiography revealed infiltration of the pericardial space overlying the right ventricle (RV), RA, and part of the left ventricle (LV). The RV was almost completely obliterated, as seen in the parasternal long-axis view (Figure 4A), the apical 4-chamber view (which was difficult to image and shows the best possible view obtained) (Figure 4B), and the parasternal short-axis (Figure 4C) view, with a severe reduction in chamber dimension and contractility; whereas, the LV dimension and function were normal. RA and left atrium (LA) were normal, with mild tricuspid regurgitation (Figures 4A to 4C).

Ultrasonography of the patient’s abdomen and pelvis showed hepatomegaly with dilated inferior vena cava and hepatic veins. Multiple irregularly margined collections in epigastric and bilateral hypogastric regions, with sinus tracts extending from muscular to subcutaneous and cutaneous plane, with indention of the superior surface of the left lobe of the liver were noted. Plain and contrast-enhanced 128-slice thorax MSCTs revealed multiple, tiny well-
defined peripheral enhancing collections in the pericardium with diffuse pericardial wall thickening, poorly maintained fat planes with adjacent ventricles, and pulmonary artery. The collection was extending cranially into the superior mediastinum in the retrosternal plane and along with the origins of the aorta and pulmonary arteries. Caudally, the collection was seen extending into the peritoneal cavity in the pre-hepatic space anterior to the left lobe of the liver. Peri-collection extensive fat infiltration was noted. A well-defined nonenhancing soft tissue density collection measuring $32 \times 27$ mm was seen adjacent to the RA causing a mass effect. These collections were noted to extend across the anterior chest and abdominal wall into the subcutaneous planes forming multiple sinuses in the anterior chest and abdomen with well-defined lytic lesions in the anterior ends of the ribs and sternum. Surgical excision biopsy and histopathology from 2 of the discharging sinuses over the anterior chest.
showed actinomycotic bacteria with sulfur granules (Figures 5A, 5B, and 6A to 6D).

**MANAGEMENT**

Once the diagnosis was clinically suspected, the patient was started on high doses of intravenous (IV) benzyl (crystalline) penicillin at 4 million units every 6 h along with IV fluids and other symptomatic therapy for 2 weeks, followed by a combination of oral amoxicillin and clavulanic acid twice a day as the patient declined to continue IV therapy. No surgical intervention was planned as the disease was disseminated and beyond any scope for drainage or excision.

**DISCUSSION**

Actinomycosis is a rare infection by a family of filamentous, gram-positive, non-acid-fast, anaerobic-to-microaerophilic bacteria first described in humans in 1896 by Kruse (1). The bacteria in this family include Actinomyces israelii, A. naeslundii, A. viscosus, and A. odontolyticus, along with many other species (2,3). The infection is characterized by contiguously spread, suppurative, granulomatous inflammation with multiple abscesses and sinus tracts that may discharge sulfur granules. It is well established that actinomyces species reside on mucosal surfaces as flora and cause endogenous infection. Risk factors include male sex, immunosuppression of any cause, malnutrition, and poor general and oral hygiene. Infection is prevalent in farmers who work in fields with bare feet and hands, after surgical procedures (4) and so forth. “Madura foot,” described first in Madurai, India, in 1842 (5), is caused by actinomycetes in 60% of the cases (when it is termed actinomycetoma), and the remaining 40% of cases are caused by true fungi eumycetoma, in which case it is called “mycetoma” (6). The present patient possibly had actinomycetoma of the left lower limb 10 years ago, when he underwent left BK amputation, which was either incompletely treated for actinomycetoma or misdiagnosed. Hence, as the underlying infection was “Madura foot” secondary to actinomycetes, it could have disseminated through hematogenous and/or lymphatic spread over 10 years. By the time the patient presented to the present authors, the disease had spread to thoracic and abdominal structures such as pericardium, RV, lymph nodes, ribs, subcutaneous tissues, liver, and peritoneum, forming multiple sinus tracks with sinuses draining to the surface.

**FIGURE 4** 2D Echocardiogram Shows Normal Left Ventricle With Obliterated Right Ventricle Beyond the Mid-Cavity and Pericardial Space Infiltration With Loss of Demarcation Overlying the RV

(A) Parasternal long-axis view. Note only the right ventricular (RV) outflow tract is partly visible and beyond that the loss of the RV cavity due to infiltration. (B) Apical 4-chamber view (although it is off-axis, this was the best possible view obtained) shows RV cavity obliteration beyond the mid-cavity due to infiltration. Note the absence of the pericardial demarcation overlying the RV. (C) Parasternal short-axis view shows almost complete obliteration of the RV beyond the mid-cavity. Ao = aorta; AV = aortic valve; IVS = inter-ventricular septum; LV = left ventricle; Per = pericardium.
DISSEMINATED ACTINOMYCOSIS. Although hematogenous dissemination to distant organs is uncommon, it may occur in any stage of actinomycosis, and lymphatic dissemination is unusual. A medical literature review suggested that disseminated actinomycosis in the post-antibiotic era is rare and constitutes approximately 15.9% of cases (4). Disseminated actinomycosis causes constitutional symptoms such as fever, malaise, night sweats, anorexia, weight loss, and so forth, and is surprisingly indolent at the time of diagnosis. Symptoms do not correlate with the extent of disease. Weese et al. (7) reported that disseminated actinomycosis was correctly diagnosed in only 7% of patients at the time of admission. Although disseminated actinomycosis can involve any organ system, commonly, the lungs, skin, long bones, liver, brain, and muscles are affected.

CARDIAC ACTINOMYCOSIS. Actinomycosis rarely involves the heart. A review of cardiac actinomycosis in the medical literature since the first report of “lumpy jaw” in 1877 by Bollinger (8) suggests that there are hardly any reports of actinomycosis causing extensive cardiac involvement and death (4) due to right heart failure. Although there are a few reports of actinomycotic pericardial involvement, Kasper and Pinner (9) and Cornell and Shookhoff (10) collected the largest series of cases of cardiovascular actinomycosis and the reported incidence was <1.2%. With the currently available published studies, the present authors could not find a case with such widespread dissemination and extensive cardiac involvement causing right heart failure with the initial infection possibly coming from the left foot (Madura foot). The authors believe the kind of dissemination noted in the present case with extensive cardiac involvement will add to our understanding and recognition of the spectrum of this rare disease.

TREATMENT
Actinomycetomas are usually amenable to antibiotic treatment, and in early stages, prognosis is excellent. Rarely in localized variants, surgical drainage or excision may speed up recovery along with antibiotic therapy. The duration of treatment is prolonged sometimes, extending up to 1 year or beyond (average duration is 6 to 12 months). Several antibiotics, such as benzylpenicillin, cotrimoxazole, dapsone, streptomycin, trimethoprim, rifampicin, and the amoxicillin-clavulanic acid combination have been used and found to be effective (11,12).

PROGNOSIS
The availability of a wide number of antibiotics and the absence of resistance has greatly improved the prognosis of all forms of actinomycosis. Presently, cure rates are high, and neither deformity nor death is common if actinomycosis is diagnosed and treated at early stages before dissemination and organ damage (11,12). However, studies guiding the management of disseminated actinomycosis with cardiac involvement, although rare, are sparse.

FOLLOW-UP
Even though the patient showed signs of initial improvement (decrease in discharge from sinuses,
drop in erythrocyte sedimentation rate to 60 mm/h, and weight gain), his echocardiogram showed no changes in RV and pericardial space infiltration with severely reduced RV function, luminal diameter, and filling. Despite continued treatment, the patient succumbed to his illness after 2 months with refractory right-heart failure.

CONCLUSIONS

This case emphasizes the need for prompt diagnosis and meticulous treatment with appropriate antibiotics for any type of actinomycosis. The untreated or partially treated disease can run an indolent course and become disseminated. Thoracoabdominal and disseminated variety of actinomycosis can involve the heart, which can be fatal. The involvement of pericardium, RV, and other surrounding structures without any limitation by the fibrous planes in the present case demonstrates fatal cardiac complications of this disease.

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REFERENCES

1. Kruse W. Systematik der Streptothricheen und Bakterien. In: Flugge C, editor. Die Mikroorganismen. 3rd edition, volume 2. Leipzig: Vogel, 1896: 48-96.

2. Hall V. Actinomycetes—gathering evidence of human colonization and infection. Anaerobe 2008; 14:1-7.

3. Schaal KP, Lee HJ. Actinomycete infections in humans—a review. Gene 1992;115:201-11.

4. Kanna B, Soni A. Disseminated actinomycosis with unusual cardiac involvement. Infect Dis Clin Pract 2002;11:408-13.

5. Fahal AH. Mycetoma: a thorn in the flesh. Trans R Soc Trop Med Hyg 2004;98:3-11.

6. Lichon V, Khachemoune A. Mycetoma A review. Am J Clin Dermatol 2006;7:315-21.

7. Weese W, Smith J. A study of 57 cases of actinomycosis over 36 years. Arch Intern Med 1975; 135:1562-8.

8. Bollinger O. Ueber eine neune Pilzkrankheit beim Rinde. Centralbl Med Wissensch 1877;15:481.

9. Kasper JA, Pinner M. Actinomycosis of the heart: report of a case with actinomycotic emboli. Arch Pathol 1930;10:687-95.

10. Cornell A, Shookhoff H. Actinomycosis of the heart simulating rheumatic fever. Arch Intern Med 1944;11:74.

11. Gomez A, Saul A, Bonifaz A, Lopez M. Amoxicillin, and clavulanic acid in the treatment of actinomycetoma. Int J Dermatol 1993;32: 218-20.

12. Mahaisavariya P, Chaiprasert A, Sivayathorn A, Khemngern S. Deep fungal, and higher bacterial skin infections in Thailand: clinical manifestations and treatment regimens. Int J Dermatol 1999;38: 279-84.

KEY WORDS chronic right heart failure, disseminated actinomycosis, pericardial infiltration, RV infiltration
Beyond the Diagnosis of Group IV Pulmonary Hypertension
Chronic Thromboembolic Pulmonary Hypertension Mimickers

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ABSTRACT

We present 3 patients with similar clinical presentation of group IV pulmonary hypertension but with totally different diagnoses. This case series highlights the need to keep a broad differential diagnosis and to utilize more diverse imaging modalities for the diagnosis of group IV pulmonary hypertension. (Level of Difficulty: Beginner.)

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Pulmonary hypertension (PH) has different etiologies that could all share the same presentation and diagnostic imaging. The World Health Organization identifies 5 distinct groups of PH based on pathogenesis and etiology. Among these, group IV is PH secondary to chronic thromboembolic pulmonary hypertension (CTEPH) (1). With improving diagnostic modalities, the incidence and prevalence of CTEPH are increasing. However, CTEPH can cause a diagnostic dilemma in many cases because any disease that causes pulmonary artery occlusion can mimic and easily be mistaken for CTEPH (2,3). Here we present a case series of patients who presented similarly but had vastly different diagnoses.

CASE DESCRIPTIONS

CASE 1. A 72-year-old man presented with progressively worsening dyspnea, lower extremity edema, and abdominal swelling. Pertinent history includes pulmonary embolism diagnosed the year before presentation, permanent atrial fibrillation, and prostate cancer post-resection. On examination, the patient had an irregularly irregular rhythm, with jugular venous distension and bilateral lower extremity edema.

Computed tomography angiography (CTA) of the chest revealed failure to opacify the right middle and lower lobe branches of the right pulmonary artery, possibly secondary to occlusion from a right hilar mass with middle lobe pulmonary emboli. Due to the patient’s severe orthopnea, he was unable to undergo...
a right heart catheterization or biopsy of the mass. Magnetic resonance angiogram (MRA) of the chest was performed and showed a large nonenhancing mass-like filling defect involving the right main, interlobar, middle, and lower lobe pulmonary arteries with signal characteristics consistent with bland thrombus and no evidence of extension outside the lumen (Figures 1). A pulmonary ventilation/perfusion (V/Q) scan confirmed numerous mismatch perfusion defects. Echocardiography was performed given the suspicion of PH, and it showed a dilated right ventricle with severely depressed right ventricular (RV) systolic function; RV pressure was consistent with severe PH.

After aggressive diuresis, the patient improved clinically and was able to undergo pulmonary endarterectomy, with good results (Figure 1C). Pulmonary pressures taken intraoperatively (Table 1) confirmed CTEPH.

**CASE 2.** A 37-year-old woman presented for chronic exertional dyspnea and lower extremity edema. Pertinent medical history includes nonischemic cardiomyopathy with recovered ejection fraction, papillary thyroid carcinoma post-partial thyroidectomy, and iatrogenic hypothyroidism. On examination, she had an accentuated P2, parasternal heave, jugular venous distention, and mild bilateral pitting lower-limb edema. Echocardiography showed a mildly dilated right ventricle with normal RV systolic function; however, Doppler findings suggested PH.

**FIGURE 1 A 72-Year-Old Man With Chronic Thromboembolic Pulmonary Hypertension**

(A) Magnetic resonance angiogram (MRA) of the chest without contrast showing a large mass-like filling defect (arrow) involving the right main pulmonary artery. (B) MRA of the chest with contrast showing a nonenhancing filling defect (arrow) in the right main pulmonary artery, consistent with a bland thrombus rather than mass. (C) Pulmonary MRA with filling defects in the branches of the right pulmonary artery (arrow).
Given the patient’s persistent symptoms, CTA of the chest (Figure 2A) was performed, revealing chronic central pulmonary thrombus with increasingly irregular margins. This was concerning for an underlying mass at the site of thrombosis. Subsequently, magnetic resonance imaging of the chest (Figures 2C and 2D) with and without contrast revealed an infiltrative enhancing mass extending into the left and right main pulmonary artery system with intravascular extension. This imaging was followed by a whole-body positron emission tomography (PET) scan. This scan showed a hypermetabolic mass involving the heart: the main pulmonary arteries extending into the left lobar arteries and veins, narrowing the left main stem and lobar bronchi and mediastinal lymphadenopathy. Fine needle aspiration of the mediastinal lymph nodes showed spindle cell sarcoma, and the patient was started on chemotherapy followed by immunotherapy with decreasing disease burden on follow-up.

**Case 3.** A 32-year-old woman presented to our hospital with a 2-month history of progressive dyspnea and chest pain. She was previously being seen for recurrent pericarditis, Raynaud’s phenomenon, arthralgias, and syncope with a working diagnosis of mixed connective tissue disease. She was taking hydroxychloroquine and methotrexate.

On examination, the patient had a mildly accentuated P2 with an II/VI systolic murmur at the right upper sternal border. Her erythrocyte sedimentation rate was 67 mm/h, and C-reactive protein was 86 mg/l.

Computed tomography scan of the patient’s chest showed peripheral bilateral lower lobe pulmonary artery filling defects with wedge-shaped peripheral parenchymal densities in the right middle and lower lobes. The peripheral distribution was suggestive that these may be resolving or chronic (Figure 3A). V/Q scan showed multiple peripheral wedge-shaped perfusion defects bilaterally, with the right worse than the left. The patient was referred for evaluation of PH and consideration for pulmonary endarterectomy. Echocardiography did not show PH, and she was discharged home with rivaroxaban and outpatient hypercoagulable evaluation, which was only positive for heterozygous Factor V Leiden.

The patient was later seen in the heart failure clinic for worsening dyspnea. A right heart catheterization showed moderate PH (Table 1). Pre-admission testing for pulmonary endarterectomy was ordered, including a carotid ultrasound that showed bilateral carotid occlusions. Given the patient’s age, previous symptoms, atypical presentation, and the findings of her carotid ultrasound, a whole-body PET scan (Figure 3B) along with MRA of carotids, chest (Figures 3C and 3D), and abdomen were ordered.

