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Prosthetic Valve Endocarditis From *Trichosporon asahii* in an Immunocompetent Patient

Lizy Marial Paniagua, MD,a Deepthi Sudhakar, MD,b Lara Erika Perez, MD,c David Miranda, MD,d,e Pedro Urena, MD,c Igor Gregoric, MD,1 Biswajit Kar, MD,1 Hani Jneid, MD,b,g Jonalis Ramirez, MD,h David Paniagua, MD,b,g

**ABSTRACT**

Fungal endocarditis is a rare clinical entity. This report describes an unusual case of fungal endocarditis caused by infection with *Trichosporon asahii* in a 20-year-old immunocompetent man who received the diagnosis 1 year following biological aortic valve replacement. (Level of Difficulty: Beginner.) (J Am Coll Cardiol Case Rep 2020;2:693–6)

Our patient is a 20-year-old man with a history of severe aortic stenosis who underwent biological aortic valve replacement (AVR) with an EPIC valve (St. Jude Medical, Minneapolis, Minnesota), with no immediate post-operative complications. His medical history was negative for human immunodeficiency virus infection, diabetes mellitus, neutropenia, malignant disease, or connective tissue diseases. One month following surgery, the patient noted drainage of serous fluid from his sternal wound. He was treated with topical antibiotics with resolution of the drainage. One year following AVR, he was admitted for low-grade fever and erythematous macules on his palms, soles, and conjunctiva. The initial work-up included a negative transesophageal echocardiogram (TEE) and negative blood cultures. Because of the high clinical suspicion of bacterial endocarditis, he was subsequently treated with 2 weeks of intravenous vancomycin and gentamicin, followed by long-term oral antibiotics.

One month following initiation of antibiotics, our patient presented with recurrent fever, nausea, and severe headache. Vitals signs were stable on admission. Physical examination demonstrated small, erythematous, macular lesions consistent with Janeway lesions on bilateral palms and soles (Figure 1A). Cardiopulmonary examination was remarkable for a systolic ejection murmur and a diastolic decrescendo murmur. Neurologic examination was significant for right-sided weakness in upper and lower extremities.

**LEARNING OBJECTIVES**

- To understand the risk factors for fungal endocarditis.
- To highlight the role of multidisciplinary management of fungal endocarditis.

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and right quadrantanopia. Laboratory examination was significant for leukocytosis (white blood count: 13.85 × 10 cells/mm³) with eosinophilia (eosinophils: 25.41%).

1. HOW IS INFECTIVE ENDOCARDITIS DIAGNOSED?

The presentation of infective endocarditis is often variable and requires a high index of suspicion. The Duke criteria, which incorporate serological, physical, and imaging findings, is recommended to risk stratify patients into 3 categories of definite, possible, and rejected diagnosis (1). A minimum of 3 sets of blood cultures obtained from different sites with an interval of at least 1 hour between the first and last set is recommended (1). Echocardiography plays a crucial role in the diagnosis and must be performed expeditiously, ideally within 12 h of initial evaluation (1). If the clinical suspicion of endocarditis is high and the initial transthoracic echocardiogram (TTE) findings are negative, a repeat TTE or a TEE should be performed. The use of other imaging modalities such as computed tomography and cardiac magnetic resonance imaging (MRI) may also play an important role (1). Intraoperatively, immediate identification of the pathogen using polymerase chain reaction has also proven useful (1). Figures 1A to 1E show the various manifestations of endocarditis in our patient.

MRI of the brain showed multiple embolic lesions in the right occipital and left parietal lobes with hemorrhagic transformation (Figures 1D and 1E). The patient was restarted on vancomycin, gentamicin, and rifampin while further work-up was conducted. Findings on an initial TEE were negative. However, computed tomography of the chest demonstrated a lesion above the prosthetic aortic valve. A repeat TEE 2 days following admission showed large vegetations on the anterior wall of the aorta, and this finding was confirmed with MRI of the chest. The patient was subsequently taken to surgery for treatment of infective endocarditis. Following surgery, intravenous amphotericin was started.

2. WHAT ARE THE OPTIONS FOR VALVE REPLACEMENT IN FUNGAL ENDOCARDITIS?

Our patient received an EPIC bioprosthetic valve, which was chosen on the basis of on patient and family preference. The patient was reluctant to take warfarin, and there was concern for the risk of hemorrhagic conversion with anticoagulation. Selection of a replacement valve is based on consideration of life expectancy, patient preference, compliance with anticoagulant agents, lifestyle, risk of bleeding, and risk of recurrent surgery (2). The patient’s age alone should not be the determining factor. Structural valve dysfunction over time, leading to regurgitation or stenosis, is the major disadvantage of bioprosthesis valves and the major reason for repeat intervention.

3. WHAT IS THE TIMING OF SURGERY FOR INFECTIVE ENDOCARDITIS IN THE SETTING OF STROKE?

The management of complications of infective endocarditis or neurological sequelae is controversial. Cerebrovascular complications secondary to embolization from endocardial vegetations have a 20% to 40% incidence and are associated with an increased risk of post-operative morbidity and mortality (1,3). Guidelines from the American Heart Association and the European Society of Cardiology recommend delaying surgery for at least 4 weeks following intracranial hemorrhage (1,3,4). Results of a previous retrospective study demonstrated higher mortality when valve replacement was performed within 7 days of intracranial hemorrhage (5). Our patient’s brain lesions were embolic with hemorrhagic transformation, which raised concern regarding the use of high-dose heparin during the surgical procedure. Following extensive discussions with the patient, family members, and the multidisciplinary care team, the decision was made that the benefit of surgery outweighed the risks. The patient tolerated the surgery without complications, and MRI performed following surgery showed no evidence of hemorrhage or enlargement of prior lesions.

Intraoperatively, a vegetation measuring 10 mm was discovered on the anterior wall of the aorta, and a perforation was noted on 1 leaflet of the EPIC valve. The valve was replaced, and the anterior wall was patched with bovine pericardium. A wet mount of the vegetation showed numerous hyphae, and the final pathology examination that showed positive results for *Trichosporon asahii* yielded the diagnosis of fungal endocarditis (Figure 1B).

4. WHAT IS THE ORIGIN OF FUNGAL ENDOCARDITIS?

The etiologic agents most frequently isolated are *Candida* and *Aspergillus* (6). The genus *Trichosporon* currently contains 37 recognized species, of which 8 are associated with infection or allergy: *T. asahii*, *T. asteroides*, *T. cutaneum*, *T. inkin*, *T. mucoides*, *T. ovoides*, *T. domesticum*, and *T. montevideense* (6,7).
Fungal endocarditis is a rare clinical entity that has been associated with prior drug use, indwelling catheters, prosthetic valves, or immunocompromised states (1,6). Trichosporon infection can lead to disseminated fungal infection in immunocompromised individuals, particularly in patients with malignant disease (8). Fungal infection with *T. asahii* carries a grave prognosis with a high mortality rate (1,8). Invasive *Trichosporon* infections have been associated with prior antibiotic therapy, a history of central catheter use, malignant disease, and hospitalization in intensive care units (8). The route by which *T. asahii* invades the human body remains unknown, however (8,9). One prior study of *Trichosporon* infections determined that blood, urine, and surgical wounds were the most common sites of infection, and *T. asahii* was the most frequently isolated species (8). This study also identified neutropenia, central venous catheters, malignant disease, surgical wounds, and male sex as risk factors for infection. We believe that the surgical wound was the likely source of infection in our patient. Few reports have described *T. asahii* infection of heart valves. Our review of publications yielded 1 report of *T. asahii* endocarditis of the mitral and aortic valve, and the patient was treated with fluconazole and valve replacement (9).

### 6. HOW IS FUNGAL ENDOCARDITIS MANAGED?

Infections with *Trichosporon* spp. are susceptible to treatment with amphotericin B, ketoconazole, and itraconazole. However, evidence suggests an emerging resistance to treatment because of the formation of biofilms (10). Our patient was successfully treated with amphotericin B, ketoconazole, and voriconazole. Current guidelines recommend treatment of fungal endocarditis with valve surgery in addition to parenteral antifungal therapy, followed by lifelong suppressive therapy with an azole agent (1).
Following valve replacement, our patient received intravenous treatment with amphotericin B and ketoconazole for 2 weeks. He was then transitioned to an 18-month course of oral voriconazole: 400 mg 3 times a day for 6 months, followed by 400 mg twice a day for 6 months, and 400 mg daily for 6 months. Our patient made a complete recovery without further complications. A repeat TTE showed normal function of the new prosthetic valve, without vegetations, and an intact anterior wall pericardial patch. Antifungal therapy was stopped on the basis of normalization of biological markers of inflammatory response and brain and cardiac imaging findings. On recent follow-up 5 years after surgery, and 31/2 years after stopping voriconazole, the patient remains stable without clinical or laboratory evidence of recurrent infection. Repeat blood cultures, C-reactive protein values, and erythrocyte sedimentation rate were unremarkable. His neurological condition improved in the first 2 weeks of treatment and completely normalized to the point that the patient graduated from college with a major in engineering.

The current case illustrates a distinctive presentation of fungal endocarditis from *T. asahii* infecting an immunocompetent man with a history of bioprosthetic AVR. Our patient presented 1 year following his initial valve replacement and was treated for a sternal wound infection, which is a recognized risk factor for fungal endocarditis (8). The patient’s first signs of disease were skin lesions localized to the palms of the hands and soles of the feet. Although the skin manifestations were very suggestive of endocarditis, the presence of negative blood culture results made the diagnosis of endovascular infection particularly challenging. The duration of treatment is also poorly understood. This case highlights the importance of consideration of fungal endocarditis in patients with prosthetic valves.

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**REFERENCES**

1. Baddour LM, Wilson WR, Bayer AS, et al. Infective endocarditis in adults: diagnosis, antimicrobial therapy, and management of complications: a scientific statement for healthcare professionals from the American Heart Association. Circulation 2015;132:1435-86.
2. Saito M, Oren A. Aortic valve replacement: choice between mechanical valves and bioprostheses. J Card Surg 2008;23:299-306.
3. Morris NA, Mafioli M, Lyons JI, Samuels MA. Neurologic complications in infective endocarditis. Neurohospitalist 2014;4:213-22.
4. Okita Y, Minalata K, Yasuo S, et al. Optimal timing of surgery for active infective endocarditis with cerebral complications: a Japanese multicentre study. Eur J Cardiothorac Surg 2016;50:374-82.
5. Habib G, Lancellotti P, Antunes MJ, et al. 2015 ESC Guidelines for the management of infective endocarditis: the Task Force for the Management of Infective Endocarditis of the European Society of Cardiology (ESC). endorsed by: European Association for Cardio-Thoracic Surgery (EACTS), the European Association of Nuclear Medicine (EANM). Eur Heart J 2015;36:3075-128.
6. Mattev P, Revet M, Lefort A, Michelet C, Lortholary O. Fungal endocarditis: current challenges. Int J Antimicrob Agents 2014;44:505-11.
7. Mekha N, Sugita T, Ikeda R, et al. Genotyping and antifungal drug susceptibility of the pathogenic yeast Trichosporon asahii isolated from Thai patients. Mycopathologia 2009;169:67-70.
8. Ruan S, Chien J, Hsu M. Invasive trichosporonosis caused by Trichosporon asahii and other unusual Trichosporon species at a medical center in Taiwan. Clin Infect Dis 2009;49:e11-7.
9. Isu K, Hisata Y, Hazama S. A rare case of infective endocarditis complicated by Trichosporon asahii fungemia treated by surgery. Ann Thorac Cardiovasc Surg 2009;15:350-3.
10. Iturrieta-Gonzalez IA, Padovan ACB, Bizerra FC, Hahn RC, Colombo AL. Multiple species of Trichosporon produce biofilms highly resistant to triazoles and amphotericin B. PLoS One 2014;9:e109555.
Takayasu Arteritis With Extensive Cardiovascular, Neurovascular, and Mesenteric Involvement

Adam Custer, MD,* Nicholas Villano, MD,* Deepak Ravi, MD, Hilary Shapiro, MD, Tanaz Kermani, MD, Henry M. Honda, MD

ABSTRACT

Takayasu arteritis is a rare large vessel vasculitis with an incidence of 1 to 3 per million. This disease typically involves the aorta and its primary branches but has been found to involve the coronary arteries in 7% to 9% of cases. We highlight the need for prompt diagnosis and treatment. (Level of Difficulty: Beginner.) (J Am Coll Cardiol Case Rep 2020;2:697–701) © 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 33-year-old man was recently diagnosed with Takayasu arteritis (TA) after a 1-year history of postprandial abdominal pain, a 40-pound unintentional weight loss, and moderate renal insufficiency. Computed tomography imaging at that time revealed significant mural thrombosis and stenosis of the aortic arch and great vessels (Figures 1A and 2A), severe stenosis of the distal aorta with involvement of the mesenteric arteries, and bilateral renal artery stenosis (Figure 3). His symptoms improved with high-dose prednisone (40 mg/day for 2 weeks, 30 mg/day for 2 weeks, and 20 mg/day thereafter), but 4 months later he presented with intermittent confusion and blurry vision.

PAST MEDICAL HISTORY

The past medical history included hypertension, chronic kidney disease, and multivessel TA.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis included acute ischemic stroke, central nervous system infection, vasculitis, carotid artery stenosis, and coronary artery disease.
INVESTIGATIONS

In the emergency room, he was afebrile with stable vital signs. Magnetic resonance imaging revealed a new subacute infarct in the right posterior cerebral artery distribution. Magnetic resonance angiography disclosed near complete occlusion of both carotid arteries with extensive collateral formation. Initial work-up also revealed an elevated troponin of 19.3 ng/ml and ischemic electrocardiogram changes despite no angina. Additional blood tests including antinuclear antibodies, antineutrophil cytoplasmic antibodies, erythrocyte sedimentation rate, C-reactive protein, and lipid panel were unrevealing. Chest computed tomography and head and neck magnetic resonance angiography showed evidence of disease progression (Figures 1B and 2B). Coronary angiography revealed triple vessel disease with complete occlusion of the ostial left anterior descending artery, proximal and distal left circumflex artery, and mid and distal right coronary artery (Figures 4 and 5).

MANAGEMENT

The patient was treated with aspirin, cangrelor, and a heparin drip, with plans for emergent cardiac catheterization. The mid right coronary artery was stented to improve collateral filling of the left anterior descending artery as a temporizing measure, with plans for possible coronary artery bypass grafting. To reduce myocardial demand from persistent tachycardia and hypertension, he was started on nitroglycerin and esmolol drips. He was also started on prednisone 30 mg, with plans to discuss the need for high dose steroids. However, the patient’s hospital course was complicated by a jejunal perforation on hospital day 6 that was surgically managed with a partial jejunal resection. His post-operative course was complicated by peritonitis, which was managed with broad-spectrum antibiotics. He later developed dysmetria and worsening confusion for which repeat magnetic resonance imaging revealed extension of his cerebral infarcts to involve the bilateral temporal and occipital lobes as well as the left parietal lobe. After discussion with family, he was transitioned to comfort care and passed on hospital day 17. Autopsy revealed widespread aortic and branching arterial wall thickening and irregularity, confirming the diagnosis of TA. It also revealed significant chronic inflammatory changes involving the coronary arteries (Figure 6).

DISCUSSION

TA is a rare large-vessel vasculitis that affects the aorta and its primary branches. It is a poorly understood, chronic inflammatory disease that predominantly affects young female patients (1–3). The early inflammatory phase involves constitutional symptoms including fevers, chills, night sweats, and arthralgias. The chronic phase involves inflammatory changes of the aorta and its branches, resulting in vascular bruits, claudication, decreased pulses, renovascular hypertension, myocardial and mesenteric ischemia, and neurovascular compromise. Diagnosis is primarily based on the presence of symptoms in the setting of imaging showing disease involvement of the aorta and its main branches (3). Elevated erythrocyte sedimentation rate and C-reactive protein may support the diagnosis; however, one study of 60 TA patients found erythrocyte
sedimentation rate to be normal in 28% of patients with clinically active disease and in 44% of those with disease remission (4). In 1990, the American College of Rheumatology developed diagnostic criteria for TA, with a reported specificity 97.8% and sensitivity of 77% to 90% if a patient demonstrates 3 of 6 characteristics: age of onset before 40 years, extremity claudication, decreased brachial pulse, systolic blood pressure differential of over 10 mm Hg in the arms, a subclavian or aortic bruit, and an abnormal arteriogram. Currently, validation of a broader Diagnostic and Classification Criteria for Vasculitis is underway (5).

The primary treatment for active disease is high-dose glucocorticoids, while maintenance therapy involves tapering of steroids in combination with immunomodulatory and biologic agents, such as methotrexate or azathioprine (6). Many patients experience relapse or disease progression despite treatment, with estimated relapse rates of ~40% (6). A recent randomized controlled trial of 36 TA patients in remission assigned to placebo or the novel interleukin-6 receptor antagonist tocilizumab showed a trend toward increased time to relapse without reaching significance (p = 0.0596) (7). Surgical options for those with vascular
FIGURE 4  Coronary Angiography of Left Coronary Artery Showing Significant Diffuse Sclerosis

FIGURE 5  Coronary Angiography of Right Coronary Artery Before Stenting Showing Significant Diffuse Sclerosis

FIGURE 6  Histology Examination From Autopsy

(A) Aortic wall with marked intimal fibrous thickening without inflammation (hematoxylin and eosin [H&E] stain, original magnification ×2.5), (B) left anterior descending artery with fibrous obliteration of lumen (trichrome stain, original magnification ×40), (C) serial section of the left anterior descending artery stained by H&E showing absence of inflammation in the fibrous obliteration of the lumen (H&E, original magnification ×40), and (D) higher magnification showing only focal chronic inflammatory infiltrate of lymphocytes and macrophages (ovals, H&E stain, original magnification ×100).
complications include stenting or bypass grafting, although restenosis in areas of active tissue inflammation poses significant concern. One study reports restenosis in 31.7% of surgical interventions, with decreased incidence when performed after medical therapy or during a quiescent stage of disease (8).

The patient’s multiorgan involvement presented a unique diagnostic and therapeutic challenge. Coronary artery involvement is seen in only 7% to 9% of cases and typically results in ostial occlusion, unlike the diffuse triple-vessel stenosis seen in this case (1,9). Treatment can be challenging, as coronary artery revascularization in TA is often unsuccessful due to ostial involvement, active inflammation, and high rates of restenosis (10,11). Although enhanced atherosclerosis has been reported with TA, this was not seen in this patient (10). Autopsy revealed chronic inflammatory changes in the coronary arteries, suggesting that earlier immunosuppression or immunologic therapy may have slowed the progression of disease.

CONCLUSIONS

The diagnosis of TA remains challenging, owing to its indolent nature and nonspecific symptoms, which may belie significant underlying vascular damage. Early diagnosis is essential as immunosuppression may slow disease progression.

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REFERENCES

1. Watanabe Y, Miyata T, Tanemoto K. Current clinical features of new patients with Takayasu arteritis observed from cross-country research in Japan: age and sex specificity. Circulation 2015;132(7):701–9.
2. Lupi-Herrera E, Sánchez-Torres G, Marcushamer J, Mispireta J, Horwitz S, Vela JE. Takayasu’s arteritis. Clinical study of 107 cases. Am Heart J 1977;93:94–103.
3. Arend WP, Michel BA, Bloch DA, et al. The American College of Rheumatology 1990 criteria for the classification of Takayasu arteritis. Arthritis Rheum 1990;33:1129–34.
4. Kerr GS, Hallahan CW, Giordano J, et al. Takayasu arteritis. Ann Intern Med 1994;120:919–29.
5. De Souza AW, De Carvalho JF. Diagnostic and classification criteria of Takayasu arteritis. J Autoimmun 2014;48-49:79-83.
6. Hoffman GS, Leavitt RY, Kerr GS, Rottem M, Sneller MC, Fauci AS. Treatment of glucocorticoid-resistant or relapsing Takayasu arteritis with methotrexate. Arthritis Rheum 1994;37:578–82.
7. Nakaoka Y, Isoe M, Takei S, et al. Efficacy and safety of tocilizumab in patients with refractory Takayasu arteritis: results from a randomised, double-blind, placebo-controlled, phase 3 trial in Japan (the TAKT study). Ann Rheum Dis 2018;77:348–54.
8. Park MC, Lee SW, Park YB, Lee SK, Choi D, Shim WH. Post-interventional immunosuppressive treatment and vascular restenosis in Takayasu’s arteritis. Rheumatology (Oxford) 2006;45:600–5.
9. Amano J, Suzuki A. Coronary artery involvement in Takayasu’s arteritis. Collective review and guideline for surgical treatment. J Thorac Cardiovasc Surg 1991;102:554–60.
10. Rav-Acha M, Plot L, Peled N, Amital H. Coronary involvement in Takayasu’s arteritis. Autoimmun Rev 2007;6:566–71.
11. Kuijer A, Van Oosterhout MFM, Kloppenbug G, Morshuis WJ. Coronary artery bypass grafting in Takayasu’s disease-importance of the proximal anastomosis: a case report. J Med Case Rep 2015;9:283.

KEY WORDS: coronary artery disease, Takayasu arteritis, vascular disease
MINI-FOCUS ISSUE: INTERVENTIONAL CARDIOLOGY AND CORONARY PATHOLOGIES

CASE REPORT: CLINICAL CASE

Supporting High-Risk Percutaneous Coronary Interventions With Mechanical Devices

Stephen E. Wilkinson, MD,a Duane C. Berkompas, MD,b Justin S. Fanning, MD,b Hanna S. Park, MDc

ABSTRACT

The use of mechanical circulatory support to maintain appropriate hemodynamics in high risk percutaneous coronary intervention cases is a new frontier. Treatment of cases that were once considered prohibitive may now be possible. Due to a paucity of data, guidelines offer no guidance about the use of mechanical circulatory support in such cases. This case, the first documented case of extracorporeal membrane oxygenation support for percutaneous coronary intervention (PCI) of a vein graft supplying the entire coronary circulation, adds to the medical literature demonstrating a likely benefit in the use of mechanical support during high risk PCI in patients without shock. (Level of Difficulty: Intermediate.) (J Am Coll Cardiol Case Rep 2020;2:702–4) © 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/).

PRESENTATION

A 62-year-old man presented to an outside hospital with complaints of resting and exertional interscapular back pain over the past few weeks that had progressed. These complaints were consistent with prior stable anginal-equivalent pain but were no longer responsive to nitroglycerin therapy. The patient had a blood pressure 109/70 mm Hg, and he was bradycardic with heart rate 47 beats/min and saturations 97% in room air. On physical examination, he had normal rate, regular rhythm, normal heart sounds, and intact distal pulses. Exam revealed no gallop and no friction rub.

LEARNING OBJECTIVES

- To recognize the correlation between PCI in lesions supplying large territories of myocardium and the risk for ventricular decompensation and failure.
- To consider the role of novel mechanical circulatory support during PCI for hemodynamically stable patients undergoing PCI with 1 vessel supplying their coronary circulation.

From the aSpectrum Health/Michigan State University Cardiovascular Disease Fellowship, Grand Rapids, Michigan; bSpectrum Health Medical Group, Department of Cardiovascular Care, Grand Rapids, Michigan; and the cSpectrum Health/Michigan State University Cardiothoracic Surgery Fellowship, Grand Rapids, Michigan. Dr. Berkompas is a consultant for Medtronic and Boston Scientific. All other 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.

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ventricular tachycardia with an implanted cardioverter-defibrillator for primary prevention, hypertension, hyperlipidemia, and transient ischemic attack. The CABG had been performed solely with vein grafts: one to the left anterior descending, one to the right coronary artery, and one as a jump graft to both the first and the second obtuse marginal arteries. A left heart catheterization performed 2 years previous to his presentation showed subtotally occluded left main and right coronary arteries and totally occluded vein grafts to the right coronary artery and to the left anterior descending.

DIFFERENTIAL DIAGNOSIS. Differential included myocardial infarction (both type I and type II), aortic dissection, and noncardiovascular pain including musculoskeletal pathologies.

INVESTIGATIONS. Serum troponin level was elevated. Given the consistency of the pain with the patient’s previously stable angina, coronary angiography was performed. This showed ostial left main and proximal right coronary artery chronic total occlusions with a saphenous vein graft (SVG) to the obtuse marginal branch artery as his only remaining conduit supplying essentially his entire coronary circulation through distal collateral vessels. The patient graft had 2 high-grade lesions in the proximal and mid-to-distal portions (Figure 1, Video 1).