MRA showed complete bilateral common carotid artery occlusion with subtle mural thickening of the

**Table 1: Comparison Between Study Cases of CTEPH, Spindle Cell Sarcoma, and Takayasu Arteritis**

|                      | CTEPH | Spindle Cell Sarcoma | Takayasu Arteritis |
|----------------------|-------|----------------------|--------------------|
| **Age (yrs)**        | 72    | 37                   | 32                 |
| **Clinical presentation** | Dyspnea, lower extremity edema, chest pain, history of PE, or deep venous thrombosis | Dyspnea, lower extremity edema, profound weight loss and cachexia, and hemoptysis | Arm and leg pain from limb claudication, peripheral cyanosis, weight loss, low-grade fever, fatigue, arthralgias, progressive dyspnea, and chest pain |
| **TTE**              | Dilated right ventricle with severely depressed RV systolic function; RV pressure was consistent with severe PH | Echocardiography showed mildly dilated right ventricle with normal RV systolic function; however, Doppler findings suggested PH | Echocardiography did not show PH |
| **CT chest scan with and without intravenous contrast** | Filling defects in the pulmonary arteries consistent with chronic emboli | Filling defects in the pulmonary arteries with irregularities of the arterial wall, features of local invasion or systemic metastasis | Filling defects in the pulmonary arteries consistent with chronic emboli with mural wall thickening that can also be seen in other arterial vasculature (e.g., the aorta) |
| **Hemodynamic parameters** | RAP: unable to estimate | RAP systolic/diastolic (mean): 12/8 (7) mm Hg | RAP systolic/diastolic (mean): 5/2 (4) mm Hg |
|                       | Peak PAP: 95 mm Hg | PAP systolic/diastolic (mean): 30/10 (20) mm Hg | PAP systolic/diastolic (mean): 43/13 (26) mm Hg |
|                       | POD1 systolic/diastolic (mean): 42/21 (30) mm Hg | PCWP systolic/diastolic (mean): 22/17 (15) mm Hg | PCWP systolic/diastolic (mean): 12/10 (8) mm Hg |
|                       | PCWP (mean): 20 mm Hg | PVR: 1.20 Wood units | PVR: 4.30 Wood units |
| **Pathology**         | Arterial wall and organizing thrombus | Biopsy results positive for spindle cell sarcoma | Was not performed during right heart catheterization |
| **Treatment**         | Surgical endarterectomy/balloon pulmonary angioplasty, medical therapy | Surgical resection and chemotherapy | High-dose steroids |

*CT* = computed tomography; *PAP* = pulmonary artery pressure; *PCWP* = pulmonary capillary wedge pressure; *PE* = pulmonary embolism; *PH* = pulmonary hypertension; *POD1* = post-operative day 1; *PVR* = pulmonary vascular resistance; *RAP* = right atrial pressure; *RV* = right ventricular; *TTE* = transthoracic echocardiogram.
thoracic aorta suggestive of Takayasu arteritis. This was confirmed on whole-body PET scan.

The patient’s condition improved with steroids.

**DISCUSSION**

Following the 6th World Symposium of PH in 2019, the European Respiratory Journal updated the clinical classification and now recommends that group IV be defined as PH due to pulmonary artery obstructions (4). Application of this definition broadens our differential to include obstructive diseases other than CTEPH.

CTEPH, spindle cell sarcoma, and Takayasu arteritis can all be mistaken for the other (5) when causing pulmonary artery occlusion. All 3 study cases presented with exertional dyspnea, peripheral edema, perfusion mismatch on V/Q scan, and filling defects on imaging. However, their management was dictated by the underlying etiology. One patient underwent pulmonary endarterectomy, the second received chemotherapy, and the third required immunosuppression.

Table 1 highlights the similarities and differences between these diseases.

Many other mimickers also exist such as pulmonary cement embolism after kyphoplasty, and thoughtful evaluation with a multidisciplinary approach involving an experienced radiologist is paramount. Certainty of the diagnosis is crucial as taking the patient to the operating room without the correct diagnosis can lead to significant morbidity and mortality (6).

**CONCLUSIONS**

Compared with CTEPH, spindle cell sarcomas and Takayasu arteritis are rarer diagnoses with atypical presentations that include PH (2,7). Therefore, while evaluating patients for signs of right heart failure, the index of suspicion for these diseases should be high, especially if there is concern of refractory or worsening obstructive burden while on anticoagulation. Timely diagnosis can help reduce significant morbidity and mortality.
The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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REFERENCES

1. McLaughlin VV, Archer SL, Badesch DB, et al. ACCF/AHA 2009 expert consensus document on pulmonary hypertension: a report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents and the American Heart Association: developed in collaboration with the American College of Chest Physicians, American Thoracic Society, Inc., and the Pulmonary Hypertension Association. J Am Coll Cardiol 2009;53:1573–619.

2. Lee Y, Kim HJ, Yoon H, et al. Clinical characteristics and treatment outcomes of primary pulmonary artery sarcoma in Korea. J Korean Medical Sci 2016;31:1755–60.

3. Shingaki M, Kobayashi Y. Bilateral pulmonary artery occlusion due to primary pulmonary artery sarcoma; report of a case. Kyobu Geka 2014;67:575–7.

4. Simonneau G, Montani D, Celermajer DS, et al. Hemodynamic definitions and updated clinical classification of pulmonary hypertension. Eur Respir J 2019;53:1801913.

5. Belge C, Renckens I, Van Puijenbroeck R, Wuyts W, Meyns B, Delcroix M. Intima sarcoma of the pulmonary artery mimicking Takayasu disease. Case Reports Vasc Med 2011;2011:510708.

6. Soulaidopoulos S, Madenidou AV, Daoussis D, et al. Cardiovascular disease in the systemic vasculitides. Curr Vasc Pharmacol 2020 Jan 29 [E-pub ahead of print].

7. Sari A, Sener YZ, Fırat E, et al. Pulmonary hypertension in Takayasu arteritis. Int J Rheumatic Dis 2018;21:1634–9.

KEY WORDS autoimmune, cancer, spindle cell sarcoma, Takayasu arteritis, thrombosis
Single Ectopy-Triggering Ganglionated Plexus Ablation Without Pulmonary Vein Isolation Prevents Atrial Fibrillation

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ABSTRACT

A 58-year-old woman with drug-refractory symptoms of paroxysmal atrial fibrillation (AF) was referred for AF ablation. A single site of ganglionated plexus triggering pulmonary vein ectopy and AF was ablated, without pulmonary vein isolation. This procedure led to long-term freedom from AF. (Level of Difficulty: Advanced.)

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HISTORY OF PRESENTATION

A 58-year-old woman presented with paroxysmal atrial fibrillation (AF) and a report of symptomatic episodes occurring at least once a month and lasting several days at a time. Because of her drug-refractory symptoms, she was referred for AF ablation and underwent ganglionated plexus (GP) ablation as part of a pilot study.

PAST MEDICAL HISTORY

The patient had hypertension, good left ventricular systolic function, and a left atrial diameter of 3.6 cm. Flecainide was used as “pill-in-the-pocket” therapy. She previously had an electrophysiology study, which detected a concealed septal accessory pathway but no inducible tachycardia. This condition was left untreated.

DIFFERENTIAL DIAGNOSIS

The differential diagnoses included atrial tachycardia, atrial flutter, and AF.

INVESTIGATIONS

A 12-lead electrocardiogram confirmed AF (Figure 1).
The procedure was performed while the patient was under general anesthesia. Access to the left atrium was guided by fluoroscopy and transesophageal echocardiography. A 3-dimensional electroanatomic map of the left atrium was created using the CARTO system ( Biosense Webster, Irvine, California).

At the beginning of mapping, frequent and spontaneous AF episodes were seen, and they became sustained. We then commenced mapping of GP sites with high-frequency stimulation (HFS) delivered to the left atrial endocardium by using the ablation catheter. Continuous HFS (10-s stimulation at 10V, 20 Hz) delivered during AF identified atrioventricular dissociating GP (AVD-GP). AVD-GP are defined as causing asystole during HFS, or >50% prolongation in the average RR interval during HFS (compared with baseline) secondary to atrioventricular dissociation (1). After approximately 50 min, AF spontaneously reverted to sinus rhythm. Therefore, the remaining left atrium was mapped with synchronized HFS to identify ectopy-triggering GP (ET-GP). ET-GP cause pulmonary vein (PV) or atrial ectopy and atrial arrhythmia when stimulated with synchronized HFS (2) (100-ms, 10-V, 40-Hz bursts synchronized to atrial-paced stimuli, delivered within the local atrial refractory period to capture GP and not myocardium). A total of 64 sites were tested with HFS, which identified 19 GP (30%); 2 ET-GP, and 17 AVD-GP. Figure 2 shows the effect of synchronized HFS identifying an ET-GP near the left inferior PV (LIPV) ostium. Multiple repeat tests at this site consistently triggered PV ectopy from the LIPV, thus causing AF. Radiofrequency ablation at this ET-GP immediately triggered AF (Figure 3A), and during ablation AF terminated to sinus rhythm (Figure 3B). In total, 197 s of ablation were performed in a cluster at this ET-GP. The ablated ET-GP was tested again with synchronized HFS, which did not trigger ectopy or AF (Figure 4). There was no further spontaneous AF (which had occurred frequently before ablation). Other GP were not ablated. All PVs at the end of the procedure remained electrically connected. There were no complications.

DISCUSSION

This is the first report of a single site of ablation outside the PV, without PV isolation (PVI), resulting in sustained freedom from AF. The landmark study by Haïssaguerre et al. (3) first described focal PV ectopy triggering AF. However, because of difficulties with mapping these PV foci and the unpredictable nature of AF initiation, PVI became established as the...
recommended empirical therapy for AF treatment (4). Despite improvements in catheter ablation techniques, the success rate of PVI is only modest, at 50% to 60% (5). Incomplete PVI has also been associated with freedom from AF (6). Therefore, other mechanisms and therapeutic approaches need consideration.

The autonomic nervous system plays an important role in both triggering and maintenance of AF. The importance of “vagally mediated” AF is well established historically (7). The human intrinsic cardiac autonomic nervous system contains a complex network of GP, located abundantly in the atrial epicardium. However, different GP mapping and ablation techniques have produced mixed results: HFS-mapped AVD-GP ablation prevented AF in 42.5% of patients (8), and anatomically identified left atrial GP ablation prevented AF in 48% of patients (9). Targeting the GP alone did not confer greater benefit over standard PVI. The previous GP ablation series indicated that GP ablation can prevent AF, but not as well as PVI. Our case report illustrates that GP ablation can be specific and limited to a single triggering site. Further studies are needed to determine whether this was an isolated phenomenon or whether it is possible in other patients with AF.

Another HFS technique synchronizes to the local atrial refractory period to identify ET-GP (2). It is not known what role ET-GP have in prevention of AF without PVI. The ET-GP identified in this report was a reproducible trigger for LIPV ectopy. After ablating this site, we were no longer able to trigger LIPV ectopy or AF. Subsequent 48-h Holter monitors did not show recurrence of atrial arrhythmia, and the patient remained symptom free after several years. This finding suggests that the upstream focal PV trigger responsible for the paroxysmal AF was exclusively from the ET-GP situated at the LIPV antrum. It
is possible that interrupting this specific site of neural connection also affected other PVs in the left atrium. This is the first report of a single site of ET-GP ablation without PVI in a patient who achieved long-term freedom from AF. In this case we stopped ablation after a single ET-GP because there were no further spontaneous AF episodes after ablating this GP site. This an important, but fortuitous, observation because it implies that the other GP sites that were identified were not part of the AF triggering mechanisms. We cannot compare this with previous GP studies because data on the exact ablation performed...
in successful patients are limited. Current guidelines still mandate PVI, and a large case-series is needed before ET-GP mapping and ablation can be incorporated into routine clinical practice.

**FOLLOW-UP**

After the procedure, the patient had 3 separate 48-h Holter monitor sessions: after 74 days, 262 days, and 483 days. None revealed any atrial arrhythmia. The patient has been completely free of AF symptoms for more than 4 years. However, we cannot rule out asymptomatic AF without continuous monitoring.

**CONCLUSIONS**

A single ET-GP site was identified and ablated as the upstream trigger for this patient’s PV-mediated AF. This acutely terminated sustained AF and led to long-term AF prevention without requiring an empirical PVI. Successful targeting of a specific ET-GP without PVI warrants further investigation to understand the role of ET-GP in AF. Mapping and ablating specific ET-GP in patients with AF may provide a more patient-centric approach to treatment and help improve our ablation strategy.

**AUTHOR RELATIONSHIP WITH INDUSTRY**

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**FIGURE 4** Synchronized HFS at Ablated ET-GP Inducing No Further AF

After ablation of the ectopy-triggering ganglionic plexus (ET-GP) near left inferior pulmonary vein (LIPV), repeat synchronized high-frequency stimulation (HFS) was performed at the same ablated site. The pulmonary vein (PV) catheter remained in the left inferior pulmonary vein. The first 2 artifacts are from pacing the left atrium at high output, thus confirming atrial capture. Subsequently, synchronized high-frequency stimulation was performed; it did not trigger pulmonary vein ectopy or atrial fibrillation (AF) again. Abbreviations as in Figures 2 and 3.
REFERENCES

1. Kim MY, Sikkel MB, Hunter RJ, et al. A novel approach to mapping the atrial ganglionated plexus network by generating a distribution probability atlas. J Cardiovasc Electrophysiol 2018;29:1624–34.

2. Lim PB, Malcolm-Lawes LC, Stuber T, et al. Intrinsic cardiac autonomic stimulation induces pulmonary vein ectopy and triggers atrial fibrillation in humans. J Cardiovasc Electrophysiol 2011;22:638–46.

3. Haisaguerre M, Jais P, Shah DC, et al. Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. N Engl J Med 1998;339:659–66.

4. Calkins H, Hindricks G, Cappato R, et al. 2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation: executive summary. Europace 2018;20:157–208.

5. Andrade JG, Champagne J, Dubuc M, et al. Cryoballoon or radiofrequency ablation for atrial fibrillation assessed by continuous monitoring. Circulation 2019;140:1779–88.

6. Nery PB, Bélliveau D, Nair DM, et al. Relationship between pulmonary vein reconnection and atrial fibrillation recurrence: a systematic review and meta-analysis. J Am Coll Cardiol EP 2016;2:474–83.

7. Aksu T, Güler TE, Mutluer FO, et al. Vagal denervation in atrial fibrillation ablation: a comprehensive review. Anatol J Cardiol 2017;18:142–8.

8. Pokushalov E, Romanov A, Shugayev P, et al. Selective ganglionated plexi ablation for paroxysmal atrial fibrillation. Heart Rhythm 2009;6:1257–64.

9. Katritsis DG, Pokushalov E, Romanov A, et al. Autonomic denervation added to pulmonary vein isolation for paroxysmal atrial fibrillation: a randomized clinical trial. J Am Coll Cardiol 2013;62:2318–25.

KEY WORDS atrial fibrillation, atrial fibrillation ablation, autonomic nervous system, ganglionated plexus, pulmonary vein ectopy
Atrial fibrillation (AF) is the most prevalent cardiac dysrhythmia across the globe, and its invasive management, although widespread, poses a challenge when aiming for long-term freedom from AF. With success rates at approximately 60%, in absence of antiarrhythmic drugs, after a first procedure for paroxysmal AF (pAF) (1), we are yet to find the silver bullet for AF ablation.

In this issue of *JACC: Case Reports*, Kim et al. (2) describe the case of a 58-year-old lady with symptomatic pAF refractory to medical therapy and report the successful ablation of a single ganglionated plexus (GP), triggering ectopy causing AF, resulting in freedom from atrial arrhythmias. This proof-of-concept case describes an innovative potential strategy for ablation in patients with pAF, and we are grateful to the authors for sharing this case with the medical community.

There is a breadth of options for managing pAF and, as described in this case, antiarrhythmic medications, such as flecainide, are often used with a “pill in pocket” strategy. Use of many of the antiarrhythmic medications available is hindered by both side effects and contraindications in certain patient groups, notably those with structural or ischemic heart disease, which both have an increased incidence as people age. As AF disproportionately affects the elderly population, this poses challenges in clinical practice. It is clear that an ablative strategy over antiarrhythmic therapy is the preference for pAF management with regard to improvement in symptoms, maintaining sinus rhythm, and changing its natural history (3).

The history of AF ablation dates back to the 1980s, starting with surgical cut-and-sew techniques resulting in isolation of the atria (4), and as the authors note, it was not until 1998 that the landmark observation associating pulmonary veins to the origin and maintenance of AF was published (5). Subsequent extensive research into AF ablation has resulted in pulmonary vein isolation (PVI) becoming the established recommended procedure in all AF ablations. Following PVI, there are many targets for ablation that have been identified over the years (6): GPs are one of the most attractive among them, both on a pathophysiological and on a procedural standpoint.

Innervation of the heart occurs via the extrinsic (central) and intrinsic cardiac autonomic nervous system. The intrinsic cardiac autonomic nervous system is composed of GPs, which are the point of interest in this case. These GPs comprise afferent and efferent neurons, nerve axons, and ganglia clusters and are located on the epicardial surface of the heart, with the majority embedded in epicardial fat pads (7). The majority of neurons are located on the posterior atrial surface, and the 4 major atrial GPs are anatomically located in close proximity to the pulmonary veins and have projections to atrial tissue (8). These GPs have been found to play a role in the initiation and maintenance of AF (9). When performing wide PVI, the slowing of the RR interval is likely due to the interrupting axons of passage between ganglia.

As described in this case, the location of GPs are identified by delivering high-frequency stimulation (HFS) to the left atrial endocardium with the ablation
catheter, and while the patient is in AF, this can identify an “atrioventricular dissociating GP,” should there be transient complete atrioventricular block or a >50% prolongation in the average RR interval (Central Illustration A). The majority of studies identify GP location this method or base GP ablation on known anatomy without prior identification using HFS.

The novel approach proposed by Kim et al. (2) is to look for GPs also in sinus rhythm. The authors propose to perform synchronized HFS in the left atrium in sinus rhythm in order to identify specifically a particular type of GP, called ectopy-triggering GP (ET-GP) (Central Illustration B). HFS on these locations triggers short-cycle atrial ectopics and subsequently AF. The authors demonstrated that ablation on this site resulted in restoration of sinus rhythm during ablation and freedom from atrial arrhythmias at midterm follow-up.

GP ablation for the treatment of AF is not a novel technique: it has long been a controversial topic and is not recommended in current established guidance (10); however, this case describes the first ablation in humans, solely targeting the GP triggering AF, resulting in long-term freedom from AF, for which the authors must be applauded. The limitation of this technique stands in a potential lower reliability compared with PVI because localization of this particular type of GP could be cumbersome and time-consuming or not doable in patients in whom sinus rhythm cannot be restored with electrical or pharmacological cardioversion.

Furthermore, it is still debatable if GP ablation should be performed with or without PVI. Indeed, on the one hand, there is evidence that ablation of GPs in conjunction with traditional PVI confers a higher success rate when treating pAF (74% success, compared with 56% in PVI alone, in freedom from AF at 12 months) (11). On the other hand, when GPs were ablated without PVI, on an anatomical basis, this led to only 48% of success rate (11).

To confirm that when it rains it pours, there are data from canine studies suggesting that there could be not only no benefit in reduction of AF burden, but also proarrhythmic sequelae to GP ablation potentially secondary to reduction in the atrial effective refractory period in the long term, although all data are again based on anatomical ablation of GPs (12–14). On the clinical side, more recently the AFACT (Ganglionated Plexus Ablation in Advance Atrial Fibrillation) study showed no additional benefit to epicardial GP ablation when undergoing
thoracoscopic ablation for advanced AF and indeed resulted in a higher proportion of adverse events (15).

A theory behind the limitation of long-term success of GP ablation lies in the diverse effects of ablation on atrial tissue and nervous tissue. Localized ablation performed on atrial tissue results in the creation of infarction and scar; however, neural tissue can exhibit plasticity whereby, should cell bodies be preserved (which may occur after GP ablation), nerve sprouts can emerge from each parent axon, leading to regeneration. In this case, the limited ablation of only 1 ET-GP as opposed to widespread GP ablation may prevent the previously mentioned potential adverse consequences.

When considering an ablative strategy for patient with pAF, this case highlights that there may well be a focal ET-GP trigger to target in certain patients. More data are needed to demonstrate if this approach may prevent the need for further widespread ablation and if it may reduce procedure time, adverse events, and the need of redo procedures. Anyway, this patient-centered approach to ablation with such success should be encouraged and warrants further consideration.

AUTHOR RELATIONSHIP WITH INDUSTRY

The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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REFERENCES

1. Takigawa M, Takahashi A, Kuwahara T, et al. Long-term follow-up after catheter ablation of paroxysmal atrial fibrillation. Circ Arrhythm Electrophysiol 2014;7:267–73.

2. Kim M-Y, Lim PB, Coyle C, Sandler B, Kao-Wing M, Kanagaratnam P. A single ectopy-triggering ganglionated plexus ablation without pulmonary vein isolation prevents atrial fibrillation. J Am Coll Cardiol Case Rep 2020;2:2004–9.

3. Jais P, Cauchemez B, Macle L, et al. Catheter ablation versus antiarrhythmic drugs for atrial fibrillation. Circulation 2008;118:2498–505.

4. Defauw JJ, Guiraudon GM, van Hemel NM, Vermeulen FE, Kingma JH, de Bakker JM. Surgical therapy of paroxysmal atrial fibrillation with the “corridor” operation. Ann Thorac Surg 1992;53:564–71.

5. Haisaguerre M, Jais P, Shah DC, et al. Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. N Engl J Med 1998;339:659–66.

6. O’Neill MD, Jais P, Takahashi Y, et al. The stepwise ablation approach for chronic atrial fibrillation—evidence for a cumulative effect. J Interv Card Electrophysiol 2006;16:153–67.

7. Armour JA, Murphy DA, Yuan B-X, MacDonald S, Hopkins DA. Gross and microscopic anatomy of the human intrinsic cardiac nervous system. Anat Rec 1997;247:89–98.

8. Pauza DH, Skripka V, Pauziene N, Stropus R. Anatomy of the human intrinsic cardiac nervous system. Anat Rec 2000;259:353–62.

9. Nakagawa H, Scherlag BJ, Patterson E, Ilieda A, Lockwood D, Jackman WJ. Pathophysiological basis of autonomic ganglionated plexus ablation in patients with atrial fibrillation. Heart Rhythm 2009;6:526–34.

10. Calanti G, Hindricks G, Cappato R, et al. 2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation. Heart Rhythm 2017;14:e275–444.

11. Katritsis DG, Pukushalov E, Romanov A, et al. Autonomic denervation added to pulmonary vein isolation for paroxysmal atrial fibrillation. J Am Coll Cardiol 2013;62:2318–25.

12. Mao J, Yin X, Zhang Y, et al. Ablation of epicardial ganglionated plexi increases atrial vulnerability to arrhythmias in dogs. Circ Arrhythm Electrophysiol 2014;7:711–7.

13. Oh S, Zhang Y, Bibeviski S, Marrouche NF, Natale A, Mazgalev TN. Vagal denervation and atrial fibrillation inducibility: epicardial fat pad ablation does not have long-term effects. Heart Rhythm 2006;3:701–8.

14. Wang X, Zhang M, Zhang Y, et al. Long-term effects of ganglionated plexi ablation on electrophysiological characteristics and neuron remodeling in target atrial tissues in a canine model. Circ Arrhythm Electrophysiol 2015;8:1276–83.

15. Driessen AHG, Berger W, Krul SPJ, et al. Ganglion plexus ablation in advanced atrial fibrillation. J Am Coll Cardiol 2016;68:1155–65.

KEY WORDS ablation, atrial fibrillation, electrophysiology
MINI-FOCUS ISSUE: COVID-19

IMAGING VIGNETTE: CLINICAL VIGNETTE

Ventricular Septal Rupture in 2 Patients Presenting Late after Myocardial Infarction during the COVID-19 Pandemic

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ABSTRACT

Ventricular septal rupture (VSR) following myocardial infarction is rare in the reperfusion era. The decrease in patients presenting with myocardial infarction during the coronavirus-2019 (COVID-19) pandemic could result in more frequent VSR. This report describes two patients with VSR presenting late after myocardial infarction and treated at a single institution. (Level of Difficulty: Beginner.) (J Am Coll Cardiol Case Rep 2020;2:2013–5) © 2020 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Mechanical complications of myocardial infarction are rare in the reperfusion era (1,2). During the coronavirus-2019 (COVID-19) pandemic, reports of presentations of ST-segment elevation myocardial infarction (STEMI) have decreased (3). It is therefore conceivable mechanical complications might have become more prevalent. This report describes 2 patients with ventricular septal rupture (VSR) treated at a single center during the pandemic.

CASE 1

A 67-year-old male presented with 5 days of epigastric pressure and dyspnea. He initially resisted seeking care after symptom onset due to fear of contracting COVID-19 infection. Initial vital signs were blood pressure of 143/63 mm Hg, heart rate of 118 beats/min, and respirations of 26 breaths/min. He was diaphoretic with mottled extremities. Electrocardiography showed inferior Q waves. Result for COVID-19 infection testing was negative. Coronary angiography demonstrated an occluded right coronary artery, and echocardiography demonstrated a VSR (Figure 1). Venoarterial extracorporeal membrane oxygenation was initiated. Due to progressive multiorgan failure, surgical and percutaneous VSR repair were deemed futile. He expired on day 7 of hospitalization.

CASE 2

A 60-year-old female presented with dyspnea 1 to 2 weeks after an illness characterized by chest pain and vomiting that she thought was a viral infection. Initial vital signs were blood pressure of 135/78 mm Hg, a heart rate 95 beats/min, and respirations of 20 breaths/min. Electrocardiography showed anterior Q waves. Coronary angiography revealed left anterior descending artery occlusion, and echocardiography revealed a VSR.
An intra-aortic balloon pump was placed. Percutaneous VSR closure was performed, but she developed apical extension 4 days later (Figure 1), which was treated with open surgical repair. She ultimately progressed to hospital discharge.

**DISCUSSION**

This report describes 2 late-presenting myocardial infarctions complicated by VSR. It is notable that the COVID-19 pandemic seemingly influenced each patient to avoid seeking immediate care after symptom onset. At the time of this writing, the authors were aware of 3 additional VSR cases treated during the pandemic at our institution. Historically reported to occur in 0.21% of hospitalizations for STEMI (1), the occurrence of 5 VSR cases at a single institution during the pandemic was indeed curious. Among 366 patients treated for STEMI at the authors’ institution in 2019, 2 (0.5%) had VSR. In contrast, the rate of VSR per STEMI hospitalizations at the authors’ institution during the pandemic was 6.7%.

**AUTHOR RELATIONSHIP WITH INDUSTRY**

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**FIGURE 1** Findings in Cases 1 and 2

Case 1: Right coronary artery occlusion (A, arrow). Ventricular septal rupture (VSR) by echocardiography (B, arrow). Case 2: Left anterior descending artery occlusion (C, arrow). VSR by echocardiography (D, arrow). Closure device in the ventricular septum (E, arrow). Flow around the device several days after percutaneous closure (F, arrow).
REFERENCES

1. Elbadawi A, Elgendy IY, Mahmoud K, et al. Temporal trends and outcomes of mechanical complications in patients with acute myocardial infarction. J Am Coll Cardiol Intv 2019;12:1825–36.

2. Jones BM, Kapadia SR, Smedira NG, et al. Ventricular septal rupture complicating acute myocardial infarction: a contemporary review. Eur Heart J 2014;35:2060–8.

3. Garcia S, Albaghdadi MS, Mesaj PM, et al. Reduction in ST-segment elevation cardiac catheterization laboratory activations in the United States during COVID-19 pandemic. J Am Coll Cardiol 2020;75:2871–8.

KEY WORDS: mechanical complication, myocardial infarction, STEMI, ventricular septal defect, ventricular septal rupture
Catheter-Directed Thrombolysis of Iliocaval Thrombosis in Patients With COVID-19 Infection

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ABSTRACT

We present the characteristics and outcomes of the first 2 cases of catheter-directed thrombolysis performed in patients presenting with coronavirus disease-2019 (COVID-19)-related iliocaval thrombosis. (Level of Difficulty: Beginner.) (J Am Coll Cardiol Case Rep 2020;2:2016–20) © 2020 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Deep vein thrombosis (DVT), a common disorder affecting approximately 600,000 patients each year in the United States (1), is frequently complicated by a debilitating post-thrombotic syndrome (2). The severe acute respiratory syndrome-associated coronavirus-2 (SARS-CoV-2) virus is associated with a hypercoagulable state and a DVT incidence of 16% to 27% and pulmonary embolism (3,4). As of June 1, 2020, the U.S. Centers for Disease Control and Prevention reported >1.8 million cases of coronavirus disease-2019 (COVID-19) in the United States, >75% of them were <65 years of age (5), and a high proportion presented with or were destined to develop thrombosis of large veins, including iliocaval thrombosis. In these patients, anticoagulation alone is often insufficient and, in the absence of COVID-19, they would be considered candidates for catheter-directed thrombolysis (CDT) to alleviate symptoms and improve quality of life (6).

Current guidelines recommend treatment of proximal DVT in hospitalized COVID-19 patients by using low-molecular-weight heparin (LMWH) therapy; however, the CDC did not address the use of advanced therapies such as CDT (7). The present cases illustrate...
the potential role of CDT in selected young patients at low risk for bleeding. To the best of the authors’ knowledge, CDT of symptomatic iliocaval thrombosis in COVID-19 patients has not been reported, which is likely because of the potential risks of bleeding complications and viral transmission to the catheterization laboratory staff. This paper reports on 2 cases of COVID-19 patients presenting with severely symptomatic iliofemoral and inferior vena cava (IVC) thrombosis, successfully treated with CDT.

CASE REPORTS

CASE 1. A 34-year-old man with COVID-19-positive nasopharyngeal swab presented with increasing left lower extremity swelling and pain persisting for 1 week. Physical examination showed the presence of prominent edema from the foot to the proximal thigh. Initial laboratory test results were notable for a D-dimer of 11,864 ng/ml; partial thromboplastin time (PTT) of 36.4 s; a platelet count of 277 K/mm³; a hemoglobin concentration of 14.1 g/dl; a fibrinogen concentration of 488 mg/dl; lactate dehydrogenase concentration of 230 U/l; and a ferritin concentration of 411 ng/ml. Left venous duplex ultrasonography showed acute occlusive DVT extending from the common femoral vein (CFV) to the popliteal vein (PV) (Figures 1A and 1B). A thoracic CT scan revealed the presence of small, bilateral, lower lobe thrombi and was also evidence of chronic DVT in the left lower extremity with atretic left common iliac vein (CIV) and EIV. The patient was treated with anticoagulation using IV unfractionated heparin at a rate of 2,100 U/h for 72 h with serial therapeutic PTT without any improvement in swelling or pain. The risks and benefits of CDT, including the conflict of interest associated with the use of the Bashir endovascular catheter (BEC) (Thrombolex, New Britain, Pennsylvania) were explained to the patient after which written consent was obtained. The patient was taken to the catheterization laboratory where, under ultrasonography guidance, PV access was obtained. After baseline venography was performed, the BEC-40 was introduced to perform pharmacomechanical thrombolysis. Pulse sprays of 4.0 mg of recombinant tissue plasminogen activator (rtPA) were sequentially delivered from the PV to the EIV by repeatedly expanding and collapsing the infusion basket (Figures 1E and 1F). The BEC was repositioned across the left EIV and CFV, and a 30-cm infusion shaft was placed across the CFV and PV for continuous infusion of rtPA. The patient was monitored overnight in the COVID-19 unit. Follow-up venography performed the following day after administration of 16 mg of rtPA showed >90% lysis of the thrombus, with brisk flow across the left EIV, CFV, femoral vein (FV), and PV (Figures 1G and 1H), associated with marked decrease in swelling and pain. The patient was discharged home on the same day with a therapeutic dose of enoxaparin.