MANAGEMENT. The patient was transferred to the authors’ tertiary facility for evaluation and a discussion about redoing the sternotomy and CABG versus performing high-risk percutaneous coronary intervention (PCI). The advanced heart failure team met with the patient and discussed possible left ventricular assist device implantation. He emphatically declined long-term mechanical circulatory support (MCS) but accepted the proposition of short-term mechanical assistance. A nuclear myocardial viability study showed viability only in the circumflex territory. The cardiothoracic surgery team declined to redo the sternotomy.

After serial discussions, a joint plan was made by the cardiology and cardiothoracic surgery teams to pursue extracorporeal membrane oxygenation (ECMO)-supported PCI. As the patient’s cardiac function was completely dependent upon 1 SVG, it was felt that Impella support (AbioCor, Danvers, Massachusetts) would be insufficient for augmenting cardiac output should he experience significant cardiac decompensation during the PCI, as this could quickly lead to biventricular failure.

Both teams were present on the day of the procedure in the catheterization laboratory. A 25-F venous ECMO cannula was placed in the right femoral vein, and a 19-F arterial cannula was placed in the left femoral artery. After ECMO support was initiated, PCI of the SVG was performed with balloon angioplasty and stenting of both discrete lesions (Figure 2, Video 2). There were no immediate complications. The patient was weaned from ECMO support, and decannulation was performed in the catheterization laboratory. The patient was transferred to the intensive care unit and received low-dose inotropic support that was rapidly tapered. He was discharged 3 days later and was able to walk hundreds of feet without any chest discomfort.

DISCUSSION

There are increased risks of ventricular decompensation and eventual failure when myocardial territories have decreased perfusion during percutaneous interventions. The larger the at-risk area becomes, the less favorable the risk:benefit ratio for intervention becomes. Many nonsurgical patients have anatomy that is considered too high risk for attempting intervention, as operators may feel that there is no reasonable expectation against mortality with the risks of intervention in these patients. Looking at the role of MCS in shock lends some hope for future developments that will improve that risk:benefit ratio.

ECMO, for example, has shown a life-saving role in the treatment of some patients with cardiogenic shock (1). The American College of Cardiology/American Heart Association’s ST-segment elevation
myocardial infarction (STEMI) guidelines have a Class IIa recommendation for use of MCS in STEMI patients with unstable hemodynamics (2). The European Society of Cardiology’s myocardial revascularization guidelines have a Class IIb recommendation for short-term use of MCS in patients with acute coronary syndromes and unstable hemodynamics (3). New research is bringing light to its role in supporting high-risk PCI in patients without shock (4–7).

However, there are no current guideline recommendations for or against MCS in hemodynamically stable patients.

**FOLLOW-UP.** After his initial recovery period, the patient went home in good condition and has continued to follow-up with his medical team outside of the authors’ healthcare system.

**CONCLUSIONS**

As with other forms of MCS, ECMO support for nonshock, high-risk PCI is terrain still being charted in the modern era. The practice is increasingly substantiated by case reports and case series. Studies of patients with non-STEMI without cardiogenic shock have been promising. After reviewing PubMed and Google Scholar, the authors believe this is the first report of a successful ECMO-supported PCI of an SVG to preserve a patient’s only remaining viable myocardium. This case adds to a growing body of medical literature in support of further research of MCS during coronary interventions. It is anticipated that future research will be able to help guide the role of MCS in patients without shock who require PCI.

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**REFERENCES**

1. Hajjar LA, Teboul JL. Mechanical circulatory support devices for cardiogenic shock: state of the art. Critical Care 2019;23:76.
2. O’Gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHA guidelines for the management of ST-elevation myocardial infarction. J Am Coll Cardiol 2013;61:e78–140.
3. Neumann FJ, Sousa-Uva M, Ahlsson A, et al. ESC scientific document group, 2018 ESC/EACTS guidelines on myocardial revascularization. Eur Heart J 2019;40(2):87–165.
4. Parr CJ, Sharma R, Arora RC, Singal R, Hiebert B, Minhas K. Outcomes of extracorporeal membrane oxygenation support in the cardiac catheterization laboratory. Catheter Cardiovasc Interv 2019 Sep 5 [E-pub ahead of print].
5. Tomasello SD, Boukhris M, Ganyukov V, et al. Outcome of extracorporeal membrane oxygenation support for complex high-risk elective percutaneous coronary interventions: A single-center experience. Heart Lung 2015;44:309–13.
6. Pender P, Gibbs O, Faru A, et al. Mechanical circulatory support for semi-elective PCI in high-risk patients with extracorporeal membrane oxygenation (ECMO) compared to Impella heart pump device. Heart Lung 2019;28:5414.
7. Wang W. 16 ECMO and MCS for patients undergoing PCI: experience from Taipei veterans General Hospital. Heart Asia 2019;11:A7.

**KEY WORDS** cardiac assist devices, myocardial infarction, myocardial revascularization, percutaneous coronary intervention

**APPENDIX** For supplemental videos, please see the online version of this paper.
Embolic Stroke Caused by Aortic Ruptured Plaque and Thrombus Visualized by Angioscopy

Yoshiharu Higuchi, MD, a Atsushi Hirayama, MD, a Sei Komatsu, MD, b Kazuhisa Kodama, MD b

ABSTRACT

Aortogenic embolization is among the major mechanisms of cryptogenic stroke. Angioscopic surveillance of the aortic wall clearly visualized the existence of thrombi and spontaneously ruptured plaques, which dynamically liberated embolic materials. (Level of Difficulty: Beginner.) (J Am Coll Cardiol Case Rep 2020;2:705–6) © 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/).

An 84-year-old woman was transferred for acute stroke. Five years ago, she underwent a graft replacement for an ascending aortic aneurysm. Brain magnetic resonance imaging showed acute cerebral infarction (Supplemental Figure 1A). No carotid and intracranial arteriosclerotic changes were observed (Supplemental Figure 1B). She had no history of atrial fibrillation. Transesophageal echocardiography revealed no intracardiac thrombus (Supplemental Figure 1C).

The brain-heart team in our institute diagnosed this as embolic stroke of undetermined source, and surveillance of aortic wall was performed for embolic source detection. We examined aortic (and prosthetic graft) wall from the ascending graft to the proximal descending aorta with a nonobstructive general angioscopy (1) (Figure 1A). Thrombi were found on the ascending graft (Figure 1B, Videos 1 and 2), and spontaneously ruptured plaques were found on the arch and the proximal descending aorta (Figure 1C, Videos 3 and 4). It was clearly visualized that the ruptured plaques incessantly liberated embolic materials including thrombi. These findings suggested that this embolic stroke of undetermined source case was caused by aortogenic mechanism. She was prescribed aspirin 100 mg and edoxaban 30 mg, and no recurrence of cerebral infarction has been observed.

Informed consent of the patient was obtained for this case.

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REFERENCE

1. Komatsu S, Yutani C, Ohara T, et al. Angioscopic evaluation of spontaneously ruptured aortic plaques. J Am Coll Cardiol 2018;71:2893–902.

KEY WORDS: angioscopy, embolic stroke, ruptured plaques, thrombus

APPENDIX: For supplemental figures and videos, see the online version of this paper.
MINI-FOCUS ISSUE: INTERVENTIONAL CARDIOLOGY AND CORONARY PATHOLOGIES

IMAGING VIGNETTE: CLINICAL VIGNETTE

Coronary Artery Occlusion Caused by Intramural Hematoma Due to In-Stent Dissection

Yasushi Ueki, MD, Lorenz Räber, MD, Ph.D, Raminta Kavaliauskaite, MD, Tatsuhiko Otsuka, MD, George C.M. Siontis, MD, Ph.D

ABSTRACT

A 54-year-old man developed ST-segment elevation myocardial infarction 1 week after percutaneous coronary intervention of the left anterior descending artery. Optical coherence tomography at the emergent percutaneous coronary intervention revealed an intramural hematoma extending from the in-stent dissection. We highlight that in-stent dissection, although generally considered a benign finding, can extend and cause intramural hematoma, resulting in coronary artery occlusion. (Level of Difficulty: Intermediate.) (J Am Coll Cardiol Case Rep 2020;2:707–8)

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A 54-year-old man with previously known coronary artery disease and percutaneous coronary intervention (PCI) of the distal left anterior descending artery (LAD) 4 years ago underwent invasive coronary angiography because of non-ST-segment elevation myocardial infarction. The coronary angiography revealed a de novo high-grade stenosis of the proximal LAD (Video 1), which was treated in an optical coherence tomography (OCT)-guided PCI with a cobalt-chromium everolimus-eluting stent (3.5 × 33 mm). According to pre-PCI OCT measurements, post-dilatation with a noncompliant balloon (4.5 mm, 20 atm) for the proximal stent segment and kissing balloon technique for LAD (3.5 mm) and the diagonal branch (2.0 mm) were performed. Final angiography and OCT revealed an optimal stent expansion (≈95%) and apposition with a minor in-stent dissection (Figures 1A and 1B, Videos 2 and 3) but neither dissection/hematoma at the diagonal ostium nor distal stent edge (Figures 1C to 1E).

The minor in-stent dissection was decided to be managed conservatively without additional post-dilatation during the index intervention. The patient was discharged the following day under dual antiplatelet therapy with aspirin 100 mg daily and prasugrel 10 mg daily. He was normotensive during the initial hospitalization under long-term antihypertensive therapy with an angiotensin-converting enzyme inhibitor. One week after the index PCI, the patient was urgently admitted to the hospital because of acute chest pain. The electrocardiogram showed ST-segment elevations in anterior leads. Emergent coronary angiography showed a subtotal occlusion distal to the recently implanted stent (Figure 1F, Video 4). After pre-dilatation of the occluded...
segment with a 2.0-mm balloon, OCT revealed an intramural hematoma (Figures 1H to 1J, Supplemental Figure 1, Video 5) extending from the in-stent dissection (Figure 1G) to the stent implanted 4 years ago. The in-stent dissection was now more pronounced compared with observations made at the index PCI. No other dissections in the mid-LAD between the 2 stents were detected, which could have been the trigger for the intramural hematoma. These findings suggest that the in-stent dissection extended to the stent distal and caused intramural hematoma, leading to coronary artery occlusion. The coronary flow was completely restored after implantation of an additional drug-eluting stent (2.75 × 48 mm) overlapping the 2 previously implanted stents in the proximal and distal LADs (Video 6).

Although in-stent dissection is generally considered a benign complication after PCI (1,2), operators should note that in-stent dissection can extend to the distal segment and cause intramural hematoma in a subacute setting, resulting in coronary artery occlusion (3). Nevertheless, it is challenging to associate in-stent dissection with hematoma at the time of PCI if no hematoma can be identified. High-pressure post-dilatation aiming to compress the in-stent dissection should be considered. Further investigations are needed to better understand the mechanism and management of this rare but critical condition.

**FIGURE 1** Coronary Angiography and OCT Findings

(A) Angiography after stent implantation (3.5 × 33 mm) to the proximal left anterior descending artery. Optical coherence tomography (OCT) showed the minor in-stent dissection (B, white arrow) but neither dissection/hematoma at the diagonal ostium (C) nor distal stent edge (D and E). (F) Angiography 1 week after the index percutaneous coronary intervention showed subtotal occlusion distal to the implanted stent. (G) In-stent dissection (white arrow) was more pronounced compared with that observed at the index percutaneous coronary intervention (B). (H and I) Hematoma (asterisk) was confirmed around in-stent dissection. (J) Circumferential hematoma (asterisk) causing significant luminal stenosis.

**REFERENCES**

1. Soeda T, Uemura S, Park SJ, et al. Incidence and clinical significance of poststent optical coherence tomography findings: one-year follow-up study from a multicenter registry. Circulation 2015;132:1020–9.
2. De Cock D, Bennett J, Ughi GJ, et al. Healing course of acute vessel wall injury after drug-eluting stent implantation assessed by optical coherence tomography. Eur Heart J Cardiovasc Imaging 2014;15:800–9.
3. Asakura K, Minami Y, Sato D, Shiono T, Ako J. Intramural hematoma due to in-stent dissection causing acute coronary occlusion. J Am Coll Cardiol Intv 2018;11:e131–3.

**KEY WORDS** acute myocardial infarction, dissection, intramural hematoma, optical coherence tomography, percutaneous coronary intervention

**APPENDIX** For supplemental videos, please see the online version of this paper.
Orbital Atherectomy Through Left Main Stent Struts Complicated by Catheter Entrapment and Stent Avulsion

Yutaka Matsuhiro, MD, Ryu Shutta, MD, Yasuyuki Egami, MD, Masami Nishino, MD, PhD, Jun Tanouchi, MD, PhD

ABSTRACT

We performed orbital atherectomy in the left circumflex artery through a stent that jailed the circumflex artery ostium. The orbital atherectomy catheter was entrapped within the stent and the stent was avulsed during catheter withdrawal. We should consider this potential complication when performing orbital atherectomy in a jailed side branch.

Level of Difficulty: Advanced.

A 60-year-old woman previously had percutaneous coronary intervention in the left main coronary artery (LM) and left anterior descending artery with implantation of a 3.5 mm × 22 mm Resolute Onyx stent (Medtronic, Santa Rosa, California). Two years later, follow-up angiogram showed severe stenosis in the left circumflex artery jailed by the LM-left anterior descending artery stent (Figure 1A). Intravascular ultrasonography revealed the ostial and mid-left circumflex artery had calcified stenosis (Figure 1B, Video 1).

Percutaneous coronary intervention was performed with a Diamondback 360 Coronary Orbital Atherectomy System (CSI, St. Paul, Minnesota). The lesion was crossed with the assistance of a 7-F Guidezilla extension catheter (Boston Scientific, Marlborough, Massachusetts). First, the lesion was ablated at 80,000 rpm. Then, the speed was increased to 120,000 rpm. Suddenly, the catheter became entrapped within the LM stent struts (Video 2). The double guiding catheter technique was performed. Another wire was advanced across the stent and a 2.25-mm balloon was inflated. However, the catheter still could not be withdrawn. Intravascular ultrasonography was performed using the parallel wire and revealed that the stent had been avulsed and was wrapped around the catheter (Figure 1C, Video 3). Finally, we exchanged the Guidezilla for a Guideplus (Nipro, Osaka, Japan) and pulled and pushed the Guideplus, which succeeded in withdrawing the Orbital Atherectomy catheter (Figure 1D). We implanted 3 drug eluting stents, which resulted in sufficient lesion dilatation by angiography with TIMI (Thrombolysis In Myocardial Infarction) flow grade 3.
A similar complication with a cutting balloon catheter was previously reported (1). This potential complication should be considered when evaluating whether to perform orbital atherectomy in a jailed side branch, especially when the side branch has an obtuse angle.

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REFERENCE
1. Kawamura A, Asakura Y, Ishikawa S, et al. Extraction of previously deployed stent by an entrapped cutting balloon due to the blade fracture. Catheter Cardiovasc Interv 2002;57:239–43.

KEY WORDS complication, intravascular ultrasound, percutaneous coronary intervention

APPENDIX For supplemental videos, please see the online version of this paper.

FIGURE 1 Coronary Angiogram, Intravascular Ultrasonography, and Retrieval of Entrapped Orbital Atherectomy Catheter

(A) Stenosis in left circumflex artery (LCX) (black arrows). (B) Calcified stenosis at the ostial lesion (white arrows). (C) Orbital atherectomy catheter (white arrow) with metallic mass (white arrowheads) in left main coronary artery and absence of left main stent struts (yellow arrowheads). (D) Withdrawn stent (black arrows) and orbital atherectomy catheter (white arrows). The proximal part of the stent was wrapped around the catheter (white arrowheads). LAD = left anterior descending.
MINI-FOCUS ISSUE: TAVR

CASE REPORT: CLINICAL CASE

Massive TAVR
Complex Transcatheter Aortic Valve Replacement in the Setting of an Enormous Adnexal Mass

Siddharth Chauhan, MD,a Simbo Chiadika, MD,b Tariq Dayah, MD,c Sam Chitsaz, MD,b Prakash Balan, MD, JDb

ABSTRACT

A 65-year-old woman with a large adnexal mass was found to have severe bicuspid aortic valve stenosis. Transcatheter aortic valve replacement was chosen rather than surgical aortic valve replacement because of concerns over risks. We demonstrate the value of pre-operative transcatheter aortic valve replacement before prompt noncardiac surgery. Furthermore, it illustrates some useful bailout techniques in this challenging scenario. (Level of Difficulty: Intermediate.) (J Am Coll Cardiol Case Rep 2020;2:711-5) © 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/).

Surgical resection of an intraperitoneal or abdominal mass is considered an intermediate-risk surgery; however, patient comorbidities play an important role in the estimation of operative risk. The presence of severe aortic stenosis (AS) considerably increases the risk of a cardiac event with such a noncardiac surgery (NCS) (1). Transcatheter aortic valve replacement (TAVR) provides a minimally invasive method of minimizing the risks.

HISTORY OF PRESENTATION

A 65-year-old woman presented to the hospital with dyspnea and demonstrated New York Heart Association functional class III symptoms of congestive heart failure.

PAST MEDICAL HISTORY

The patient has a history of hypertension, hyperlipidemia, diabetes mellitus, and obesity.

INVESTIGATIONS

Computed tomography scan revealed a large adnexal mass measuring 36.2 × 24.7 × 33.6 cm, and occupying...
most of the pelvis and lower abdomen (Figure 1). The mass was deemed likely a benign ovarian serous or mucinous tumor. The primary consequence was the mass effect, which was elevating both hemidiaphragms and compressing both lungs. Furthermore, echocardiography revealed severe bicuspid AS with a mean gradient of 66 mm Hg, peak velocity of 5.4 m/s, and a calculated aortic valve area of 0.6 cm² in the setting of normal ejection fraction (60% to 65%) and mild-to-moderate aortic insufficiency (AI) (Supplemental Figure 1, Videos 1 and 2).

MANAGEMENT

The patient was referred for consideration of aortic valve replacement before adnexal mass resection. The patient was deemed intermediate risk for surgical aortic valve replacement (SAVR) because of the risk of prolonged intubation and respiratory failure related to the mass effect of the growth. The multidisciplinary heart team did not want to delay the patient’s progress toward mass resection by subjecting the patient to a more prolonged recovery post-SAVR. Simultaneous mass resection and SAVR as combined procedure was considered but deemed high risk. Balloon aortic valvuloplasty (BAV) as a bridge to NCS was not an option given the baseline AI and the bicuspid valve. The gynecologic oncology team deemed her to have well over a 1-year life expectancy. Hence, TAVR was chosen as the optimal treatment strategy. Balloon-expandable prosthesis was chosen over a self-expandable prosthesis for the following reasons. The angle of entry from aorta into the left ventricle measured 62° (Figure 2) making it more difficult to seal with a self-expanding prosthesis (2). A balloon expandable SAPIEN 3 prosthesis was used for its greater radial force (Figure 3). Outcomes with TAVR in bicuspid versus tricuspid AS have been studied and are largely comparable with later-generation devices (3).

The TAVR procedure posed numerous technical challenges. The size of the mass posed some challenges with respect to vascular access and fluoroscopic visualization (Figures 4 and 5). Given the excellent quality of her iliac-femoral vasculature, a transfemoral access was chosen compared with such alternatives as transaxillary, transcarotid, or transapical accesses because it provided the least invasive method for this patient. After the valve delivery system (VDS) was successfully introduced, despite numerous maneuvers, there was difficulty crossing the stenotic native valve with the

ABBREVIATIONS AND ACRONYMS

AI = aortic insufficiency
AS = aortic stenosis
BAV = balloon aortic valvuloplasty
NCS = noncardiac surgery
SAVR = surgical aortic valve replacement
TAVR = transcatheter aortic valve replacement
VDS = valve delivery system

FIGURE 1 Abdominal-Pelvic Computed Tomography Scan

Computed tomography scan illustrating the large adnexal mass.

FIGURE 2 Aortoventricular Fluoroscopy

Aortoventricular angle of 62°.
transcatheter valve. We ultimately had to resort to a second valve crossing with BAV via this second crossing to facilitate passage of the valve (Figures 6 and 7, Video 3). We ultimately achieved successful valve deployment with minimal residual gradient and excellent hemodynamics (Figure 8, Videos 4 and 5, Supplemental Figure 2). There was a new left bundle branch block with prolonged PR interval.

**DISCUSSION**

This case was unique for several reasons. This was a relatively young patient with a severe bicuspid AS (Sieverts type I with R-L fusion) with concomitant significant AI without an ascending aortic aneurysm in the setting of an enormous adnexal mass that needed prompt resection. Our patient was hospitalized because of respiratory compromise resulting from the combination of her severe AS and the extrathoracic compression of the lungs by the mass. The reduced lung volumes create an increased risk of prolonged intubation post-SAVR. More so, prompt valve intervention was required to facilitate operative resection of the adnexal mass. TAVR is an excellent method of providing a safe and effective treatment for this patient with low morbidity/mortality and short recovery time (4).

This case serves as a reference for patients needing prompt NCS in the setting of severe AS. Although an enormous adenexal mass needing prompt resection is somewhat rare, more commonly patients present with AS-related syncope complicated by orthopedic injuries, such as hip fracture, and are in need of prompt valve intervention before definitive correction of the orthopedic injury. Although the mass presented a technical challenge, the case illustrates the advantages of performing TAVR on low-risk patients. Recent publications of the low-risk TAVR trials demonstrate that in low surgical risk patients, TAVR is at least as good if not superior to SAVR (5,6).

The intraprocedural aspects of the case were also illustrative of useful techniques in managing a complicated TAVR. Because of difficulty with fluoroscopic penetration and thus visualization through the mass, vascular access was obtained using the stiff, and radiopaque Meier wire and long sheaths. With the VDS in place, passage of the prosthetic valve across the native valve was surprisingly challenging. Preparatory BAV was not chosen because of the moderate AI at baseline. Multiple unsuccessful techniques were attempted to cross the valve including flexion and angulation of the catheter and nominal inflation of the VDS balloon. Recent data have suggested that elimination of routine BAV during TAVR may be beneficial (7); however, cases such as ours raise the question as to when it is necessary. Certainly the presence of
high gradients, extensive leaflet calcification, and bicuspid valve should be considerations favoring preparatory BAV. Inability to primarily pass the prosthetic valve resulted in performing a BAV from the contralateral femoral access. However, rather than attempting a second crossing with a straight wire, we placed the stiff Meier wire within the pigtail catheter and forced our way across the native valve (Figure 2, Video 3). This “battering-ram” technique was used because the patient was becoming hypotensive and unstable. Such a forceful technique should not be used routinely but was necessary under urgent circumstances. The Meier wire was exchanged for a standard J-wire and a 10 × 40 mm peripheral balloon was used to perform BAV. Valve passage was again attempted but was unsuccessful. Valvuloplasty was repeated but the transcatheter heart valve was simultaneously passed with the peripheral balloon inflated across the native valve. Use of this “buddy-balloon technique” propping the leaflets open just enough to allow simultaneous advancement of the VDS allowed for advancement and successful deployment of the prosthesis. The patient did, however, develop a new left bundle branch block with first-degree atrioventricular block.

**FOLLOW-UP**

An electrophysiology study the next day demonstrated infrahisian and intrahisian disease resulting in placement of a permanent pacemaker. The patient did well subsequently and was discharged home with a plan for adnexal mass resection in the near future as an outpatient.

**CONCLUSIONS**

TAVR is a useful tool in patients with severe AS facing necessary NCS. Careful attention to access and groin management was essential in dealing with the enormous adnexal mass. Furthermore, bailout techniques, such as use of a “buddy-balloon,” helped in facilitating valve passage and ultimately obtaining a good clinical outcome.

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REFERENCES

1. Zahid M, Sonel AF, Saba S, Good BC. Perioperative risk of noncardiac surgery associated with aortic stenosis. Am J Cardiol 2005;96:436-8.

2. Abramowitz Y, Maeno Y, Chakravarty T, et al. Aortic angulation attenuates procedural success following self-expanding but not balloon-expandable TAVR. J Am Coll Cardiol Img 2016;9:964-72.

3. 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.

4. Arora S, Vaidhya SR, Strassie PD, et al. Meta-analysis of transfemoral TAVR versus surgical aortic valve replacement. Catheter Cardiovasc Interv 2018;91:806-12.

5. Mack MJ, Leon M, Thourani VH, et al. Transcatheter aortic valve replacement with a balloon expandable valve in low-risk patients. N Engl J Med 2019;380:1695-705.

6. Popma JJ, Deeb GM, Yakubov SJ, et al. Transcatheter aortic valve replacement with a self-expanding valve in low-risk patients. N Engl J Med 2019;380:1706-15.

7. Deharo P, Jaussaud N, Grisoli D, et al. Impact of direct TAVR without balloon aortic valvuloplasty on procedural and clinical outcomes: insights from the FRANCE TAVI Registry. J Am Coll Cardiol Intv 2018;11:1956-65.