CASE 2. A 64-year-old, COVID-19-positive female with a history of morbid obesity (body mass index 62 kg/m²), chronic left lower extremity DVT, and prior IVC filter placement presented with a 5-day history of swelling extending from the right foot to the inguinal region. Initial laboratory tests were notable for a D-dimer of 7,069 ng/ml, a PTT of 33.6 s; a platelet count of 203 K/ mm³; a hemoglobin concentration of 13.1 g/dl; a fibrinogen concentration of 499 mg/dl; a lactate dehydrogenase concentration of 856 U/l; and a ferritin concentration of 1,711 ng/ml. Duplex ultrasonography revealed an occlusive DVT from the right CFV to the PV. CT venography showed acute occlusive thrombosis from the IVC filter at the renal veins’ confluence to the right FV (Figure 2A). There was also evidence of chronic DVT in the left lower extremity with atretic left common iliac vein (CIV) and EIV. The patient was treated with anticoagulation using IV unfractionated heparin at a rate of 2,100 U/h for 72 h with serial therapeutic PTT without any change in the swelling or pain. The risks and benefits of CDT, including the conflict of interest associated with the use of the BEC were explained to the patient, after which a written consent was obtained. After ultrasonography-guided right popliteal venous access was successfully obtained, venography revealed the presence of a thrombus extending from the IVC filter to the right popliteal vein (Figure 2B). Manual thrombectomy was performed using an 8-F multipurpose guiding catheter. CDT was performed by using a BEC-40 catheter, by delivering a 6-mg pulse of rtPA through the infusion basket, which was sequentially expanded along the infrarenal IVC, the right CIV, EIV, CFV, and FV. The rtPA infusion was continued overnight through the basket (placed at the level of the IVC filter) (Figure 2C) and the 40-cm shaft, infusing across the infrarenal IVC, and the iliac and femoral veins. Follow-up venography after a total of 24 mg of rtPA infusion revealed >80% clot lysis, with brisk flow between the PV and the suprarenal IVC (Figures 2D and 2F). Residual thrombus was
removed with an 8-F AngioJet Zelante DVT catheter thrombectomy system (Boston Scientific, Marlborough, Massachusetts). IV ultrasonography showed severe stenosis of the right CIV, which was stented using an 18- × 90-mm Wallstent endoprosthesis (Boston Scientific). The patient continued taking IV heparin, with resolution of the right lower extremity swelling and pain, and supplemental oxygen for management of viral pneumonia.

**CONCLUSIONS**

These cases illustrate the successful implementation of CDT with a novel pharmacomechanical device for the management of COVID-19-related proximal iliofemoral and iliocaval DVT. A single case of acute pulmonary embolism successfully treated with CDT has been reported (8), although the present cases are the first to report CDT for DVT in COVID-19 patients.
FIGURE 2  CT Venogram Shows Thrombus in the IVC Filter

(A) CT venogram shows thrombus in the IVC filter (the arrow points toward the clot above the IVC filter at the level of renal veins). (B) Venogram shows thrombus in the IVC below the IVC filter. (C) BEC+ with basket deployed in the IVC for tPA infusion. (D to F) Venogram shows resolution of thrombus in the IVC, right CIV, EIV, CFV, and femoral vein. BEC = Bashir endovascular catheter; CFV = common femoral vein; CIV = common iliac vein; CT = computed tomography; EIV = external iliac vein; IVC = inferior vena cava; tPA = tissue plasminogen activator.
Both of these patients benefited from nearly complete resolution of the clot burden and marked clinical improvement. It is particularly noteworthy that the first patient could be discharged from the hospital within hours following the CDT. At a time when hospital resources are being used to their limit by COVID-19 cases (9), safely reducing the length of hospital stay by CDT represents a major benefit, particularly in young patients and those who are at low risk for bleeding.

**REFERENCES**

1. Beckman MG, Hooper WC, Critchley SE, Ortel TL. Venous thromboembolism: a public health concern. Am J Prev Med 2010;38 4 Suppl: S495-S501.
2. Kahn SR, Ginsberg JS. Relationship between deep venous thrombosis and the postthrombotic syndrome. Arch Int Med 2004;164:17-26.
3. Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. J Thromb Haemost 2020;18:844-7.
4. Middeldorp S, Coppens M, van Haaps TF, et al. Incidence of venous thromboembolism in hospitalized patients with COVID-19. Thromb Haemost 2020;18:1995-2002.
5. U.S. Centers for Disease Control and Prevention. Cases in the U.S.: Coronavirus Disease 2019 (COVID-19). August 20, 2020. Available at: https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/cases-in-us.html. Accessed August 20, 2020.
6. Comerota AJ, Kearon C, Gu CS, et al. Endovascular thrombus removal for acute iliofemoral deep vein thrombosis: analysis from a stratified multicenter randomized trial. Circulation 2019;139: 1162-73.
7. Spyropoulos AC, Levy JH, Ageno W. Scientific and standardization committee communication: clinical guidance on the diagnosis, prevention and treatment of venous thromboembolism in hospitalized patients with COVID-19. Thromb Haemost 2020;18:1859-65.
8. Qadili SD, Gudmundsson L, Rotzinger DC. Catheter-directed thrombolysis in COVID-19 pneumonia with acute PE: thinking beyond the guidelines. Thromb Res 2020;192:9-11.
9. Bartsch SM, Ferguson MC, McKinnell JA, et al. The potential health care costs and resource use associated with COVID-19 in the United States. Health Aff (Millwood) 2020;39:927-35.

**KEY WORDS** clot burden, COVID-19 infection, COVID-19 infection complication, deep vein thrombosis, femoral vein thrombosis

**AUTHOR RELATIONSHIP WITH INDUSTRY**

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Mini-focus Issue: COVID-19

Imaging Vignette: Clinical Vignette

Cardiac Tamponade in a Patient With Myocardial Infarction and COVID-19: Electron Microscopy

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Abstract

We present the case of a patient with myocardial infarction and COVID-19 disease who developed hemorrhagic pericardial effusion and cardiac tamponade. The differential diagnosis included post-infarction pericarditis and mechanical complications, thrombolysis, Dressler syndrome, and viral pericarditis. The histopathologic examination of the pericardial tissue sample and electron microscopic examination established the diagnosis. (Level of Difficulty: Advanced.) (J Am Coll Cardiol Case Rep 2020;2:2021–3) © 2020 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

A 64-year-old man was admitted to the Ignacio Chávez National Institute of Cardiology in Mexico City, Mexico with chest pain, dry cough, and fever (38.3°C). He was dyspneic, with 85% arterial oxygen saturation, a heart rate of 84 beats/min and blood pressure of 106/87 mm Hg. Diffuse pulmonary rales were found, predominantly at the left lung base. The electrocardiogram showed ST-segment elevation on the inferior and posterior leads. The chest radiograph showed bilateral diffuse interstitial infiltrates, predominantly in the left lung. The result of real-time reverse transcription-polymerase chain reaction for detection of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) RNA was positive, so antiviral therapy was added. A transthoracic echocardiogram (TTE) showed ST-segment elevation on the inferior and posterior leads. The chest radiograph showed bilateral diffuse interstitial infiltrates, predominantly in the left lung. The result of real-time reverse transcription-polymerase chain reaction for detection of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) RNA was positive, so antiviral therapy was added. A transthoracic echocardiogram (TTE) showed inferolateral and inferior wall akinesia and an ejection fraction of 30% without pericardial effusion. Given the rapid progression (<12 h after chest pain onset), thrombolysis with alteplase was established with reperfusion criteria. On the ninth day of the illness, he had oliguria, sinus tachycardia, and dyspnea. A new TTE showed echogenic pericardial effusion with tamponade physiology (Figures 1A and 1B, Video 1). A pericardial window was performed, with drainage of 750 ml.
A pericardium sample was sent to the pathology department for evaluation: the hematoxilin and eosin stain findings were compatible with acute pericarditis (Figures 1C and 1D); electron microscopy showed viral particles (Figures 1E and 1F). During the coronavirus-2019 (COVID-19) pandemic, the treatment of ST-segment elevation myocardial infarction has changed to prioritize a safe intrahospital environment with thrombolysis preferred to primary angioplasty (1). In this patient with hemorrhagic pericardial effusion, the differential diagnosis included post-infarction pericarditis, mechanical complications of myocardial infarction, complications associated with thrombolysis, Dressler syndrome, and viral pericarditis. Viral pericarditis has been recognized as the cause of up to 62% of hemorrhagic pericardial effusions (2). The presence of SARS-CoV-2 in pericardial fluid has

**FIGURE 1** Viral Hemorrhagic Pericardial Effusion With Cardiac Tamponade

(A) Transthoracic echocardiographic apical 4-chamber view with separation of pericardial layers of 28 mm. (B) Respiratory variation in transmitral flow of 25%. (C and D) Hematoxylin and eosin–stained sections of the pericardium tissue sample. (C) Capillary congestion and wall infiltration of polymorphonuclear leukocytes (original magnification ×40). (D) Incipient periarteriolar fibrinoid necrosis and leukocyte infiltrate (original magnification ×40). (E and F) Electron microscopy of the pericardium ultrastructure. (E) Viral particles (arrowhead) are shown in a blood vessel (original magnification ×50,000). (F) Viral particles (arrowhead) are shown in the interstitium of a vessel and an epithelial cell (original magnification ×50,000).
been recently reported (also hemorrhagic) (3). For this reason, we sent a pericardium sample to the pathology service, where changes compatible with acute pericarditis were found and where the presence of viral particles was documented by electron microscopy, so the final diagnosis was hemorrhagic pericardial effusion with cardiac tamponade secondary to COVID-19. This is the first case reported with histopathologic evidence of the virus in pericardial tissue.

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**REFERENCES**

1. Jing Z, Zhu H, Yan X, Chai W, Zhang S. Recommendations from the Peking Union Medical College Hospital for the management of acute myocardial infarction during the COVID-19 outbreak. Eur Heart J 2020;41:1791-4.
2. Meyers D, Meyers R, Prendergast T. The usefulness of diagnostic tests on pericardial fluid. Chest 1997;111:1213-21.
3. Dabbagh M, Aurora L, D’Souza P, Weinmann A, Bhargava P, Basir M. Cardiac tamponade secondary to COVID-19. J Am Coll Cardiol Case Rep 2020;2:1326-30.

**KEY WORDS** coronavirus, myocardial infarction, tamponade

**APPENDIX** For a supplemental video, please see the online version of this paper.
MINI-FOCUS ISSUE: COVID-19

VIEWPOINT: VOICES IN CARDIOLOGY

Have a Heart
Addressing the Gradient of Social Determinants of Health During the COVID-19 Era

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We have Mr. Jordan, a 35-year-old African-American man with a past medical history significant for recurrent syncope admitted for further management of critical aortic stenosis with a mean gradient of 100 mm Hg. He has no medical insurance, is unemployed, and has a history of recreational drug abuse. His COVID-19 testing is pending.

This was the “one-liner” presentation of Mr. Jordan by the medical intern to me, the service attending on our cardiology hospital service at the start of our morning wards rounds. The astronomically high gradient of his aortic valve stenosis was undoubtedly the cause of his syncopal episodes—the highest I had ever seen in my clinical training and career. The severity of his valvular heart disease was overshadowed only by the severity of his negative social factors.

As our team went in to speak with Mr. Jordan to apprise him of his diagnosis and our care plan, I could not help but notice his lack of eye contact and rather curt responses to questioning. I initially thought it was because of our donning of seemingly sterile personal protective equipment that created a barrier to communication or the mere presence of the medical team towering over his bed. But I came to find that there was much more to the story. With further questioning, he indicated that over the past 2 years he had experienced more than 10 episodes of complete loss of consciousness but had not sought medical care because he attributed his symptoms to stress. He revealed reluctance to seek care given his lack of health insurance from unemployment and indicated that he just “didn’t have the best experiences” with the healthcare system in the past. As is common on rounds, we reviewed our plan of action inclusive of additional cardiac imaging and blood tests. We also explained that the state of his heart valve was life-threatening from a condition he was born with—bicuspid aortic valve—and that he would need open heart surgery to replace his valve. Appearing very subdued, he said, “Can you call my wife and tell her?” Given the coronavirus disease-2019 (COVID-19) pandemic, no visitors were allowed. As we exited the room, he called out and made what the team thought was an unusual request, “Can you all bring me a picture of Scrappy Doo? I really want to draw today.”

Afterwards, the team and I reflected, why would he not seek care after his repeated syncopal episodes? Why is he uninsured in the Obamacare era? I asked my team to continue to reflect on these issues and seek ways to better understand the context of his situation. We discussed the importance of exploring and addressing his psychosocial factors or social determinants of health (SDOH) and how best to consider the patient as a whole to tailor care plans to meet his multidimensional needs. This brought us back to the resounding values instilled into our medical institution that “the needs of the patient come first.”

Unfortunately, a patient’s SDOH are often considered only as an afterthought by clinicians and other healthcare team members, if they are addressed at all. Ignoring the primacy of the patient sociocultural context for healthcare delivery can lead to detrimental downstream effects—the creation and...
exacerbation of health disparities and, in Mr. Jordan’s case, with a potentially fatal outcome resulting from a late diagnosis. This is especially important for cardiovascular disease (CVD) outcomes in African-American men because they have the highest overall CVD death rate among racial and ethnic minority groups (2). He also fell into the “COVID-19-increased risk” group given his pre-existing CVD and—for being a Black individual (3). These disparities are even greater among persons of lower socioeconomic status who are faced with high burdens of pre-existing negative SDOH, such as adverse childhood experiences, criminalization, institutional or structural racism, and income inequality. SDOH are well defined by the U.S. Department of Health and Human Services as “conditions in the environments in which people are born, live, learn, work, play, and worship” that affect health outcomes (1). Examples of negative SDOH include greater exposure to crime and violence and reduced access to educational opportunities, employment, and health care.

One could argue that clinicians are extremely busy and have so many competing demands, how could we impose on them such a challenging task of addressing the plethora of psychosocial issues of their patients? Clinicians are faced with increasing time constraints with higher patient volumes and are challenged by pressures to meet quality and productivity metrics that increase health system financial gains. These challenges inherently hinder their ability to foster the patient-provider relationship, so this additional “burden” could surely lead to provider burnout. Further, during the COVID-19 pandemic, many argue that there should be a primary focus on treating the acute illness and maintenance of patient and staff safety. However, this viewpoint is unacceptable and truly undermines the core covenant of the Hippocratic Oath that physicians pledge to their patients. There are 3 key reasons that addressing the SDOH is so crucial in underserved, socioeconomically disadvantaged patients: 1) these patients have an overwhelmingly high burden of negative SDOH; 2) these patients are disproportionately affected by health and healthcare disparities leading to shortened life spans and reduced quality of life; and 3) it is the only way that we will truly achieve health equity. We must use a systems approach to these issues. The provision of high-quality patient care should not be viewed as the sole responsibility of an individual clinician confined to the walls of a clinic or hospital, but as a commitment of a collaborative multidisciplinary team, including social workers, community health workers, and public health and community stakeholders. This responsibility should not fall on community health centers and underresourced clinics primarily serving vulnerable populations as if somehow these issues are not relevant to larger, more resourced medical institutions. It is imperative not only that clinicians at all levels be trained to identify and address the SDOH as a professional competency, but also that health systems purposefully embed mechanisms and policies within practice to allow clinicians to translate these actions easily and meaningfully within the communities they serve (4). This system-wide solution can counteract burnout, avoid schisms in clinician values, and promote professional well-being (5).

Aligned with this patient-centered and contextually relevant approach, we worked to develop a genuine rapport with Mr. Jordan through open communication, transparency, and empathy. As he became more comfortable with our team, he expressed that he had endured significant childhood trauma that left him in a state of posttraumatic stress that affected his sleep patterns and thrusted him into substance abuse. He found sketching cartoon characters as a means to relieve his anxiety and pain. He shared that he had experienced judgmental attitudes in prior clinical interactions that dismissed the effects of his experiences on his well-being. He had never been formally evaluated by a psychiatrist but was open to seeing one while hospitalized. We also garnered that he had low health literacy and self-efficacy to participate actively in his care. With this in mind, we deployed our off-site, on-call social work and case management teams to assist him directly with completing the seemingly endless and daunting medical insurance paperwork. We advocated for and secured on his behalf charity coverage of his medical expenses by our institution, given that his insurance would not be instated during his hospitalization. Further, we recognized the exceedingly difficult situation of not having loved ones present at a time of greatest need—before undergoing a major surgical procedure. To adjust to the visitor restriction policy, we held a Zoom video conference with his wife to discuss his diagnosis, hospital course, and anticipated surgery. Mr. Jordan and his wife expressed sincere gratitude for our time because they had not previously perceived that level of attentiveness by clinicians. Fortunately, his COVID-19 test result was negative. He subsequently underwent a successful aortic valve replacement. Our team reflected on how gratifying and humbling it was that we had the opportunity not only to help alleviate his high aortic valve gradient but also, at least in part, to reduce his high gradient of adverse SDOH—even with limited staffing and resources during the COVID-19 pandemic. In this case, Mr. Jordan had clearly called
out his needs to us as we first exited his room and emblematically drew out the importance of our call and purpose as his healthcare team.

We as clinicians must “have a heart”—take our own empathy pulse and take a more active role in addressing the SDOH in patients from socially disadvantaged populations because this is a form of health justice to achieve health equity. This will allow us to better meet the needs of these most vulnerable patients, enhance the patient-provider relationship, and ultimately improve population health outcomes. It is essential that medical institutions and health systems better support clinicians in accomplishing this goal by directly investing in initiatives designed to address these determinants on a community level and providing assistance to socioeconomically disadvantaged patients in profound ways beyond traditional provision of medical services. This is critical now, in the COVID-19 era, when these patients are faced with an even greater burden of negative SDOH.

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**REFERENCES**

1. HealthyPeople.gov. Social Determinants of Health. Available at: https://www.healthypeople.gov/2020/topics-objectives/topic/social-determinants-of-health. Accessed July 27, 2020.

2. Graham G. Disparities in cardiovascular disease risk in the United States. Curr Cardiol Rev 2015;11:238–45.

3. Williams DR, Cooper LA. COVID-19 and health equity—a new kind of “herd immunity”. JAMA 2020;323:2478–80.

4. Hardeman RR, Medina EM, Boyd RW. Stolen breaths. N Engl J Med 2020;383:197–9.

5. American Medical Association. The 12 factors that drive up physician burnout. Available at: https://www.ama-assn.org/practice-management/physician-health/12-factors-drive-physician-burnout. Accessed August 31, 2020.

**KEY WORDS** COVID-19, health disparities, health equity, patient-physician relationship, social determinants of health
MitraClip Implantation in a Patient With Post-Surgical Repair of Primum Atrial Septal Defect and Residual Mitral Cleft

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ABSTRACT

This paper presents the case of a 67-year-old female with primum atrial septal defect and congenital mitral cleft status-post surgical repair 40 years previously who was recently found to have severe mitral regurgitation. Percutaneous mitral valve repair was successfully performed using implantation of 2 MitraClips with mild residual mitral regurgitation. (Level of Difficulty: Advanced.)

Percutaneous mitral valve (MV) repair is primarily used for patients with acquired degenerative mitral regurgitation (MR) and high surgical risk and for patients with secondary MR with suitable anatomy if still symptomatic on optimal medical therapy (1). MitraClips (Abbott Vascular, Santa Clara, California) are considered unfavorable for patients with MR due to congenital mitral cleft, and surgical correction is the mainstay of treatment. This paper describes a novel approach to MitraClip implantation in a patient who had surgical repair of partial atrioventricular canal defect and mitral cleft 40 years previously.

A 67-year-old female with severe lung disease (forced expiratory volume in 1 s = 43%) requiring home oxygen and who previously underwent surgical repair of an atrioventricular canal defect using a fabric membrane patch (Gortex, Gortex, Reisterstown, Maryland) and an attempted MV repair was referred to the authors’ center for evaluation of progressive dyspnea. Echocardiography showed severe MR and mild left ventricular dilation with reduced ejection fraction of 40%. Transesophageal echocardiography (TEE) showed severe MR from 2 regurgitant jets (Figure 1A, Video 1); one MR jet was centered between A2 and P2 (A2/P2), whereas the other jet was placed through the residual anterior leaflet cleft laterally. Three-dimensional (3D) TEE revealed a thickened mid-A2 segment and a cleft between A2/A1 with distorted anterior mitral leaflet shape (Figure 1B). Given the patient’s high surgical risk and severe chronic lung disease, the heart team decided to attempt transcatheter repair using a MitraClip.

Initially, an NTR MitraClip was placed at the A2/P2 scallops medial to the residual cleft (Figure 1B), which eliminated the central MR jet (Figure 1C, right, Video 2). However, there appeared to be moderate residual MR lateral to the clip secondary to the mitral cleft (Figure 1C, left). A second NTR MitraClip was then aligned...
perpendicular to the first clip and deployed between A1/A2 at the base with adequate tissue grasp, thus closing the cleft (Figure 1D, left, E; Supplemental Figure 1; Video 2). This transformed a trileaflet MV with cleft (A1, A2/A3, and P1/P2/P3) to a double-orifice functional bileaflet MV (Figure 1D, right) with 1+ residual MR (Figure 1F, Video 2). The transmitral mean gradient was 5 mm Hg, and there was significant improvement in the pulmonary venous flow pattern (Supplemental Figure 2).

This case illustrates some unique aspects. The usual approach to implant a second MitraClip would be to grasp it as parallel as possible lateral to the first clip (2). In the present case, the A1/A2 cleft limited the grasp of a second clip immediately adjacent to the first clip. Thus, this novel approach, implanting the second MitraClip so that it grasped the cleft scallops (perpendicular to the initial clip), resembles the surgical repair and could be an effective strategy to decrease residual MR in challenging anatomies.

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The authors have reported that they have no relationships relevant to the contents of this paper to disclose.
REFERENCES

1. Arnold SV, Chinnakondepalli KM, Spertus JA, et al. Health status after transcatheter mitral-valve repair in heart failure and secondary mitral regurgitation: COAPT trial. J Am Coll Cardiol 2019; 73:2123–32.

2. Willemsen HM, van den Heuvel A, Schurer R, et al. Mitral cleft repair by mitraclipping. Eur Heart J 2014;35:1021.

KEY WORDS mitral cleft, MitraClip, mitral regurgitation

APPENDIX For supplemental videos, please see the online version of this paper.
A Mitral Cleft Treated by Clipping
Is That the Future?*

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Mitral regurgitation (MR) is the most common valvular disease worldwide and causes serious complications such as excess mortality and frequent heart failure for affected patients (1). MR standard treatment is surgical replacement or repair of the mitral valve, which are life-saving in many circumstances. Despite these successes, many patients (85%) diagnosed with MR in the community are not offered surgical treatment throughout their lifetime (2) and are left to incur the frequent untoward consequences of MR (Figure 1, top row). MR undertreatment, while predominant in functional MR, is considerable in all MR forms and has led to the development of transcatheter mitral valve therapies for those in whom mitral surgery is undesirable, risky, or simply not performed. Despite the complexity of the native mitral valve structure, the simple edge-to-edge mitral repair device, implanting a clip at the tip of the mitral leaflets to create a bridge between them, is the most used and most successful nonsurgical device to treat patients with MR. Recently, treatment of functional MR using this device has been proven in a randomized clinical trial to significantly reduce the recurrence of heart failure in patients with left ventricular dysfunction. In patients with organic MR (i.e., with intrinsic mitral valve lesions causing the MR), the proof of benefit is much weaker but has gained Food and Drug Administration approval in patients at prohibitive risk for surgery.

In this issue of JACC: Case Reports, Russo et al. (3) report a very unusual case of organic MR, with very unusual utilization of the MitraClip (Abbott Laboratories, Menlo Park, California) to treat the MR. What were the circumstances, what was the therapy and what lessons can we learn? Russo et al. (3) discussed a patient with ostium primum atrial septal defect and congenital anterior mitral cleft previously treated by surgery, with success on the shunt but less success on the mitral valve with residual MR post-surgical repair due to a persistent cleft, and who was treated transcatheter by MitraClip implantation with success.

The first question arising pertains to “the cleft.” This wording is often poorly used. One should distinguish the real clefts that are congenital, are located at the central long axis of the anterior leaflet and much more exceptionally of the posterior leaflet and due to improper development of endocardial cushions with most often an ostium primum atrial septal defect. In patients with complex congenital heart disease, the cleft is often associated with malposition of chordae and is difficult to correct. Even in isolated cleft leaflets, the fibrosis affecting the lip of the cleft borders makes the correction difficult, and residual MR may be present with notable clinical complications. The congenital clefts should be distinguished from cleft-like indentations. These indentations separate the scallops of the posterior leaflet (the anterior leaflet is not scalloped) and can be deep, mostly visible in single-scallop prolapse of the posterior leaflet (4) and potentially may cause recurrent MR post-repair of the prolapse.

An important issue regards imaging of the lesions, as both true clefts and indentations are difficult to diagnose by 2-dimensional echocardiography, emphasizing the central role (Figure 1) of

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*Editorials published in JACC: Case Reports reflect the views of the authors and do not necessarily represent the views of JACC: Case Reports or the American College of Cardiology.

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3-dimensional transesophageal echocardiography (TEE) in the difficult anatomic evaluation of patients with MR of unclear mechanism. 3D TEE is central to selecting the most appropriate treatment modality of patients who cannot undergo surgery. During surgery, the surgeon has a direct view of the lesions and their location, which is not available with transcatheter treatment. This fundamental difference, whereby all evaluations for transcatheter therapies with no direct visualization of lesions, requires imaging, mostly with 3D TEE not only to direct the intervention, but also to select the most appropriate intervention (5,6). The increasing use of 3D TEE allows more cases to be diagnosed before surgical or percutaneous intervention (7).

The second question regards the intervention selected. Mitral surgery and now percutaneous interventions involve a wide array of single-action procedures (e.g., implantation of artificial chordae or edge-to-edge attachment) that respond to the lesions uncovered and allow correction of the MR. The MitraClip approximates anterior and posterior leaflet, preventing a prolapse or a gap due to tenting and was considered contraindicated when the leaflets were too separated, the lesions too commissural, or when a cleft or indentation was present. The large experience accumulated over the years has shown that wider separation can be addressed with clips of longer arms or that commissural lesions can in fact be collapsed by clipping (Figure 1, lower part). However, a cleft has remained a contraindication to clipping the mitral valve because in its classic positioning it cannot address the discontinuity of the leaflet affected. Rare case reports have mentioned clipping both sides of the cleft. In the present case, the authors used an atypical positioning across the cleft, with success including appropriate control of the MR. The fact that this implantation was successful does not resolve whether this case (and the few others published) will remain anecdotic or whether atypical

After diagnosis of moderate/severe mitral regurgitation, avoiding the MR serious undertreatment requires imaging the MR cause/mechanisms with a particular emphasis on 3D transesophageal echocardiography if the lesions are unusual or poorly seen. Mitral surgery is the standard of treatment but mitral transcatheter therapies are increasingly performed whenever surgery is risky or with poor probability of success. Whether atypical lesions (right lower cartouche) will become more accessible to interventions remains to be determined. 3D = 3-dimensional; MR = mitral regurgitation; MVR = mitral valve replacement.

**FIGURE 1** Schema Showing Diagnosis and Treatment Options for Moderate-to-Severe MR

- Moderate/Severe Mitral Regurgitation
- Undertreatment
- Surgical treatment
- All anatomical Repair>Replacement
- 3D Echocardiography
- Adequate anatomy?
- Functional MR
- Degenerative MR
- Edge-to-edge repair
- Commisural lesion
- Annular/leaflet calcification
- Large flail gap/width
- Cleft vs indentation
- Percutaneous MVR

After diagnosis of moderate/severe mitral regurgitation, avoiding the MR serious undertreatment requires imaging the MR cause/mechanisms with a particular emphasis on 3D transesophageal echocardiography if the lesions are unusual or poorly seen. Mitral surgery is the standard of treatment but mitral transcatheter therapies are increasingly performed whenever surgery is risky or with poor probability of success. Whether atypical lesions (right lower cartouche) will become more accessible to interventions remains to be determined. 3D = 3-dimensional; MR = mitral regurgitation; MVR = mitral valve replacement.
Implantation of clips will become more widespread and will demonstrate durability.

In summary, the paramount consideration in patients with MR is the MR volume (or orifice size), which in all MR types, organic or functional, directly determines the excess mortality incurred by patients and requires MR quantitation. Next, in evaluating patients with MR, we aim at avoiding undertreatment and, if possible, at eliminating the MR by surgery or intervention, and for that purpose, understanding cause and mechanisms by appropriate imaging is essential. Although we are still far from the goal of eliminating MR undertreatment, new transcatheter therapies offer an array of choices supplemental to mitral surgery that may fulfill this goal in the future.

Irrespectively, our cardiology community needs to remain attentive to distinguish and separate the toys for interventionalists from the legitimate new ways of treating MR.

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**REFERENCES**

1. Nkomo VT, Gardin JM, Skelton TN, Gottlieb DS, Scott CG, Enriquez-Sarano M. Burden of valvular heart diseases: a population-based study. Lancet 2006;368:1005-11.
2. Dziadzko V, Clavel M-A, Dziadzko M, et al. Outcome and undertreatment of mitral regurgitation: a community cohort study. Lancet 2018;391:960-9.
3. Russo MJ, Garg A, Okoh A, et al. MitraClip implantation in a patient with post-surgical repair of primum atrial septal defect and residual mitral cleft. J Am Coll Cardiol Case Rep 2020;2:2027-9.
4. Mantovani F, Clavel MA, Vatury O, et al. Cleft-like indentations in myxomatous mitral valves by three-dimensional echocardiographic imaging. Heart 2015;101:1111-7.
5. Oguz D, Eleid MF, Dhesi S, et al. Quantitative three-dimensional echocardiographic correlates of optimal mitral regurgitation reduction during transcatheter mitral valve repair. J Am Soc Echocardiogr 2019;32:1426-14235.e1.
6. Thaden JJ, Malouf JF, Nkomo VT, et al. Mitral valve anatomic predictors of hemodynamic success with transcatheter mitral valve repair. J Am Heart Assoc 2018;7:e007315.
7. Narang A, Addetia K, Weinert L, et al. Diagnosis of isolated cleft mitral valve using three-dimensional echocardiography. J Am Soc Echocardiogr 2018;31:1161-7.

**KEY WORDS** 3-dimensional imaging, mitral valve, valve repair
Despite considerable efforts, gender disparity exists in cardiology all over the world. In the United States and the United Kingdom, approximately 50% of medical students and nearly 50% of internal medicine residents are female. Despite this, only 20% (United States) and 28% (United Kingdom) of cardiology fellows are female, and only 12% (United States) and 13% (United Kingdom) of board-certified cardiologists are women (1,2). There are limited data on female representation in cardiology in South America, Asia, Africa, and Australia.

The reasons for the under-representation of women in cardiology (WIC) are multiple (Figure 1). The primary objective for the collaboration of Global WIC-Early Careers is to improve female representation, for both cardiologists and patients. Our focus is directed primarily on 5 major issues we have identified, as described in Figure 1: the impact on the personal, professional, and academic life of female cardiologists and the personal and academic implications for female patients. The under-representation of women in cardiology has multiple far-reaching consequences. The quality of patient care is not only related to gender diversity in cardiology; there is also the issue of the ramifications on physicians’ well-being if the workplace lacks diversity (3). Women researchers in clinical trials are a predictor for the enrollment of female participants. The engagement of women in academia and collaboration with industry sponsors has the potential to offer a wide range of opportunities for female cardiologists, ranging from speaking, networking, and participation in research trials, resulting in higher professional visibility and the possibility for career advancement. Women also appear to have a lower likelihood of receiving guideline-based therapies.