KEY WORDS abdominal masses, aortic stenosis, preoperative evaluation, transcatheter aortic valve replacement

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

CASE REPORT: CLINICAL CASE

Transcatheter Aortic Valve Replacement of a Bicuspid Aortic Valve in a Heart Transplant Recipient

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ABSTRACT

Patients with heart transplants who present with severe aortic stenosis may be deemed high-risk surgical candidates due to immunosuppression and multiple comorbid conditions. Appropriately selected patients may be successfully treated with transcatheter aortic valve replacement. (Level of Difficulty: Advanced.) (J Am Coll Cardiol Case Rep 2020;2:716–20) © 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/).

HISTORY OF PRESENT ILLNESS

A 45-year-old male who had undergone orthotopic heart transplantation in 1997 presented 22 years later with progressive dyspnea on exertion. The patient was known to have a bicuspid aortic valve in his transplanted heart (Figure 1, Videos 1 and 2). On presentation, he was afebrile, his blood pressure was 150/90 mm Hg, his heart rate was 95 beats/min, and his oxygen saturation was 95% on room air. Physical examination was significant for mildly elevated neck veins, clear lungs, 3/6 systolic murmur at the right upper sternal border with radiation to the neck and minimal lower extremity edema.

LEARNING OBJECTIVES

- To recognize that recipients with transplanted hearts are subject to a slew of complications which may include common valvular diseases.
- To understand the importance that a multidisciplinary heart team approach plays in management of complex structural heart patients.
- To illustrate the expanding role of transcatheter aortic valve replacement to serve complex patients.
DIFFERENTIAL DIAGNOSIS

The differential diagnosis for shortness of breath in a patient with prior heart transplant is extensive but includes predominantly transplant rejection, which can be acute cellular rejection, humoral rejection, and coronary artery vasculopathy (CAV) (1,2). Lung infections can also present with shortness of breath, due to either community-acquired pneumonia or opportunistic infections by organisms such as cytomegalovirus, Epstein-Barr virus, Toxoplasma gondii, Aspergillus fumigatus, or Candida albicans. Lymphoproliferative disorder of the lung and lung cancer are also in the differential.

INVESTIGATIONS

Blood work showed normal white blood count and mild anemia. B-type natriuretic peptide was elevated (600 ng/l). Creatinine was 8 mg/dl with normal electrolytes. Chest radiographs showed no lung infiltrates. Electrocardiography showed sinus rhythm, first-degree AV block, right bundle branch block, and left posterior fascicular block (Figure 2). An echocardiogram demonstrated preserved left ventricular systolic function with apical hypokinesis and severe aortic stenosis (AS) with a peak velocity across the valve of 4.7 m/s and a mean gradient of 52 mm Hg (Figures 3 and 4, Videos 3 and 4). Of note, the transplantation team was aware of progressively worsening AS, documented by both clinical examination and echocardiography. The last echocardiogram before the one showing severe AS was performed a year earlier and had shown moderate to severe AS. During that time, the patient was asymptomatic.

MANAGEMENT

Left heart catheterization revealed an 80% stenosis in the mid portion of the left anterior descending artery, which was treated with one drug-eluting stent. The lesion was focal, consistent with coronary artery disease, and lacked features concerning for CAV, but it was deemed significant enough and was fixed in preparation for valve intervention. Approximately 2 to 3 months after undergoing revascularization, the patient was seen by the valve team in the authors’ institution and was evaluated by 2 cardiothoracic surgeons. He was deemed to be at high risk for surgical valve replacement due to prior heart transplantation, ESRD, and immunosuppression with a calculated Society of Thoracic Surgery risk score of 12.9%. A computed tomography angiogram demonstrated adequate common femoral artery diameters for a transfemoral approach to transcatheter aortic valve replacement (TAVR). He underwent successful placement of a balloon-expandable transcatheter valve. Immediately after valve deployment, complete heart block (CHB) was noted, and a transvenous pacemaker was placed at the conclusion of the case (Central Illustration). He was monitored in the coronary care unit for 24 to 36 h without atrioventricular conduction recovery. He was evaluated by electrophysiology for potential right axillary/subclavian access, but venography confirmed inadequate venous access. Thus, he received a permanent epicardial pacemaker 48 h after the valve placement, through a left thoracotomy. This was further complicated by a moderately sized hemothorax, thought to be due to significant adhesions, which were dissected to place the leads, requiring chest tube placement. The tube remained in place for 4 days and drained 855 cc of blood. He was discharged home 6 days after the valve procedure in a stable condition. His echocardiogram at discharge revealed normal left

ABBREVIATIONS AND ACRONYMS

AS = aortic stenosis  
AV = atrioventricular  
CAV = coronary artery vasculopathy  
CHB = complete heart block  
ESRD = end-stage renal disease  
TAVR = transcatheter aortic valve replacement  
TEE = transesophageal echocardiogram  
TTE = transthoracic echocardiogram

Continuous-wave Doppler across the aortic valve demonstrates a mean gradient of 16.6 mm Hg, consistent with normal functioning of an aortic valve in 2014. AV VTI = aortic valve velocity time integral (52.1 cm); AV Vmax = aortic valve peak (maximum) velocity (2.9 m/s); AV Max PG = aortic valve peak gradient (35 mm Hg); AV Vmean = aortic valve mean velocity (1.9 m/s); BPM = beats/min.
ventricular function and a well-seated prosthesis in the aortic position with a mean gradient of 8 mm Hg and trace paravalvular regurgitation (Video 5).

**DISCUSSION**

For a heart to be considered for transplantation, donors must be younger than 55 years of age, although select donors over the age of 55 years are acceptable for older recipients without a history of chest trauma or cardiac disease, appropriate hemodynamics on minimal or no inotropic support, and a normal or nearly normal echocardiogram results (3). In the absence of stenosis, the presence of a bicuspid valve in the donor does not exclude the heart from transplantation, as the average life span of an adult recipient after heart transplantation is approximately 11 years. Our patient lived 22 years after receiving a heart transplant, and the donor bicuspid valve likely underwent accelerated calcification due to hemodialysis.

TAVR is feasible in patients with bicuspid aortic valve, and research has shown that the overall complication rate is comparable to TAVR in trileaflet valves (4–6). TAVR in bicuspid aortic valve is more prone to paravalvular regurgitation and adverse procedural events, such as aortic rupture, although that was not demonstrated with the newer generation devices. The major difference is the higher propensity for paravalvular leak in patients with bicuspid valve. Cumulative all-cause mortality was found to be similar in these 2 groups, but more research is needed (6).

Data with regard to TAVR in patients who have previously received a heart transplant, however, are limited to case reports only (7-10). Four previous cases reported successful TAVR in patients with previous heart transplants, all of whom had a trileaflet aortic valve. These case reports suggest TAVR may
represent a feasible alternative in patients with severe AS in a transplanted heart.

Furthermore, this patient’s course was complicated by CHB. Periprocedural pacemaker rates in patients with a bicuspid versus a tricuspid valve have not been well studied. A retrospective study suggested there are no significant differences (6). It is unknown whether TAVR in a transplanted heart bicuspid valve is associated with a higher risk for CHB and need for pacemaker compared to TAVR in native hearts.

**FOLLOW-UP.** The patient was seen in follow-up at 1 and 6 months, and he was free of symptoms, without diastolic murmur on examination. The patient is scheduled for follow-up echocardiogram at 1 year after the procedure.
CONCLUSIONS

Heart transplant patients are subject to many complications over their lifetimes, including common diseases such as aortic stenosis. TAVR may be a feasible alternative treatment in patients with transplanted hearts who develop severe AS.

REFERENCES

1. Michaels PJ, Espejo ML, Kobashigawa J, et al. Humoral rejection in cardiac transplantation: risk factors, hemodynamic consequences and relationship to transplant coronary artery disease. J Heart Lung Transplant 2003;22:58-69.

2. Lee MS, Tadwalkar RV, Fearon WF, et al. Cardiac allograft vasculopathy: a review. Catheter Cardiovasc Interv 2018;92:E527-36.

3. Kilic A, Emani S, Sai-Sudhakar CB, Higgins RS, Whitson BA. Donor selection in heart transplantation. J Thorac Dis 2014;6:1097-104.

4. Yoon SH, Sharma R, Chakravarty T, et al. Clinical outcomes and prognostic factors of transcatheter aortic valve implantation in bicuspid aortic valve patients. Ann Cardiothorac Surg 2017;6:463-72.

5. Yoon SH, Makkar R. Transcatheter aortic valve replacement for bicuspid aortic valve: challenges and pitfalls. Interv Cardiol Clin 2018;7:477-88.

6. Makkar RR, Yoon SH, Leon MB, et al. Association between transcatheter aortic valve replacement for bicuspid vs tricuspid aortic stenosis and mortality or stroke. JAMA 2019;321:2193-202.

7. Ahmad K, Terkelsen CJ, Terp KA, et al. Transcatheter aortic valve implantation in a young heart transplant recipient crossing the traditional boundaries. J Thorac Dis 2016;8:e711-4.

8. Zanuttini D, Armellini I, Bisceglia T, et al. Transcatheter aortic valve implantation for degenerative aortic valve regurgitation long after heart transplantation. Ann Thorac Surg 2013;96:1864-6.

9. De Praetere H, Ciarka A, Dubois C, Herijgers P. Transapical transcatheter aortic valve implantation in a heart transplant recipient with severely depressed left ventricular function. Interact Cardiovasc Thorac Surg 2013;16:906-8.

10. Seiffert M, Meyer S, Franzen O, et al. Transcatheter aortic valve implantation in a heart transplant recipient: a case report. Transplant Proc 2010;42:4661-3.

KEY WORDS bicuspid valve, heart transplant, transcatheter aortic valve replacement

APPENDIX For supplemental videos, please see the online version of this paper.
A young male presented to the hospital with chest pain. A coronary angiogram and a subsequent computed tomography coronary angiogram revealed a single coronary artery arising from the right coronary sinus which bifurcated into the right coronary artery and a large branch which supplies the left coronary artery territory. (Level of Difficulty: Beginner.) (J Am Coll Cardiol Case Rep 2020;2:721–2) © 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 32-year-old male with hypertension and hyperlipidemia presented to the hospital with complaints of central chest pain which was worse on exertion. Results of serum troponin analysis and resting electrocardiograms were normal. He underwent an exercise treadmill test which returned normal results. In view of the nature of his chest pain, he underwent a coronary angiogram. Coronary angiography (Figure 1A, Video 1) in the anteroposterior cranial view (RAO 1 CRAN 39) revealed a single coronary artery arising from the right coronary sinus giving rise to the right coronary artery and a large branch that supplies the left anterior descending and left circumflex arteries. An aortogram did not reveal any other coronary origin.

Computed tomography coronary angiography (CTCA) (Figure 1B) 3-dimensional volume-rendered computed tomography heart image (LAO 7 CRAN 56) was obtained which showed a single coronary artery arising from the right coronary cusp bifurcating into the right coronary artery and an anomalous left main artery which coursed leftward anterior to the main pulmonary artery before dividing into the left anterior descending and the left circumflex arteries. The Agatston coronary calcium score was 0. There was no coronary artery stenosis or other cardiac abnormality. He was treated with analgesia for presumed musculoskeletal chest pain, with resolution of his symptoms. There was no symptom recurrence during the subsequent 2 years of follow-up.

Single-coronary artery is a rare congenital anomaly that is usually isolated but may be associated with other congenital heart anomalies such as tetralogy of Fallot and truncus arteriosus (1). CTCA is useful for delineating the coronary anatomy and exclude associated cardiac anomalies. It is important to identify the “malignant” interarterial course of the anomalous coronary artery between the main pulmonary artery and the aorta, which is associated with myocardial ischemia and sudden death. In the present patient, the anomalous left main artery assumed a “benign” course anterior to the main pulmonary artery and was not found to be the cause of his chest pain.
FIGURE 1  Coronary Angiogram and CTCA Image of Patient

The proximal RCA bifurcates into an anterior branch (arrow) and the mid RCA. (A) AP cranial view (RAO 1 CRAN 39). The proximal RCA bifurcates into an anterior branch (arrow) and the mid RCA. (B) 3D VR CT heart image (LAD 7 CRAN 56) which shows a single coronary artery (asterisk) arising from the right coronary cusp (Δ) which bifurcates into the RCA (single arrow) and an anterior branch (double arrows) which courses leftward and further bifurcates anteriorly to the main pulmonary artery into anterior (single arrowhead) and posterolateral (double arrowheads) branches. The anterior branch courses along the anterior interventricular groove to supply the LAD territory and the posterolateral branch courses along the left atrioventricular groove to supply the LCX territory. AP = anteroposterior; CT = computed tomography; LAD = left anterior descending artery; LCX = left circumflex artery; RCA = right coronary artery; VR = volume rendered.