As trainees and early career WIC, our aim is to raise awareness about the under-representation of women trainees, encourage women to pursue cardiology, and influence subspecialty selection and academic pursuits. We especially aim to seek mentorship from senior and more experienced WIC to help us improve the gender gap. Our intention is to work closely with other WIC associations and cardiovascular societies; to establish guidelines for flexible training, maternity and shared parental leave, and dedicated research time; and to create opportunities for more structured and predictable work schedules. We believe that a joint effort including both male and female representatives from diverse cultural backgrounds can promote increased representation of women on various committees and conference programs/panels and potentially create editorial/publication opportunities. Additionally, we recognize that there are particular challenges in the early careers of WIC. Global WIC wishes to support mentorship, flexible training in view of young families; networking opportunities; navigating early career challenges, research, publications; and enhancing the visibility of trainees and early career WIC worldwide. Our vision is to change the culture in cardiology to ensure gender, geographic, and cultural diversity and to plug the leaking pipeline. With support from the wider cardiology community, we desire to improve the professional and personal well-being of female cardiologists.
cardiologists. This will ultimately improve the care women cardiologists are able to deliver to a diverse group of patients and ensure the recruitment of more women into clinical trials, which will inform future guidelines.

THE FORMATION OF GLOBAL WIC–EARLY CAREER

Global WIC–Early Career was born out of the need to focus specifically on these multiple challenges. As trainees and early career WIC ourselves, we are better positioned to not only identify the precise challenges we encounter but also to reach out to international peers at similar stages in their careers, share experiences, and in doing so, devise and facilitate solutions to the identified challenges. Although the coronavirus-2019 pandemic has wreaked havoc in the lives of many of us, the enhanced virtual networking it availed is one we have worked to our advantage. WIC have always had to up themselves a notch in terms of productivity; hence, while on maternity leave, Sarah Birkhoelzer both applied for and secured her appointment as the British Junior Cardiologists Association WIC and Flexible Training representative. As fortune and a search for opportunity would have it, the use of Twitter linked to this role resulted in an almost simultaneous connection with 2 of her WIC colleagues, Aaysha Cader, based in Asia, and Sabeeda Kadavath, in North America. The result was the formation of Global WIC–Early Careers.

Despite geographic differences and having only met virtually, we felt a genuine connection with each other, further enhanced by our shared experiences of regularly encountered challenges and an unwavering passion for advocating for WIC globally. It became very evident that although we have common challenges, there is a diversity and uniqueness peculiar to each continent. Although the conversation surrounding the importance of recruiting and creating additional opportunities for WIC has been a topic of conversation for some time in Europe and North America, the issue remains largely unaddressed at a more grassroots level in certain regions of the world. In an effort to make this initiative truly international and inclusive, we reached out to 3 other WIC, Paola Morejon (South America), Nafisa El Sammani (Africa), and Louise Segan (Australia) to form a group representing the 6 continents (Figure 2). We subsequently wrote a manifesto and planned our launch project, which, by virtue of its virtual format, ensured equal opportunity for all WIC across the world to participate, thus obviating traditional challenges such as the need for travel and related expenses as well as time away from work and family.

LAUNCH PROJECT: CREATING OPPORTUNITIES AND ENHANCING VISIBILITY AND NETWORKING

We launched our inaugural project, a global WIC case report competition, which attracted more than 60 submissions across 6 continents from aspiring
cardiologists, trainees, and early career WIC. A global webinar was held on August 15, 2020, providing an international platform for 10 women from 6 continents and the opportunity to showcase their work to the global cardiology community. It was streamed live on Facebook and resulted in more than 80,000 impressions on Twitter. A subsequent virtual happy hour offered networking opportunities and collaboration for future projects. As a trainee/early career cohort, we are predominantly millennials, and we hope to harness to maximum potential the power of social media, especially Twitter (@global_WIC) and Facebook (Women in Cardiology Global Early Career) in reaching out to a global WIC community.

The launch event proved to be a platform of inclusion and diversity, and it offered amplification of scientific education, particularly for those in less advantaged regions of the world. Furthermore, the virtual format negated the commonly cited barriers including travel, funding restrictions, and family commitments. The webinar also successfully created a ripple effect of opportunities for the presenters. For WIC from low- and middle-income countries, this webinar opened up avenues for networking with global peers that did not previously exist. The winner of the case competition was invited to speak at a virtual event organized by the Victorian WIC, Australia.

THE FUTURE

Cardiovascular disease is the leading cause of death for women across the globe. The need for gender diversity in cardiology has never been greater—we need more women to advocate for our patients, to enhance their enrollment in clinical trials, and to advocate for access to education, health, and economic resources for disadvantaged populations: an important contribution to the community and society at large. Our efforts are geared toward not only plugging the leaky pipeline but also augmenting the number of women entering cardiology. We aspire to target women interested in medicine right from their formative years all through high school, college, and, eventually, medical school. We strive to support them by providing mentorship, resources, and networking opportunities. We have had the honor of connecting with renowned women cardiologists from across the globe, both as individuals and as part of various WIC collaborations, to discuss future projects. It will take an ongoing and concerted effort, and we are already indebted to the mentorship, advice, and support of mid- and late-career WIC who have supported us in this endeavor. The experience of those who have walked the path before us has been an invaluable resource and has provided a unique perspective to our vision, guiding us as we take the less traveled path.

Cardiology and medicine as a whole stand to benefit from diversity; a heterogenous workforce translates into better decisions and outcomes by virtue of varied creative and critical thinking. It fosters effective leadership and better advocacy for minority groups, including WIC. The future begins early in our careers, and Global WIC hopes to facilitate that, promoting a network of early career WIC globally.
because, after all, in our unity lies our collective strength.

**AUTHOR RELATIONSHIP WITH INDUSTRY**

The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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**REFERENCES**

1. Sinclair HC, Joshi A, Allen C, et al. Women in cardiology: the British Junior Cardiologists’ Association identifies challenges. Eur Heart J 2019;40: 227–31.
2. Lau ES, Wood MJ. How do we attract and retain women in cardiology? Clin Cardiol 2018;41:264–8.
3. Wallace JE, Lemaire J. Physician well being and quality of patient care: an exploratory study of the missing link. Psychol Health Med 2009;14:545–52.

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**KEY WORDS** collaboration, diversity, global, women in cardiology
Women Empowerment in Cardiology

The Pink International Young Academy of Cardiology

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“We must believe that we are gifted for something, and that this thing, at whatever cost, must be obtained.”

—Marie Curie (1)

It has been widely discussed that women across the world face multiple challenges when pursuing their career of choice. Medicine, as a competitive and evolving field of science, demands great sacrifice and extreme commitment. Cardiology puts extreme physical and psychological pressure on physicians, often testing the final limits of their endurance. For a variety of reasons, cardiology attracts women less than other subspecialties.

The lack of career progress, family responsibilities, radiation exposure and its impact on female reproduction, and the discrimination and sexual harassment that are still present today are among the most common challenges in the career path of every female doctor. Despite the improvement of gender disparities in the last few decades (2), women cardiologists are still struggling with all of these issues on a daily basis.

These challenges faced by each and every woman in cardiology and the uneven playing field motivated several like-minded and strong individuals to create an organization that will raise awareness and stand united for equal rights, which today we proudly call Pink International Young Academy (Pink IYAC).

The Pink IYAC project was initiated as a council under the International Young Academy of Cardiology (IYAC), a new international group free of membership fees that was established under the auspices of the Cardiovascular Academy (CVA) in July 2019 to promote the interests of all young female doctors working in the field of cardiovascular disease worldwide. IYAC, recognizing the valuable contributions of women in cardiology, promoted the creation of this group. Currently, more than half of the IYAC board members are women, and all board members (both women and men) support projects designed by Pink IYAC to encourage female cardiologists to be more active in the field and work on an equal basis to men.

Pink IYAC, as one of those, does not pretend to stand alone, but it truly believes each group may help women in different aspects of their careers and that unifying strengths would help in achieving higher results. For this reason, Pink IYAC has already started to collaborate with other organizations, such as Global WIC.

What makes Pink IYAC different from the others is its first aim to build a community where women who experience difficulties or obstacles can feel free to share their experiences; not only they will not be judged, but they will also be listened to by colleagues who have passed through similar situations and can provide support. It is a relief to find comfort in other people’s voices, and this is one of our aims. This is the first step toward identifying a problem and addressing its solution.

Furthermore, solutions and alternative pathways can be found if a wide network is present. The Pink IYAC, in fact, aims largely at improving the recruitment of talented young female researchers from across the globe, particularly those who have been...
locally underrepresented in research teams or struggle to enter the academic track.

Currently, academic female cardiologists are defined by the research they are performing and, consequently, the publications produced. However, for many women, it is not simple, because research is the result of teamwork, and often, women are excluded. Because of this, Pink IYAC is offering support for those female colleagues who have a project with great potential, both in terms of experienced researchers who would give suggestions on how to structure it and also in terms of people helping with data collection and/or writing manuscripts.

Pink IYAC is trying to promote projects while maintaining the authors’ identity the purpose of the group is to help female cardiologists develop their ideas and feel mentored, from the conception of a project up to the final version of the manuscript. We are very proud to have embraced a family culture with regular virtual meetings and active participation of all members.

Aware of the steps that had been taken the preceding months, Pink IYAC started coming together as an organization in November 2019. The first social meeting was held in December 2019 in Vienna, Austria, with the goal of encouraging more female cardiologists to join the group and with the result of transforming, in just a short time, the Pink IYAC group into a platform that allows female cardiologists to express themselves freely, participate in new projects, and foster support for their own projects. As a matter of fact, since the initial meeting, membership of the Pink IYAC group has increased rapidly, with many talented female cardiologists from around the world choosing to join (Figure 1).

Indeed, the recruitment of talented young female researchers from across the globe has allowed the beginning of many research projects that are currently under revision. The first steps of the group have been taken during the ongoing severe acute respiratory syndrome coronavirus 2 pandemic, with the intent to realize something useful for the doctors fighting against the disease. As a consequence, an inaugural paper (3) of Pink IYAC has been launched addressing several useful topics on this field, such as the influence of pregnancy on coronavirus 2019 mortality risk, the incidence of cardiomyopathy from coronavirus 2019 during pregnancy, the breastfeeding issues during the pandemic, and the difficulties of women working on the front lines with patients (3).

Moreover, in September 2020, Pink IYAC is going to be a vital part of the IYAC annual congress, having organized its own section, where it will interview female leaders as well as emerging female leaders from all over the world about their experiences. Additionally, we are going to organize joint webinars with other important women’s organizations to increase women’s voices in cardiology.

With regard to future goals, as the Pink IYAC community, we believe in looking into the next steps. This is reflected in our plans, where we strive to create trust and an unbreakable bond between us and the millions of women who want to collaborate with our community. Because the 21st century is a time when social media is brighter than ever before, we

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**ABBREVIATIONS AND ACRONYMS**

**CVA** = Cardiovascular Academy  
**IYAC** = International Young Academy of Cardiology  
**Pink IYAC** = Pink International Young Academy

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**FIGURE 1** The Pink IYAC Logo and the Countries Where Pink IYAC Is Currently Active
aim to be more active on all major social media platforms to ensure that we can reach all women around the globe. In addition, steps will be taken to bring Pink IYAC to the level of advancement where it can hold special sessions in its name at major conventions, such as at the annual conferences of European or American societies, where we hope it can shine as a significant community in the field of cardiology. Nevertheless, a mentoring program has been established where talented women will use their experiences in a one-to-one relation to help women who are facing hard times.

Last but not least, we hope that Pink IYAC meetings will be held in all countries around the world and become occasions where we can freely present our goals and the plans that we have for the future. In these meetings, we hope that all women of Pink IYAC take an active part in representing not only Pink IYAC but also their country by showing the world articles and case reports.

Thus, each and every goal we have for the future has one idea and one idea only: to help female cardiologists from all over the world. Regardless of what situations they might be in or what they are struggling with, our group must and will do whatever it is in its power to help all female cardiologist break through the obstacles in their paths toward achieving their full potential, which is so magnificent.

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REFERENCES

1. As quoted in Madame Curie: A Biography (1937) by Eve Curie Labouisse, Part 2, p. 116.
2. Kathryn D. Female cardiologists are rare, and make less than men. Health News. Published November 18, 2015. Available at: https://www.reuters.com/article/us-health-cardiology-women-profession-idUSKCN0T731920151118. Accessed September 2020.
3. Sabatino J, Moscatelli S, Rustamova Y, et al. Women’s perspective on the COVID-19 pandemic: walking into a post-peak phase. Int J Cardiol 2020 Aug 13 [E-pub ahead of print].
4. Sabatino J. Prey in heroes’ capes. J Am Coll Cardiol Case Rep 2020;2:1419-20.

KEY WORDS awareness, Pink International Young Academy, women in cardiology
Raft of Otters

Women in Cardiology: Let Us Stick Together

Purvi Parwani, MBBS, MPH,a Janet K. Han, MD,b Toniya Singh, MBBS,c Annabelle Santos Volgman, MD,d Julia Grapsa, MD, PHDe

Narrative A*

“It was all great while I was a timid trainee. As soon as I started making a little headway and was successful, I was seen as a competition. My success was deliberately not amplified. They (other women) would try to leverage their years of expertise to make my ideas sound dumb and undermine me in every possible way. I was told by my male friends “competition between women is fierce!”

Narrative B*

“A powerful woman in leadership decided to sideline me after my promotion. I was not given any invites or talks despite my talent, expertise, and service to the organization for many years.”

*Narratives taken from women in cardiology. Their identities have been kept confidential.

“There’s a special place in hell for women who don’t help each other.”

—Madeleine Albright (1)

It was Secretary of State Madeleine Albright who voiced this remark during a 2004 panel at Wellesley College while reflecting on women’s leadership (1). Albright intended for the quote to serve as a counterpoint to stereotypical workplace dynamics, where women have been forced to function as opponents to survive in a male-dominated world. Only 14% of general cardiologists were women in 2017 (2) and 24% of cardiology trainees in 2018 to 2019 were women (3). The notion of “women not supporting women” generally remains unvoiced in cardiology, yet is brought up often behind the closed doors. In a male-dominated field like cardiology, how can women in cardiology (WIC) expect to effectively fight against gendered inequalities if they are too busy fighting one another? Is the perception true or is it the conditioning due to differences in expected gender roles?

In this paper, we will take a deep dive into the perception of women not supporting one another and discuss its relevance to female cardiologists.

QUEEN BEE PHENOMENON: PERCEPTION OR REALITY?

The “queen bee phenomenon” is a phrase first coined over 50 years ago to describe female leaders who assimilate into male-dominated organizations (i.e., organizations in which most executive positions are held by men) by distancing themselves from junior women and legitimizing gender inequality in their organizations (4). The phrase is still quoted today probably due to gendered differences in the expectations and can be weaponized against women in the workplace (5). Contemporary literature and psychological studies in nonmedical fields have shed some light into the complex issue of workplace behavior among women.

A study in 2015 by the Columbia School of Business contends that the queen bee phenomenon is a myth. Looking at the behaviors in 1,500 companies over a...
20-year period, this study found that when women were in senior roles, they promoted other women, but when men were in senior roles, only one-half as many women were promoted to senior roles (6). In a study performed in university settings in the Netherlands and Italy (7), the authors investigated gender differences in 2 factors that may contribute to the under-representation of women among university faculty—work commitment of student scientists and perceptions of these levels of work commitment by faculty members. In both countries, male and female students generally reported being equally committed to different work aspects. However, only older female, but not younger female or male faculty members perceived their female students as less committed to their work than male students. Older female faculty also had a more masculine self-description than younger female faculty. These results were thought to be due to overall smaller number of older female faculty and reflection of their own difficult career journey into their gender-stereotypical perceptions of the female students.

Other studies looking at incivility in the workplace have found that women report significantly more female-instigated incivility compared with men, but there was no difference between men and women experiencing male-instigated incivility. They also found that women who exhibit dominant behaviors at work (agentic) were likely to report receiving uncivil treatment by other women. For agentic women especially, such incivility had damaging consequences, resulting in reduced job satisfaction, lower psychological vitality, and higher turnover intentions (8).

Women perhaps start their career with low gender identification and as they progress, experience a high degree of gender discrimination. As there are fewer women in leadership positions in general, women who reach the top position are often subjected to intense scrutiny (5). Do women in leadership adapt to perceive themselves as nonprototypical women due to such discrimination? One can wonder if in these studies, as women in leadership positions contradicted the warm and nurturing female gender norm, did their assertive behavior get misinterpreted as ruthlessness by other women (and men) (7)? Is it years of societal conditioning on expected gender roles that leads to the belief that assertive behavior is expected from men but not from fewer female leaders?

It is critical to acknowledge that the queen bee phenomenon may be the result of a gender-biased milieu in the workplace rather than the cause of gender discrimination (9).

WHY IS IT IMPORTANT TO STICK TOGETHER?

While WIC have been expressing their concerns regarding gender equality for years, WIC continue to face multiple obstacles. In many countries, due to cultural expectations, women are not able to progress professionally, and it is impossible for them to hold a leadership position. Even in developed countries, women are less likely to be hired and/or promoted because of their sex (10). Compensation inequities persist for WIC, despite several studies in the past decade demonstrating that large differences in physician salaries are found when stratified by sex (11).

Sexual harassment is a huge obstacle in women’s efforts for progress and has been demonstrated to worsen burnout and affect productivity (12). However, it is severely under-reported due to fear of stigmatization or retaliation.

Motherhood can be a very important part of a woman’s life, whether she is partnered or unpartnered. To this day, many women are still forced to choose between career or family, as there continue to be significant discrepancies in parental leave policies across the world. Furthermore, pathways should be created to allow women to continue to advance professionally while taking into account prioritization of family and family responsibilities. Women are also often unfairly and negatively labeled as emotional, hysterical, or aggressive for the same actions or behaviors that in a man may be called passionate, assertive, or ambitious, due to both conscious and unconscious biases (13). When the challenges of WIC at personal, organizational, or institutional levels are the same, the time has come for WIC to band together to the battle these common issues.

FRAMEWORK OF SUPPORT:
PROPOSED SOLUTIONS FOR THE NARRATIVES

“Raft of otters” is a model discussed by Piazza et al. (14); using the analogy of a group of otters that hold hands so as to not drift apart from each other, Piazza’s model focuses on creating a tight-knit circle of women who help, support, mentor, and sponsor each other by conducting honest and effective communication and successful team building exercises among women.

We strongly believe that the following framework may help women work effectively with one another, hopefully preventing the perception of women being unsupportive of other women (Figure 1).

MORE WOMEN IN LEADERSHIP. Women in medicine are not always truly empowered and supported to
lead freely, making it difficult for them to support other women (5). The published data show that women leaders hire more women to work for them compared to when men lead (15). This effect is the strongest when a woman leader is re-elected; when a woman does not have to worry about the security of her own role or position, she is able to advance and promote other women, who in turn, continue to promote more women, learning by example (15).

Leadership training for both sexes but particularly WIC should explicitly include not only why to mentor, but how to mentor and advocate for other WICs. As more WIC leaders rise to leadership positions and promote other WICs, the hope is that like the example above, continued sponsorship and further promotion of WIC will self-sustain.

**COMPETITION AND COMMUNICATION.** Studies find little evidence that women are more competitive toward other women compared with men (16). Healthy competition can provide motivation, foster growth, and lead to progress, and should be normalized. WIC should be encouraged to communicate frequently, openly, and honestly with one another to help foster supportive interpersonal relationships in the workplace. The published data suggest that the situation of conflict between women is seen much more problematic than between men (17). In case of conflict, all parties regardless of sex should have a period of introspection to understand if their own situational interpretation has been tainted by personal biases.

It is equally important to control the narrative of the workplace dynamics, particularly when speaking to others as this may provide a skewed impression of interaction between women (17).

**ORGANIZATIONAL/INSTITUTIONAL SUPPORT.** We recognize that the critical conversations about gender equality and equity within an organization or an institute are not always easy to carry out. Suggestions that may help ensure that the organizations and opportunities are free of gender bias include: organizational focus on gender-related equality; making the solution part of leadership success; and having a gender equality officer.

Organizational resource groups or affinity groups for women, preferably sponsored by senior female leaders or mentoring programs that pair aspiring women with female leaders, may also help reduce the gender biases and change the stereotypical views about gender role in cardiology. An example of a

![Figure 1: WIC Raft of Otters and Framework of Support](image)
support channel is the WIC Council at the American College of Cardiology. The goal of the council is to help women who may be a minority at their place of practice by connecting them with peers and WIC leaders who can act as mentors and sponsors, especially if mentorship and sponsorship are not otherwise readily available at their own locality or institution. In addition, WIC councils of various cardiovascular organizations could focus on collaborative efforts to continue to mentor and sponsor early career, midcareer, and more senior WICs both nationally and internationally.

**AMPLIFYING THE WIC VOICES.** Amplifying the success stories of the WIC, particularly the ones whose accomplishments may not be acknowledged, may help empower the WIC and navigate the workplace dynamics better.

**SOCIAL MEDIA.** With the growth of the cardiovascular community on social media, it has become easier for WIC to connect with one another, network, find sponsors and mentors, and even provide support virtually without the limitations of time or distance. Social media has become an important avenue for discussing WIC issues (18).

**CONCLUSIONS**

Women in cardiology can survive, thrive, and succeed the decades-long quest for professional equity by supporting one another. Forming the raft of otters will keep us united and create a critical mass that will help us reach our goal of equality and equity within our field of cardiology. As more female cardiologists rise in leadership, we should get past the concept of queen bees and believe in the power of amplification of other women that can bring upon the change.

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**AUTHOR RELATIONSHIP WITH INDUSTRY**

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**REFERENCES**

1. McCarthy T. Albright: “special place in hell” for women who don’t support Clinton. The Guardian 2016. Available at: https://www.theguardian.com/us-news/2016/feb/06/madeleine-albright-campaigns-for-hillary-clinton. Accessed August 31, 2020.

2. AAMC. Active Physicians by Sex and Specialty, 2017. Available at: https://www.aamc.org/data-reports/workforce/interactive-data/active-physicians-sex-and-specialty-2017. Accessed August 31, 2020.

3. Accreditation Council for Graduate Medical Education. ACGME Data Resource Book. Available at: https://www.acgme.org/About-Us/Publications-and-Resources/Graduate-Medical-Education-Data-Resource-Book. Accessed August 31, 2020.

4. Derks B, Van Laar C, Ellemers N. The queen bee phenomenon: why women leaders distance themselves from junior women. The Leadership Quarterly 2016;27:456–69.

5. Salles A, Choo EK. Queen Bee phenomenon: a consequence of the hive. Lancet 2020;395:940.

6. Cummins HA. Queen bees and mommy tracking: how’s an academic woman supposed to get ahead? Advancing Women in Leadership Journal 2012;32:79–91.

7. Ellemers N, van den Heuvel H, de Gilder D, Maas A, Bonvini A. The underrepresentation of women in science: differential commitment or the queen bee syndrome? Br J Soc Psychol 2004;43 Pt 3:315–38.

8. Gabriel AS, Butts MM, Yuan Z, Rosen RL, Siler MT. Further understanding incivility in the workplace: The effects of gender, agency, and communion. J Appl Psychol 2018;103:362–82.

9. Center for Creative Leadership. Why Women Pay a Price for Promoting Other Women. Available at: https://www.ccl.org/articles/leading-effectively-articles/queen-bee-women-pay-a-price-for-not-promoting-other-women/. Accessed August 31, 2020.

10. Oza NM, Lewis S, Breathett K. Women in cardiology: fellows’ perspective. J Am Coll Cardiol 2015;65:951–4.

11. Larson AR, Cawcutt KA, Englander MJ, et al. Representation of women in authorship and dissemination of analyses of physician compensation. JAMA Netw Open 2020;3:e201330.

12. Jaggi R, Griffith KA, Jones R, Perumalswami CR, Ubel P, Stewart A. Sexual harassment and discrimination experiences of academic medical faculty. JAMA 2016;315:2120–1.

13. Maloney ME, Moore P. From aggressive to assertive. Int J Womens Dermatol 2019;6:46–9.

14. Piazza J, Kass D. Olivia Otter Builds Her Raft. Brooklyn, NY: Feminem, 2018.

15. Arvate PR, Galilea GW, Todescat I. The queen bee: a myth? The effect of top-level female leadership on subordinate females. The Leadership Quarterly 2018;29:533–48.

16. Fanko K, Ellemers N, Derks B, Lorenzi-Cioldi F. Nothing changes, really: why women who break through the glass ceiling end up reinforcing it. Pers Soc Psychol Bull 2017;43:638–51.

17. Sheppard LD, Aquino K. Sisters at arms: a theory of female same-sex conflict and its problematization in organizations. J Manage 2017;43:691–715.

18. Patel H, Volgman AS. Women in cardiology: role of social media in advocacy. Curr Cardiol Rev 2020 Feb 2 [E-pub ahead of print].

**KEY WORDS** ACC WIC, raft of otters, WIC
Women as One is a nonprofit organization with the mission of promoting talent in medicine by providing unique professional opportunities to women physicians. With a start in cardiology, the overarching goal of the organization is to fortify the pipeline of women leaders in cardiology through novel retention and promotion programs and to amplify and unify the efforts of related global organizations striving to reach gender equity in the field.

Women comprise a disproportionately low number of cardiologists worldwide. In the United States, they represent only 14% of active cardiologists (1). In subspecialty areas such as interventional cardiology, that percentage falls to the single digits (1). Work has been done in recent years to explore why women do not choose to enter the field, with primary reasons pointing to culture: the perception that cardiology is a field lacking in family friendliness and professional advancement opportunities for women (2). Dig deeper, and more startling statistics unveil that women cardiologists are indeed paid less than their male counterparts, experience professional discrimination more frequently, and are subject to a multitude of biases that stall their publication, grant, and promotion attainment (3–5). Not only are these disparities unacceptable in and of themselves, but the cyclic nature of this underrepresentation and underrecognition prevents cardiology as a field from realizing the benefit of a diverse workforce.

Many of the global cardiovascular professional organizations have rightly recognized the lack of women in the field as a problem and, in response, have launched initiatives to draw awareness to and drive improvement in professional diversity and inclusion. These are important efforts that serve to solidify and catalyze the field’s commitment to attracting and retaining more women in cardiology. The American College of Cardiology, American Heart Association, and European Society of Cardiology in particular have stood out as having made strong, significant commitments at the leadership level to supporting and promoting women across organizational activities and within leadership. Many subspecialty societies have also made similar strides to highlight the women in their organizations, putting programming in place to support their advancement.

Given these now widespread efforts, the existence of an independent organization such as Women as One outside of the parameters of these professional organizations may seem duplicative. The nature of professional organizations, however, is inevitably somewhat competitive because their business models rely largely on membership dues, meeting registrations, and grant funding from a shared pool of stakeholders. The consequence of this competition is the isolation of groups focused on gender equity in cardiology from each other; the lack of coordination across these efforts subsequently dilutes attempts to shine light on gender-based disparities and diminishes the overall ability to create lasting mechanisms for systemic change. Furthermore, the missions of cardiovascular professional organizations are not exclusively focused on women, because these organizations serve the entire cardiovascular community and the many educational, research, and advocacy-based needs across their constituencies. This means that efforts to address gender-based professional disparities falls on a longer priority list and may not be addressed with the urgency of other organizational priorities.

The premise of and need for Women as One is, therefore, to create a single global platform, exclusively focused on women, through which women can...
unite and succeed. The foundation of the organization is its Talent Directory, a sortable online database of women in cardiology. The database is used to gather feedback, share opportunities, and dive into the professional needs and preferences of women in cardiology worldwide. The Talent Directory feeds into Women as One annual programming, which currently includes a global awards program (the Escalator Awards) and procedural skills training program (CLIMB), both aimed at increasing the speed at which women in cardiology are resourced and positioned for leadership development.

Additional Women as One programming is driven by the fundamental need to attract and retain women in the field of cardiology. A radiation safety educational slide series was recently released as a first-in-kind effort to comprehensively outline radiation safety practices and abate concerns about radiation exposure for women considering entering the field. The educational slides were endorsed by 7 major global cardiovascular societies and are complemented by downloadable posters to display in work environments. A global parental leave survey was also recently launched. With such wide variances in parental leave and return-to-work practices around the world, the goal of the survey is to uncover trends and best practices so that they can be shared broadly and, ideally, set the stage for standardizing and normalizing parental leave for all cardiologists. A similar effort is also taking shape around the varied process associated with academic promotion, knowing that women account for disproportionately fewer full professors in cardiology in the United States (6).

Future Women as One efforts will focus on developing a global research network, producing research training, funding, and trial participation opportunities for women around the world. Women unsurprisingly represent a disproportionately low number of clinical trialists in cardiology. In a recent review of more than 200 cardiovascular trials, more than one-half were executed through leadership structures devoid of female physicians (7). Furthermore, only 10% of resulting publications from these studies had a first or senior female author (7). These disparities highlight the lack of women in positions to affect clinical research design and execution and their resulting impact on patient care. The goal of Women as One is to produce fruitful and ultimately impactful solutions to improve these metrics so that women can realize a seat at the table of future evidence generation.

The opportunity of Women as One is not limited, however, to the women who participate in its framework. By building a global network of women in cardiology, Women as One offers a tremendously valuable resource to partners, including professional organizations, medical device and pharmaceutical companies, and other stakeholder organizations in cardiology. The opportunity to quickly access the names and qualifications of women cardiologists who are eager to participate in educational and research activities can be of incredible import to those organizations looking to diversify the profile of the physicians who participate in these activities on their behalf. As diversity becomes a business imperative, those organizations that succeed in achieving diversity goals will maintain a distinct advantage in attracting and retaining new business growth for the future.

Beyond the matching function of the Talent Directory, Women as One also provides partner organizations with a much deeper opportunity to fully understand the interests and insights of women. Culling and sharing intelligence from women unleashes new ideas, new perspectives, and new paths that have the potential to shape the future of areas such as clinical trial design, innovation, and, ultimately, patient care. By creating a single source of this intelligence through the Talent Directory, there unfolds an opportunity to tap into these novel findings and drive new models of success across all cardiovascular stakeholders, thus catapulting the speed at which the field realizes true gender equity.

The Women as One vision is one of reciprocity. When women are put in a position to succeed, everyone succeeds. Women as One programming is aimed at positioning women for this collective success and opens its doors to all who are looking to achieve and expand on this shared goal.

To learn more about Women as One, visit www.womenasone.org.

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REFERENCES

1. Association of American Medical Colleges. 2018 physician specialty data report. Available at: https://www.aamc.org/data-reports/workforce/interactive-data/active-physicians-sex-and-specialty-2017. Accessed September 2020.

2. Douglas PS, Rzeszut AK, Bairey Merz CN, et al. Career preferences and perceptions of cardiology among US internal medicine trainees: factors influencing cardiology career choice. JAMA Cardiol 2018;3:682-91.

3. Shah RU. The $2.5 million dollar wage gap in cardiology. JAMA Cardiol 2018;3:674-6.

4. Mehta L, Sharma G, Douglas P, Rzeszut AK. Discrimination and harassment in cardiology: insights from the 2019 American College of Cardiology Global Professional Life Survey. J Am Coll Cardiol 2020;75 Suppl 1:3631.

5. Witteman HO, Hendricks M, Straus S, Tannenbaum C. Are gender gaps due to evaluation of the applicant or the science? A natural experiment at a national funding agency. Lancet 2019; 393:531-40.

6. Blumenthal DM, Olenksi AR, Yeh RW, et al. Sex differences in faculty rank among academic cardiologists in the United States clinical perspective. Circulation 2017;135:506-17.

7. Denby KJ, Szpakowski N, Silver J, Walsh MN, Nissen S, Cho L. Representation of women in cardiovascular clinical trial leadership. JAMA Intern Med 2020:e202485.

KEY WORDS cardiology, disparities, equity, gender
Belkin et al. (1) describe the impact of calcium phosphorus metabolism in the development of a cardiomyopathy. The investigators conclude that chronic renal disease should also be included when thinking about the origin of a cardiomyopathy.