REFERENCE

1. Yu FF, Lu B, Gao Y, Hou ZH, et al. Congenital anomalies of coronary arteries in complex congenital heart disease: diagnosis and analysis with dual-source CT. J Cardiovasc Comput Tomogr 2013;7:383-90.

KEY WORDS congenital coronary anomaly, single coronary artery

APPENDIX For supplemental videos, please see the online version of this paper.
EDITORIAL COMMENT

Did “Pistol” Pete Maravich Die From Congenital Coronary Artery Disease or Acquired Myocardial Disease?*

Eric R. Bates, MD

Most congenital coronary artery anomalies have no clinical importance, are asymptomatic, and do not impact longevity. However, specific anomalies (i.e., origin of the left main coronary artery from the pulmonary trunk, aberrant course of the arteries between the great vessels in association with anomalous and slit-like ostium, large coronary artery fistulas) can be associated with sudden death, myocardial ischemia, congestive heart failure, or endocarditis and can create challenges during coronary angiography, percutaneous coronary interventions, and coronary artery and valvular heart surgery.

A single coronary artery originating from an ostium in the right sinus of Valsalva is an unusual coronary anomaly. The left main coronary artery can originate from the proximal right coronary artery (RCA), as it did in the report by Ng et al. (1) in this issue of JACC: Case Reports, before dividing into the left anterior descending (LAD) artery and left circumflex (LCx) artery, or there can be separate origins of the LAD and LCx coronary arteries from the proximal RCA. The LAD coronary artery can then either pass anterior to the right ventricular outflow tract, between the aorta and pulmonary trunk, or through the crista supraventricularis portion of the septum, whereas the circumflex artery can either pass between the aorta and pulmonary trunk or dorsal to the aorta (2).

Alternatively, the LCx coronary artery may originate from the distal RCA with the LCx coronary artery a continuation of the RCA posterolateral artery in the posterior atrioventricular groove and, after the takeoff of the obtuse marginal branches, continue as the LAD in the anterior intraventricular groove. This is an extremely rare form of single coronary anomaly (3) and was the anatomy described in the autopsy of Pete Maravich (4).

Maravich was a renowned basketball player with a complex personal life (5). He established single season and career college scoring records as a player at Louisiana State University from 1967 to 1970, averaging 38 shots and 44 points per game (6). His floppy hair, sagging gray socks, and gangly limbs in an era of conservative basketball helped make him enormously popular with fans. His ball-handling, dribbling, and passing skills were extraordinary at that time, predating what is now expected from star players. He averaged 24 points per game over 10 years as a professional, won 1 scoring title, and was inducted into the Basketball of Fame a year before his death. He helped launch the modern basketball era.

He died suddenly while playing a game of pick-up basketball at 40 years of age, evidently without prior symptoms, and his single RCA anomaly was implicated as the cause of death (4). His autopsy showed an 8-mm RCA, and a 2-mm LAD with normal distribution. Interestingly, the left ventricle showed widespread interstitial fibrosis and patchy scarring, more pronounced in the subendocardium, but the right ventricle was normal. The pathologists speculated that the etiology of the cardiomyopathy was LAD supply and demand ischemia, because the LAD

*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 author attests 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.
was farthest away from the aorta and there was more visible mottling in the LAD territory, but the fibrosis was global.

Although anomalous coronary artery is the second most common cause of sudden death in athletes, the pre pulmonic course of the arterial distribution in this case report (1) and in the Maravich autopsy (4) avoids the risk of ischemia associated with an aberrant course between the great vessels. A rudimentary LAD was suggested as the cause of mild distal anterior ischemia on a myocardial perfusion scan in an asymptomatic patient in 1 prior report, but no other reports of this coronary anomaly have shown objective evidence of ischemia on stress testing (3). Therefore, it is most likely that a single RCA arising from the right sinus of Valsalva that does not pass between the great vessels is a benign condition and that Pete Maravich, who performed for years at the highest physical level in a demanding sport, died from subsequent myocardial disease, perhaps from myocarditis, and not from congenital coronary artery disease as previously assumed.

**REFERENCES**

1. Ng P, Lee R, Teo L, Chai P. Single coronary artery in a young male with chest pain. J Am Coll Cardiol Case Rep 2020;2:723–4.

2. Shirani J, Roberts WC. Solitary coronary ostium in the aorta in the absence of other major congenital cardiovascular anomalies. J Am Coll Cardiol 1993;21:137–43.

3. Ghaffari S, Pourafkari L, Nader N. Single coronary artery: Pete Maravich anomaly revisited. Am J Med Sci 2016;351:435–6.

4. Choi JH, Kornblum RN. Pete Maravich’s incredible heart. J Forensic Sci 1990;35:981–6.

5. Anderson S. The shotaholic. New York Magazine February 7, 2007.

6. Rogers T. Pete Maravich, a Hall of Famer who set basketball marks, dies. New York Times January 6, 1988. Section B, Page 4.

**KEY WORDS** congenital coronary artery disease, myocardial disease, sudden death
Severe Left Ventricular Outflow Tract Obstruction Immediately After Surgical Repair of Ebstein’s Anomaly

Isma Rafiq, BSc, MBBS, Arif A. Khokhar, BM, BCSc, MA, Rafael Alonso-Gonzalez, MD, MSc, Olivier Ghez, MD, Aleksander Kempny, MD, Konstantinos Dimopoulos, MD, MSc, PhD

ABSTRACT

A 52-year-old man following surgery for Ebstein’s anomaly after repair developed acute hemodynamically significant left ventricular outflow tract obstruction with systolic anterior motion of the mitral valve and severe mitral regurgitation. Fluid resuscitation and weaning of inotropes were unsuccessful. Left ventricular outflow tract obstruction and mitral regurgitation resolved by using esmolol. (Level of Difficulty: Intermediate.) (J Am Coll Cardiol Case Rep 2020;2:725-31) © 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/).

HISTORY OF PRESENTATION

A 52-year-old male was diagnosed with severe Ebstein malformation of the tricuspid valve (Carpentier type D) and a small secundum atrial septal defect (ASD) when he presented acutely with breathlessness, mild hypoxia, and progressively decreasing exercise tolerance. Echocardiogram and magnetic resonance imaging (MRI) demonstrated anatomy consistent with Ebstein’s anomaly, with moderate to severe tricuspid regurgitation, a dilated right atrium and right ventricular (RV) outflow tract, and small left ventricle. From his past medical history, he had known Ebstein’s anomaly.

DIFFERENTIAL DIAGNOSIS

Dilated cardiomyopathy, arrhythmogenic right ventricle cardiomyopathy, could have been considered as a differential diagnosis. In this case, the crucial aspect was making the right diagnosis and management of the case postoperatively, as the patient became progressively hypotensive, oliguric, and acidic despite fluid resuscitation and inotropic support.

INVESTIGATIONS

Preoperative echocardiogram and cardiac MRI demonstrated moderate-to-severe tricuspid regurgitation, dilated right atrium (right atrial area of 35 cm²), dilated RV outflow tract, small left ventricular (LV)
volumes and a structurally normal mitral valve with no regurgitation (Figure 1). The echocardiogram and an MRI scan helped us to establish our diagnosis. Postoperative transesophageal echocardiogram (TEE) played a key role in making the diagnosis as the patient was progressively deteriorating.

MANAGEMENT

At the start of the operation, TEE confirmed the earlier findings, with no left ventricular outflow tract (LVOT) obstruction or mitral regurgitation. Because repair of the tricuspid valve was not feasible on inspection of the valve, he underwent elective tricuspid valve replacement (Carpentier-Edwards 33 mm), along with plication of the atrialized right ventricle and right atrium, “reinforcement” of RV inlet and direct ASD closure. The patient was successfully weaned off cardiopulmonary bypass and immediate TEE demonstrated good tricuspid valve function with trace mitral regurgitation. On return to the intensive care unit, the patient became progressively hypotensive, oliguric, and acidic, despite adequate fluid resuscitation, requiring escalating doses of noradrenaline. On auscultation, there was a new grade 2/6 ejection systolic murmur over his left lower sternal edge and a grade 3/6 pan-systolic murmur over his apex.

Emergency TEE demonstrated significant turbulence within the LVOT, with a peak velocity above 4 m/s. There was significant systolic anterior motion (SAM) of the anterior leaflet of the mitral valve with resulting incoaptation of leaflets and severe mitral regurgitation (Figures 2A to 2D). Furthermore, there was reduced opening of the aortic valve because of the narrow LVOT jet directing blood flow through the posterior and left coronary cusps (Figures 2E to 2F). Despite further fluid resuscitation and weaning of the vasopressors and inotropes, there was little improvement in his hemodynamic status, and the decision was made to commence esmolol infusion. Within a few minutes of starting esmolol (starting dose 25 μg/kg/min), the LVOT obstruction significantly improved and there was no significant SAM of the mitral valve, with mild mitral regurgitation (Figures 3A to 3B). Over the next 12 h, his hemodynamic and metabolic status improved (Figures 4A to 4B), and he was extubated the following day. Esmolol was gradually weaned, and after 48 h he was discharged from the intensive care unit and continued to recover uneventfully.

DISCUSSION

Ebstein’s anomaly accounts for 1% of congenital heart disease cases, with an incidence of approximately 1 per 200,000 live births (1). The malformation affects the tricuspid valve and right ventricle in a variable manner and is characterized by adherence of the valve leaflets to the underlying myocardium, apical deviation of the atrialized septum into the small-sized left ventricular cavity.

**ABBREVIATIONS AND ACRONYMS**

| Abbreviation | Description |
|--------------|-------------|
| ASD          | atrial septal defect |
| LV           | left ventricular |
| LVOT         | left ventricular outflow tract |
| MRI          | magnetic resonance imaging |
| RV           | right ventricular |
| TEE          | transesophageal echocardiogram |
| SAM          | systolic anterior motion |

**FIGURE 1 Preoperative Cardiac MRI**

![Apical 4-chamber magnetic resonance images taken (A) in end-diastole and (B) systole. (A) The apical displacement of the point of coaptation of the tricuspid valve leaflets (solid arrow) is seen, allowing a large “atrialized” portion of the inlet of the right ventricle. (B) There is significant deviation of the atrialized septum (dashed arrow) into the small-sized left ventricular cavity.](image-url)
congenital lesions such as ASDs, ventricular septal defects, left ventricular noncompaction and abnormalities of the mitral valve (5). Even in the absence of associated lesions, patients with Ebstein’s anomaly can develop left ventricular dysfunction, which may influence perioperative risk.

Rare case reports describe an association between Ebstein’s anomaly and LVOT obstruction, usually in the context of hypertrophic obstructive cardiomyopathy (6,7). We present the case of a patient who developed hemodynamically significant LVOT obstruction following surgical repair for Ebstein’s
anomaly, in the absence of hypertrophic cardiomyopathy or mitral valve abnormalities. Below, we discuss the potential pathophysiological mechanisms involved, management options, and review the literature for the association between Ebstein’s anomaly and LVOT obstruction.

We searched Medline and EMBASE for any literature on LVOT obstruction and SAM of the mitral valve in patients with Ebstein’s anomaly. We included global publications in all ages and languages as far back as the databases would go. After screening through references for additional papers, we found 6 case reports of patients with Ebstein’s anomaly who had evidence of LVOT obstruction (Table 1).

MECHANISMS OF LVOT OBSTRUCTION IN EBSTEIN’S ANOMALY. A spectrum of left heart abnormalities can coexist with Ebstein’s anomaly (5). In a cohort of 106 consecutive Ebstein patients undergoing echocardiographic evaluation at the Mayo Clinic, 39% were found to have an abnormality of the left-sided myocardium or valves (5). Mechanisms responsible for LVOT obstruction in Ebstein’s anomaly include accessory mitral valve tissue (8), enlargement and redundancy of mitral valve leaflets (9) and, more commonly, coexisting features of hypertrophic cardiomyopathy (6,7). However, LVOT obstruction has also been noted in Ebstein patients with no associated left heart abnormalities. Severe atrialization of the ventricular septum with severe tricuspid regurgitation and a regurgitant jet directed toward the atrialized septum can result in significant deviation of the basal septum into the LVOT, causing obstruction at rest, with or without SAM of the mitral valve (10,11). Our patient had no demonstrable LVOT obstruction, neither on echocardiogram or MRI preoperatively. We submit that hemodynamically new, significant LVOT obstruction can develop postoperatively in Ebstein
patients because of the underlying anatomical substrates (e.g., reduced left ventricular end-diastolic dimensions, dyskinetic basal ventricular septum, small LV volumes), hypovolemia, and a hyperdynamic state exacerbated by inotropes. Indeed, adequate fluid resuscitation and interruption of inotropes was not sufficient to correct the LVOT obstruction, and beta blockade was required to achieve hemodynamic improvement.