We also identified a case of myocardial calcifications in a new orthotopic heart transplantation which developed within the first week after implantation in an otherwise normal heart. As Belkin et al. (1) elegantly highlight, these findings are rare and can precipitate systolic and diastolic dysfunction (2). In our center the patient received an allograft from a 28-year-old donor without significant comorbidities, and normal creatinine, calcium, and phosphorus levels. The cause of death was gunshot wound to the head with no injury to the chest. Within the first 24 h, the patient developed primary allograft dysfunction; and later on they developed multiorgan failure. A chest computed tomography scan revealed pneumonia and severe fine calcifications of the left ventricular myocardium that were not present at procurement (Figure 1). Relevant laboratory testing showed hypercalcemia and hyperphosphatemia suggestive of secondary hyperparathyroidism in the setting of renal failure and anemia. The transthoracic echocardiogram showed an ejection fraction of 30% with normal left ventricle size and thickness. Surveillance endomyocardial biopsy specimens on day 7 showed no evidence of acute cellular or antibody mediated rejection; but they had significant areas of myocardial calcium deposition. Unfortunately, the patient died of respiratory complications and no autopsy was performed.

Multifactorial settings such as recipient with pre-transplantation hyperphosphatemia, complicated post-operative course with sepsis, immunosuppression, and renal failure precipitated the calcification at a very fast pace. This could represent a tale of caution in the pre-surgical stage in which ongoing metabolic imbalances can also affect the new allografts with deleterious consequences. We agree with Belkin et al. (1) that vigilant monitoring and management of the calcium metabolism can prevent dysfunction, but we caution about the speed in which deposition can manifest, especially in complex transplantation patients.

FIGURE 1 Interval Progression of Myocardial Calcifications Evidenced by Computed Tomography

(A) Donor’s computed tomography scan at the time of procurement. (B) Computed tomography at day 7 after orthotopic heart transplantation showing fine myocardial calcifications.
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All authors have reported that they have no relationships relevant to the contents of this paper to disclose.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors’ institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the JACC: Case Reports author instructions page.

REFERENCES

1. Belkin MN, Dela Cruz M, Nadeem U, Patel AR, Kim G, Grinstein J. Massive myocardial calcium deposition: hardened heart. J Am Coll Cardiol Case Rep 2020;7:996-1003.
2. Shackley BS, Nguyen TP, Shivkumar K, Finn PJ, Fishbein MC. Idiopathic massive myocardial calcification: a case report and review of the literature. Cardiovasc Pathol 2011;20:e79-83.

Electrical Weapons and Electrophysiology

Drs. Barbhaiya and Johar wrote excellent expositions on the first documented case of an implantable cardioverter-defibrillator (ICD) shock due to conducted electrical weapon (CEW) discharges (1,2).

To appreciate the rarity of the event, there have been more than 4 million field uses of just the TASER brand (Axon, Scottsdale, Arizona) of CEW.

CEW use reduces the non firearm arrest-related death rate by 59% to 66%, consistent with the two-thirds reduction in rearm fatalities in agencies where CEW use was not overly restricted (3). The 2 key injury studies, collecting collectively more 40,000 uses of force, found that the CEW reduced subject injury by 65% to 78% (4).

It is misleading to state that CEW use is associated with asystole. Asystole is the most common cardiac arrest rhythm with drug and alcohol abuse, but it is not inducible with electrical stimulation (5). Hence, any association is artificial.

The editorial suggests a risk of myocardial capture and cites a report of a prison rioter having an asymptomatic elevated heart rate during a CEW discharge to the chest. That was not direct capture but, rather, the result of the pacemaker housing funneling some CEW charge directly into the right ventricle via the pacemaker lead (6).

Of greater concern is the repetition of the myth that humans have ever been electrocuted by a CEW. All present TASER CEWs deliver <2 W, which satisfies the 5 to 7 W allowed by the UL electric fence standard (UL, Northbrook, Illinois), as well as the international (International Electrotechnical Commission, Geneva, Switzerland) and the European (CENELEC, Brussels, Belgium) 2.5-W limit. They also satisfy the CEW-specific American National Standards Institute (Washington, DC) CPLSO-17. All TASER brand CEWs satisfy all relevant electrical safety standards and, thus, neither injury nor electrocution is expected or has ever been confirmed.

Both the report and the editorial cite a series of 8 expert-witnessing cases. What was not cited, however, was the invited case-by-case refutation of those 8 cases and 4 other published anecdotes (7).

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Dr. Kroll is a member of Axon’s Scientific and Medical Advisory Board and is on Axon’s corporate board. Drs. Calkins and Luceri are members of Axon’s Scientific and Medical Advisory Board. Dr. Witte has reported that he has no relationships relevant to the contents of this paper to disclose.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors’ institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the JACC: Case Reports author instructions page.

REFERENCES

1. Barbhaiya CR, Moskowitz C, Duraiswami H, et al. Inappropriate ICD shock as a result of Taser Discharge. J Am Coll Cardiol Case Rep 2020;2:1166-9.
2. Johar S. A shocking tale. J Am Coll Cardiol Case Rep 2020;2:1170-2.
3. Ferdik FV, Kaminski RJ, Cooney MD, Sevigny EL. The influence of agency policies on conducted energy device use and police use of lethal force. Police Q 2014;17:328-58.
4. Kroll M, Brave M, Pratt H, Witte K, Kunz S, Luceri R. Benefits, risks, and myths of TASER® handheld electrical weapons. Hum Factors Mech Eng De- fense Saf 2019;3:7.
5. Paredes VL, Rea TD, Eisenberg MS, et al. Out-of-hospital care of critical drug overdoses involving cardiac arrest. Acad Emerg Med 2004;11:71-4.
We appreciate the kind words of Dr. Kroll and colleagues regarding our case report highlighting the circumstances under which implantable cardioverter-defibrillator (ICD) shock may result from conducted energy weapon (CEW) discharge, such as the TASER device (Axon Enterprise, Inc., Scottsdale, Arizona) (1). Our expertise, and the focus of our report, is in cardiac electrophysiology. Thus, our report focused on the technical aspects of ICD tachyarrhythmia detection algorithms and the circumstances that would lead to inappropriate ICD therapy delivery. Although the less-lethal nature of CEW use is well accepted, there remains debate within the scientific community regarding the degree and nature of injury that may result from CEW discharge. We appreciate the perspective of Dr. Kroll and colleagues, who as members of the corporate, scientific, and medical advisory boards of Axon Enterprise, Inc., the manufacturer of TASER brand devices, attest to the relative safety of these devices in their letter to the editor and prior responses to reports of CEW-related injury. Speaking as physicians and citizens, we are concerned that the letter from Dr. Kroll and colleagues may downplay the important public health issues addressed in the editorial (2).

CEW use can directly result in death through cardiac arrest. A training bulletin issued by the manufacturer of the Taser device acknowledges that the risk of sudden cardiac arrest related to Taser discharge is not zero but, rather, “extremely low” (3). The reduction in power delivery in more recent models is acknowledged by the manufacturer to have a “significantly improved safety margin” (4). Furthermore, there is evidence that, in addition to being used to avoid lethal force, many U.S. police agencies deploy CEWs more routinely to subdue unarmed, noncompliant, or disturbed individuals who do not pose a serious danger to themselves or others. (5) Reassurance that the CEW death rate is low disregards the potential harms that may result from CEW discharge (4,6). A full appreciation of device risks and benefits is, therefore, made difficult or impossible.

ALARA (as low as reasonably achievable) is a concept embraced within the cardiology community regarding medical radiation use. Although the risk of radiation exposure related to medical imaging is “extremely low,” it is not zero. Because the benefits of this radiation are clear, we aim to minimize harm while optimizing benefit. Similarly, we believe that our case report contributes to the body of evidence suggesting that although there is a role for CEW use in law enforcement, its use should be ALARA.

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors’ institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the JACC: Case Reports author instructions page.

REFERENCES

1. Barbhaiya CR, Moskowitz C, Duraismwami H, et al. Inappropriate ICD shock as a result of TASER discharge. J Am Coll Cardiol Case Rep 2020;2:1166–9.
2. Johar S. A shocking tale. J Am Coll Cardiol Case Rep 2020;2:1170–2.
3. TASER International. Training bulletin 15.0 medical research update and revised warnings. 2009 2009. Available at: https://media.cdn.lexipol.com/pdfs/TASER_Media_Bulletin.pdf. Accessed August 23, 2020.
4. Gilbert C, Caputo A, Hing G. When Tasers fail. APM Reports. Available at: https://www.apmreports.org/episode/2019/05/09/when-tasers-fail. Accessed August 23, 2020.
5. Amnesty International USA. Excessive and lethal force? Amnesty International’s concerns about deaths and ill-treatment involving police use of TASERS. Available at: https://www.amnestyusa.org/reports/usa-excessive-and-lethal-force-amnesty-internationals-concerns-about-deaths-and-ill-treatment-involving-police-use-of-tasers/. Published March 26, 2011. Accessed August 23, 2020.
6. Berardini N, Stroud M. A shot to the heart. The Intercept. Available at: https://thintercept.com/2016/06/07/tased-in-the-chest-for-23-seconds-dead-for-8-minutes-now-facing-a-lifetime-of-recovery/. Published June 7, 2016. Accessed August 23, 2020.
When I was appointed as Editor-in-Chief of *JACC: Case Reports*, I realized the huge responsibility that keeps me well motivated each day. I feel accountable to my editorial board members for their well-being and to make the editorial process thoughtful and enjoyable; to the authors for honoring their work and providing them appropriate feedback; and, finally, to the Editor-in-Chief of *JACC*, Dr. Valentin Fuster, and the rest of the team within the *JACC* family of journals, who have provided helpful suggestions and advice from the first day. However, it is also my responsibility to maintain the high standards of quality of the *JACC* family. Thus, I feel it is my duty to explain in detail the editorial process and provide transparency about how a manuscript is assessed.

1. **INITIAL QUALITY CHECK**

When an author submits a manuscript on behalf of an author group, the editorial office does an initial quality check. That is why we encourage authors to carefully read the author instructions. Fairness is a priority, so we maintain standards for the word count and the number of the authors to treat all authors equally. If a paper successfully passes through the quality check, then it is “checked in” and moves to the editor-in-chief.

2. **EDITOR-IN-CHIEF READS THE MANUSCRIPT**

The next person to adjudicate the manuscript is the editor-in-chief, who provides a few comments on the manuscript. If there are important features missing, such as videos for the respective figures that are crucial for peer review, then we may ask the authors to provide them. Again, we encourage authors to read the instructions as we have listed videos as a necessary feature of a clinical case.

3. **ASSOCIATE OR DEPUTY EDITOR RECEIVES MANUSCRIPT TO ALLOCATE REVIEWERS**

When the manuscript is about to undergo peer review, the editor-in-chief sends the manuscript to an associate editor who specializes in the topic area. This is a second stage during which an associate editor may feel that the manuscript does not warrant publication or that there were important pitfalls. If that is the case, then the associate editor will provide his/her comments, and the manuscript will be sent to the editorial board agenda. If the manuscript is determined to merit peer review, we then allocate reviewers who are experts in the field. Typically, *JACC* journals’ associate editors invite 2 reviewers, but it is at the discretion of members of the editorial board to choose more reviewers or not, if they feel that the existing reviews are insufficient. Furthermore, we do not allow comments that lack collegiality to reach the authors—the aim of a review is to be constructive to each other.

4. **EDITORIAL BOARD MEETING**

Once a week, the editorial board, including the deputy and associate editors together with the editor-in-chief, holds a meeting to discuss all pending manuscripts that are decision-ready. We often have long agendas, sometimes approximately 50 pages to adjudicate all of the papers we managed within a week. Therefore, the communal discussion allows for transparency on whether papers need further discussion before a decision is made, or whether they are ready to be accepted, revised, or rejected. Most
importantly, we take the time to discuss the manuscripts one by one through a democratic process. One person cannot decide on their own, but altogether we gather a consensus on whether each manuscript is worthy of publication.

We welcome inquiries regarding manuscript decisions from authors. However, it is important to note that the appropriate forum for this discussion is in an e-mail to the editorial office (jacccr@acc.org), whereby staff will coordinate communications regarding decisions, publication timing of accepted papers, and so on. We request that authors avoid contacting members of the editorial board via social media or text message, as it is not the appropriate forum for this discussion. We also encourage feedback on content from readers, but prefer to consider that discourse in the form of a letter to an editor, which allows for the peer review process and the invitation of an author response. In the world of publishing, where we strive for fairness and transparency, texting an editor-in-chief directly on social media is not a professional approach. It is not fair for the readers, the authors, or the editors—some of whom may not have social media—and to remove the quality controls that are upheld during the editorial process to promote fairness. I hope by explaining the editorial process that our authors and readers will understand our reasonings. The meeting every week is a democratic approach to reaching an agreement on what is of value for the scientific community and, of course, meets the Journal’s objectives.

5. FINAL DECISION: REGARDLESS OF THE RESULT, DO NOT GET DISCOURAGED

In the final stage, the manuscript’s decision letter will be drafted and sent to the author. Importantly, if the decision is to reject the manuscript, the authors should not be discouraged, but should view the decision as an opportunity to submit to another journal. As an example, for the most important publication of my life, it took approximately 10 e-mails back and forth with the journal to make it acceptable for publication. If the decision is to revise, then try to handle the revision as thoroughly and quickly as possible, as it has been shown that the earlier you submit the revision, the better for you and your manuscript. If you have any questions, make sure you ask for help from the editorial office rather than submitting a revision that is inappropriately revised.

WHAT HAPPENS IF AN AUTHOR IS A MEMBER OF THE JACC: CASE REPORTS EDITORIAL BOARD OR HAS AN INSTITUTIONAL CONFLICT?

An important part of the editorial process is what happens if a member of the editorial board or authors from my institution submit a manuscript. The answer is simple: I never see the manuscript, nor does it go to a JACC: Case Reports associate or deputy editor. The manuscript will be allocated to a guest editor-in-chief who will designate guest associate editors and reviewers. All decision-making is made by the guest editors. If a manuscript is submitted from one of the deputy/associate editors’ institutions, the associate/deputy editor recuses himself/herself from the discussion of the paper during the editorial board meeting, to ensure that he/she does not influence the discussion. Commonly, the person hangs up and rejoins when we finish the discussion about the specific manuscript. This is one more step toward seeking fairness inside the editorial process.

As I mentioned earlier, we seek to ensure that everyone within the editorial process feels valued: our Associate/Deputy Editors, editorial consultants, guest editors, reviewers, and of course, the authors. On every manuscript, we aim to provide constructive feedback, but our priority is the maintenance of fairness, objectivity, and the elimination of scientific misconduct. Thus, although we had the opportunity to bombard our readers with coronavirus disease-2019 (COVID-19) manuscripts, we decided to act sensibly and to publish only the most interesting and educational cases from around the globe—as the first case reports journal to have a call for COVID-19 cases and also to help the authors publish their findings, by waiving any publication fees and expediting the peer review process. We will always aim to maintain the high quality of JACC journals to demonstrate a well-proven cause-causation relationship. In publishing, it is easier to mass produce manuscripts rather than spending time selecting the best of the best. Although it was hard work to be selective in light of the higher number of submissions, we published the special issue on COVID-19 cases in July 2020 with only the highest-quality submissions.

FINAL TIPS FOR AUTHORS

- Make sure you read the author instructions carefully.
- If you have any questions, always contact the editorial office (jaccr@acc.org).
- Watch the video of our webinar on “How To Write A Case Report” (1) before you submit. This is an important first step prior to the submission.
- Do not be discouraged if the decision of the journal is not the desired outcome. Collect feedback and plan your next move.
- Remember: Every effort, every experience—either positive or negative—is an opportunity for you to grow as cardiovascular clinicians and researchers.

We are grateful for your trust and support. This has been a great year, and we promise to do our best to encourage the authors and make the editorial process a positive publishing experience.

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REFERENCE

1. American College of Cardiology. JACC: Case Reports: how to write a case report. Available at: https://www.youtube.com/watch?v=9tk7u8HfEO/. Accessed September 20, 2020.