In cases of severe Ebstein malformation, the apical displacement of the tricuspid annulus results in the “atrialization” of the basal ventricular septum, which may be responsible for the predisposition to LVOT obstruction. This refers to the portion of the septum lying between the true and functional annulus and, in Ebstein’s anomaly, is typically thin and dyskinetic, devoid of any muscle tissue (12). Elevated right atrial pressures resulting from the tricuspid regurgitation and reduced compliance of the small (functional) right ventricle result in fixed deviation of the atrialized septum toward the LV, reducing the effective LV diameter and outflow tract (10,11). Both pathology (13) and echocardiographic (14) studies confirm the presence of altered LV geometry in Ebstein’s anomaly. On echocardiography (14), patients with Ebstein’s anomaly had higher LV eccentricity index scores compared with morphologically normal hearts (1.35 ± 0.23 vs. 1.02 ± 0.05) and a higher ratio of RV-to-LV cavity size (1.7 ± 0.44 vs. 0.65 ± 0.30). LV eccentricity correlated well with markers of Ebstein severity, such as the area of the functional right atrium and the degree of tricuspid valve displacement. All Ebstein patients had “paradoxical” motion of their atrialized septum and these alterations in
geometry were associated with impaired LV function, as determined by radionuclide angiography (14). This can act as an anatomical substrate for LVOT obstruction.

MINIMIZING THE RISK OF LVOT OBSTRUCTION IN EBSTEIN’S ANOMALY. We would advocate caution in escalating inotropes when faced with postoperative hypotension and hemodynamic instability in Ebstein patients. TEE is instrumental in differentiating between LVOT obstruction and other causes of hemodynamic compromise (e.g., ventricular dysfunction, tamponade). In the case reported here, further inotropic support would have proven detrimental, promoting further dynamic LVOT obstruction and mitral regurgitation. Given acceptable biventricular function, interruption of inotropes and initiation of a short-acting beta-blocker resulted in prompt resolution of both the LVOT obstruction and mitral regurgitation, with an obvious hemodynamic improvement.

Surgery for Ebstein’s anomaly aims at repairing the tricuspid valve, and resorts to a valve replacement only when repair is not achievable. The cone procedure is nowadays commonly employed and is applicable to almost all anatomical types of Ebstein’s anomaly (15). This uses valve tissue shaped in a cone rather than as a monocusp valve, which appears to improve durability of the valve repair. Da Silva recommended performing this repair early in life, around 5 years of age, to avoid the development of long-term complications. In fact, by performing an early childhood repair, one can hope for restoration of some muscle in the previously atrialized portion of the ventricular septum, avoiding protrusion into the LVOT and reducing the risk of dynamic obstruction (16).

FOLLOW-UP

Six months after discharge, our patient has recovered fully, and remains asymptomatic with a significantly improved exercise tolerance. Transthoracic echocardiography 6 months after his operation demonstrated a normal sized LV cavity with no evidence of LVOT obstruction, trivial mitral regurgitation, and a well-functioning tricuspid valve prosthesis.

CONCLUSIONS

In patients with Ebstein’s anomaly, LVOT obstruction can result from abnormalities of the mitral valve or underlying myocardium, or can occur in the absence of any associated left-sided abnormalities. Deviation of the thin atrialized basal ventricular septum can alter the structure and geometry of the left ventricle and lead to dynamic LVOT obstruction, exacerbated by changes in filling status and inotropy in the perioperative period. Physicians caring for postoperative Ebstein patients should be aware of this phenomenon and, once confirmed by echocardiography, should avoid a vicious cycle of escalating inotropic support and worsening LVOT obstruction. Increasing doses of a beta-blocker may prove helpful in relieving this dynamic obstruction and achieve hemodynamic stability.

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REFERENCES

1. Dearani JA, Danielson GK. Congenital heart surgery nomenclature and database project: Ebstein’s anomaly and tricuspid valve disease. Ann Thorac Surg 2000;69:5106-17.

2. Paranon S, Acar P, Ebstein’s anomaly of the tricuspid valve: from fetus to adult. Heart 2008;94:237-43.

3. Anderson KR, Zuberbuhler JR, Anderson RH, Becker AE, Lie JT. Morphologic spectrum of Ebstein’s anomaly of the heart: a review. Mayo Clin Proc 1979;54:174-80.

4. Zuberbuhler JR, Allwork SP, Anderson RH. The spectrum of Ebstein’s anomaly of the tricuspid valve. J Thorac Cardiovasc Surg 1979;77:202-11.

5. Attenhofer Jost CH, Connolly HM, O’Leary PW, Wames CA, Tajik AJ, Seward JB. Left heart lesions in patients with Ebstein anomaly. Mayo Clin Proc 2005;80:361-8.

6. Lee W-C, Fu M, Fang H-Y. Unusual combination: Ebstein’s anomaly and hypertrophic obstructive cardiomyopathy. J Echocardiogr 2016;14:42-4.

7. de Agustin JA, Perez de Isla L, Zamorano JL. Ebstein anomaly and hypertrophic cardiomyopathy. Eur Heart J 2008;29:2525.

8. Ito T. Native mitral valve causing left ventricular outflow tract obstruction in an adult with Ebstein’s anomaly. Anadolu Kardiyol Dergisi/The Anatol J Cardiol 2011;11:651-2.

9. Waterhouse DF, Murphy TM, McCreery CJ, O’Hanlon R. An unusual cause of dynamic left ventricular outflow obstruction. Int J Cardiol 2015;197:282-3.

10. Hirata K, Yagi N, Kubota S, Wake M, Tengan T. Case of Ebstein anomaly complicated by left ventricular outflow tract obstruction secondary to deformed basal septum attributable to atrialized right ventricle. Circulation 2016;133:e33-7.

11. Anderson KR, Lie JT. Pathologic anatomy of Ebstein’s anomaly of the heart revisited. Am J Cardiol 1978;41:739-45.

12. Edwards WD, Mierop L, Van Kutsche L, et al. Embryology and pathologic features of Ebstein’s anomaly. Prog Pediatr Cardiol 1993;2:5-15.

13. Benson LN, Child JS, Schaiger M, Perloff JK, Schelbert HR. Left ventricular geometry and function in adults with Ebstein’s anomaly of the tricuspid valve. Circulation 1987;75:353-9.

14. da Silva JP, Baumgardt JF, da Fonseca L, et al. The cone reconstruction of the tricuspid valve in Ebstein’s anomaly: The operation: early and midterm results. J Thorac Cardiovasc Surg 2007;133:215-23.

15. Lange R, Burri M, Eschenbach LK, et al. Da Silva’s cone repair for Ebstein’s anomaly: effect on right ventricular size and function. Eur J Cardio-Thorac Surg 2015;48:316-21.

KEY WORDS Ebstein’s anomaly, tricuspid valve, left ventricle, postoperative
IMAGING VIGNETTE: CLINICAL VIGNETTE

Norwood With Obstructed Total Anomalous Pulmonary Venous Connection and Tracheoesophageal Fistula Repair
Operating Room Delivery

Kyle W. Riggs, MD, Nina M. Price, Alan O’Donnell, MS, Haleh Heydarian, MD, Beth A. Rymeski, MD, David L.S. Morales, MD

ABSTRACT

A baby boy with prenatally diagnosed hypoplastic left heart syndrome variant with obstructed veins was born in the operating room (OR) and underwent emergent Norwood operation and repair of obstructed infra-diaphragmatic total anomalous pulmonary venous connection. Post-operatively, esophageal atresia with tracheoesophageal fistula was identified and repaired on day of life 11. The patient is thriving at 22 months of age. (Level of Difficulty: Advanced.)

We report the successful surgical management of a patient with total anomalous pulmonary venous connection (TAPVC), double outlet right ventricle with mitral atresia, and tracheoesophageal fistula (TEF) with esophageal atresia through stage II palliation, which has never been published in the literature.

A baby boy delivered at 36 weeks gestation weighing 2.0 kg was prenatally diagnosed with double outlet right ventricle with mitral atresia and infradiaphragmatic obstructed TAPVC via fetal echocardiogram at 26 weeks gestation. Doppler echocardiography showed altered flow pattern and connection from the pulmonary venous (PV) confluence to the portal vein (Video 1). Delivery occurred in a cardiac OR, and postnatal echocardiography confirmed diagnosis. At 1 min of life, the patient developed intermittent apnea and received positive pressure ventilation within 11 min of life. Oxygen saturations were initially in the 30s to 40s, but rose to the 70s. Surgery began within the hour in a neighboring OR. A Norwood with a Blalock-Taussig shunt was performed with TAPVC repair, which he tolerated well.

Failure to pass a nasogastric tube in the intensive care unit raised the suspicion of esophageal atresia with TEF, confirmed by full body X-ray (Figure 1). After consulting general pediatric surgery, gastrostomy tube placement occurred on day of life 5. We held feeds and did not extubate prior to esophageal repair. Despite the posterior TAPVC repair’s relationship to the TEF, the proximal and distal esophageal pouches were anastomosed without tension.

From the Cincinnati Children’s Hospital Medical Center, Heart Institute, Cincinnati, Ohio. The 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.

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At 5 months of age, the patient underwent a bilateral bidirectional Glenn. We believe one should be aggressive in shunted single-ventricle patients undergoing TAPVC to ensure unobstructed PV return because they often develop fibrosis at the anastomosis secondary to their increased Qp:Qs. In this case, a dilated coronary sinus was also pushing on the confluence, which was unroofed into the confluence, and the fibrosis was resected. Oxygen saturations were in the 80s. He was discharged home on post-operative day 5 with normal function and thrives at 22 months of age.

Prenatal diagnosis, paramount to his successful outcome, allowed for enhanced delivery planning, parent education, and staged surgical management. We recommend OR delivery for all patients with obstructed PVs. For patients with hypoplastic left heart syndrome or transposition of the arteries with an intact atrial septum, we advise delivery in a catheterization laboratory. A possible disadvantage of OR delivery is missed diagnoses, including intracranial hemorrhaging, but term babies rarely have significant intraventricular bleeding. Cranial ultrasonography showed no bleeding, and unless massive bleeding was present, emergent cardiac surgery would likely still proceed. Additionally, relying on sump drainage of a proximal esophageal pouch in a shunted single ventricle is a precarious situation secondary to the risk of aspiration, and coexisting congenital heart disease has been found to be an independent predictor of mortality for patients undergoing TEF/Ea surgical repair (1). We believe that immediate surgery allowed for pulmonary preservation and rapid recovery, making successful TEF repair possible within 2 weeks of birth.

FIGURE 1 Full-Body Roentgenogram of the 1-Day-Old Patient After Pulmonary Venous Repair and Norwood

Replogle tube (arrow) cannot advance past the upper intrathoracic esophagus, suggesting esophageal atresia with tracheoesophageal fistula (Video 1).

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REFERENCE
1. Diaz LK, Akpek EA, Dinavahi R, Andropoulos DB. Tracheoesophageal fistula and associated congenital heart disease: implications for anesthetic management and survival. Paediatr Anaesth 2005;15:862-9.

KEY WORDS congenital heart defect, double outlet right ventricle, pediatric surgery, pulmonary circulation

ABBREVIATIONS AND ACRONYMS
PV = pulmonary venous/vein
TAPVC = total anomalous pulmonary venous connection
TEF = tracheoesophageal fistula

APPENDIX For a supplemental video, please see the online version of this paper.
Aortoventricular Tunnel With Severely Dilated Ascending Aorta and Bicuspid Aortic Valve in a Newborn

Aya El Jerbi, MD, McKenna Murphy, MD, Hani Ghawi, MD

ABSTRACT

Aortoventricular tunnel is a rare congenital cardiovascular malformation whereby there is a paravalvular communication between the aorta and a ventricle. This unique case describes a newborn with an aortoventricular tunnel, a severely dilated ascending aorta, and a bicuspid aortic valve, which was suspected prenatally and surgically managed postnatally. (Level of Difficulty: Intermediate.) (J Am Coll Cardiol Case Rep 2020;2:734–9) © 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 male infant, born at 38 weeks to a grvida 2 para 1 to 2 mother via induced vaginal delivery because of maternal hypertension, with APGAR scores of 9 and 10 at 1 and 5 min, respectively, a birth weight of 4.1 kg, and length of 21 inches, was prenatally diagnosed by fetal echocardiogram with a dysplastic bicuspid aortic valve, a severely dilated ascending aorta, and a mildly dilated and hypertrophied left ventricle (LV) with normal systolic function.

DIFFERENTIAL DIAGNOSIS

Based on this prenatal echocardiogram (Figure 1), there was suspicion for a possible right sinus of Valsalva aneurysm into the LV versus an aortoventricular tunnel (AVT). Other less likely considerations in the differential diagnosis included coronary arteriovenous fistula, congenital isolated aortic incompetence, and aortic incompetence with ventricular septal defect.

LEARNING OBJECTIVES

- Although rare, AVT is a serious cause of abnormal blood flow from the aorta to the ventricle in infancy.
- Echocardiography is the diagnostic investigation of choice and must be used to distinguish AVT from other lesions that cause rapid runoff of blood from the aorta.
- Optimal management of patients with AVT includes prompt surgical repair to prevent progression into heart failure.
remained in the nursery and did not require transfer to the neonatal intensive care unit.

INVESTIGATIONS

A postnatal echocardiogram was performed a few hours after delivery and demonstrated a patent foramen ovale, bicuspid aortic valve with mild flow acceleration, mild aortic regurgitation, dilated aortic root and ascending aorta, and continued evidence of flow across the suspected ruptured sinus of Valsalva or AVT (Figures 2 to 4, Videos 1, 2, 3, 4, and 5). Mild left ventricular hypertrophy and moderate to severe dilation of the LV was also noted to be compressing the right ventricle. Another limited echocardiogram was performed 24 h later with similar findings. He was discharged from the nursery at 48 h after birth. His next follow-up at 2 weeks of age was in the outpatient setting, and he had remained asymptomatic and had regained birth weight.

He underwent a cardiac computed tomography angiogram, which reported a structure arising from the right coronary cusp just above the origin of the right coronary artery with a contained perforation into the interventricular septum. This communicated with the left ventricular outflow tract below the level of the aortic valve. A dilated ascending aorta was seen as well (Figure 5). He also underwent genetic evaluation and was found to have a latent transforming growth factor-beta binding protein (LTBP4) heterozygous mutation, a finding not sufficient to establish a genetic diagnosis.

MANAGEMENT

At 7 weeks of life, elective surgical repair was undergone. The delineated AVT was repaired with a sandwich technique using autologous pericardial patches on both the aortic entry side and LV exit site. The patent foramen ovale was also closed.

FOLLOW-UP

On his 2-week post-operative follow-up, he was overall thriving without any cardiac symptoms and had a reassuring physical examination. His echocardiogram revealed a residual shunt across his left ventricular patch end, a small atrial shunt, a severely dilated ascending aorta, a dysplastic aortic valve with mild aortic valve regurgitation, and a hypertrophied LV with borderline normal systolic function (Figures 6 and 7). He was followed serially, and at 3 months of age he had normalization of his left ventricular size and systolic function. At 14 months of age, he continued to be doing well clinically with improvement of dilation in ascending aorta (decreasing z-score toward normal range). There was no evidence of aortic stenosis nor worsening of mild aortic regurgitation.

DISCUSSION

AVT is a paravalvular connection between the aorta above the sinotubular junction and the ventricle. It was first reported in 1963 by Levy et al. (1) and continues to be a rare defect that only accounts for 0.1% to 0.5% of all congenital cardiac defects. Although the etiology remains uncertain, it has been suggested to result from a combination of maldevelopment of the endocardial cushions, which give rise to the pulmonary and aortic roots, and abnormal separation of these structures (2). Many times, AVTs are associated with other structural abnormalities. Associated lesions of the aortic valve occur in about 20% of patients, ranging from 2-leaflet valves without obstruction to severe dysplasia or atresia.

Hovaguimian et al. (3) proposed a classification of 4 anatomic types of AVTs and suggested that repair should be individualized according to the anatomic type. They described a slit-like opening at the aortic end with no valve distortion in 24% of the cases (type 1), a large extracardiac aneurysm in 44% (type 2), an intracardiac aneurysm of the septal portion of the tunnel with or without right ventricular outflow tract obstruction in 24% (type 3), and a combination of

![Figure 1: Prenatal Fetal Echocardiogram](image)

White arrow points toward right aortic cusp. Green arrow points toward opening of the tunnel into the left ventricle. Structure marked A depicts the aortoventricular tunnel.
types 2 and 3 in 8% (type 4). The differences between the 4 types most likely represent different degrees and stages of the same disease process and have a strong bearing on the mortality, morbidity, repair techniques, and outcome of the surgical treatment (3). In this case, the patient’s AVT was more consistent with the more advanced, type 3 to 4 variant.

Echocardiography is the diagnostic investigation of choice. Transthoracic cross-sectional imaging in a parasternal long-axis view allows for viewing of the tunnel itself, and its aortic origin and left ventricular opening. On color Doppler studies, diastolic flow can be seen passing from the aorta to the LV and systolic flow from the ventricle to the aorta. In utero diagnosis of AVT is made possible by the finding of fetal left ventricular enlargement and hypertrophy, aortic root enlargement, and aortic regurgitation on routine obstetric ultrasound screening as early as the 18th to 20th gestational week (4).

AVTs must be distinguished from other lesions that cause rapid runoff of blood from the aorta and produce cardiac failure. An AVT differs from a ruptured sinus of Valsalva aneurysm in that an AVT orifice is located in the tubular ascending aorta rather than in a sinus of the aortic valve. In addition, an AVT passes outside of the heart into the tissue plane between the muscular subpulmonary infundibulum and the aortic valvular sinuses. Echocardiography may be misleading and distinguishing between the two is difficult when there is an aneurysm at the level of the right sinus of Valsalva with aortic incompetence. This is because of prolapse of the right aortic cusp occluding the ventricular orifice of the tunnel during diastole. It is important to note that the ostium of a coronary artery may lie within an AVT and absence of the origin of the left or right have both been observed with this anomaly. It is, therefore, of utmost importance to visualize the ostium of the coronary arteries before any intervention.

Although this patient was found to have a mutation in LTBP4 (expressed in cardiac, skeletal muscle, and lung tissue), a single variant in the LTBP4 gene is not sufficient to establish a genetic diagnosis. There are currently no known molecular markers for AVT, and it is not associated with any recognized genetic syndrome. Recent findings of cystic medial necrosis within the wall of an ascending aortic aneurysm resected 15 years after repair of an AVT raises the possibility that markers of an associated or underlying connective tissue disorder may emerge in the future.

Optimal management of symptomatic AVT consists of diagnosis by echocardiography complimented with cardiac catheterization, as needed to elucidate coronary arterial origins or associated defects, followed by prompt surgical repair. The goal of any treatment modality is to obliterate the tunnel. The techniques that have been described in previous reports are summarized as follows: 1) closure of the aortic orifice of the tunnel with or without a patch (Dacron,
pericardium Teflon); 2) closure of the ventricular end of the tunnel; 3) obliteration of the tunnel (i.e., ligation of the tunnel, or partial resection of the tunnel, or filling of the tunnel with gel-foam); or 4) closure of both orifices (aortic and ventricular [i.e., sandwich technique]) (1,3,5). Ideally, both ends of the tunnel should be closed, providing support to the right aortic leaflet. This is critical to the preservation of the aortic valve competency and avoidance of subpulmonary obstruction (4,6).

The closure of the aortic orifice requires surgical opening of the ascending aorta. The same approach can be used for closure of the LV outlet through the aortic valve. Risks of this approach include potential aortic valve injury. Serino et al. (7) support closing the aortic defect by direct suture. However, this technique could distort the cusps by pulling them toward the weak aortic wall, which remains unsupported within the dilated aortic sinus. Consequently, the aortic regurgitation may persist and progress even if repaired in infancy. The surgical patch technique is believed to reduce this risk. Using a direct approach, advancing through the tunnel and closing both ostia with pericardial patches avoids distortion of the aortic valve while supporting the aortic wall.

Only patients having undergone repair in the first 6 months of life have been shown to have subsequent normalization of left ventricular size and function. Observation of the exceedingly rare, asymptomatic patient with a small tunnel may be justified by occasional spontaneous closure seen in a single documented case (7). However, most patients develop symptoms of heart failure during the first year of life. The onset, severity, and progression of heart failure is, however, variable, and ranges from many years of asymptomatic compensation to rapid decompensation, sudden death, or death in utero. Therefore, prompt surgical repair is advised at time of diagnosis. Martins et al. (5) illustrated that most patients were asymptomatic at post-surgical follow-up (median, 5 years; 1 month to 35 years), and a minority had residual AVT with, at most, mild aortic regurgitation. All patients require lifelong follow-up for recurrence of the tunnel, aortic valve incompetence, left ventricular function, and aneurysmal enlargement of the ascending aorta as well as risk of endocarditis (8).

**CONCLUSIONS**

AVT is a rare cardiac malformation that may cause progressive postnatal heart failure and is often associated with other cardiac lesions. In utero diagnosis currently improves the neonatal management of AVT through assessment of its prognosis and programmed assisted delivery. High suspicion is
warranted when a prenatal fetal echocardiogram indicates aortic regurgitation and left ventricular dysfunction (9). Patch closure is the surgical procedure of choice for repair and has good long-term outcomes (10).

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REFERENCES

1. Levy MJ, Lillehei CW, Anderson RC, Amplatx K, Edwards JE. Aortic-left ventricular tunnel. Circulation 1963;27:841-53.

2. Mitropoulos FA, Laks H, Kanakis M, Levi D. Aorto-left ventricular tunnel: an alternative surgical approach. Ann Thorac Surg 2006;82:1113-5.

3. Hovaguimian H, Cobanoglu A, Starr A. Aortico-left ventricular tunnel: a clinical review and new surgical classification. Ann Thorac Surg 1988;45:106-12.

4. Tuna IC, Edwards JE. Aortico-left ventricular tunnel and aortic insufficiency. Ann Thorac Surg 1988;45:5-6.

5. Martins JD, Sherwood MC, Mayer JE, Keane JF. Aortico-left ventricular tunnel: 35-year experience. J Am Coll Cardiol 2004;44:446-50.

6. Knott-Craig CJ, van der Merwe PL, Kalis NN, Hunter J. Repair of aortico-left ventricular tunnel associated with sub-pulmonary obstruction. Ann Thorac Surg 1992;54:557-9.

7. Serino W, Andrande JL, Ross D, de Leval MR, Somervill J. Aorto-left ventricular communication after closure: later post-operative problems. Br Heart J 1983;49:501-6.

8. Toganel R, Benedek T, Suteu C, Benedek I. Aneurysmal aorto-left ventricular tunnel causing right ventricular outflow tract obstruction, associated with bicuspid aortic valve. Heart Vessels 2013;30:140-2.

9. Singh Anju, et al. Case series of antenatally diagnosed aortico-left ventricular tunnel. Pediatr Cardiol 2011;32:822-5.

10. Ziesenitz VC, Gorenflo M, Loukanov T. Repair of an aorto-right ventricular tunnel in a newborn. Cardiol Young 2015;26:147-8.

KEY WORDS aortoventricular tunnel, bicuspid aortic valve, dilated ascending aorta, fetal echocardiography

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

CASE REPORT: CLINICAL CASE

TGA With Interarterial Course and Athletes Heart
A Diagnostic Dilemma Answered by Stress CMR

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ABSTRACT
We report a case of coronary artery compression and athlete’s heart in a patient with a history of transposition of the great arteries. We present the diagnostic dilemmas and demonstrate the use of cardiac magnetic resonance imaging and cycle-ergometer stress cardiac magnetic resonance in the management of our patient. (Level of Difficulty: Intermediate.)

A 20-year-old Chinese male was referred to our adult congenital heart disease clinic for routine follow-up. He led an active lifestyle reporting an exercise duration of >12 h/week, running half-marathons and playing competitive tennis at an amateur level. Physical examination revealed a pansystolic murmur radiating to the left axilla.

MEDICAL HISTORY
He had a history of D-transposition of the great arteries and underwent a balloon atrial septostomy on day 1 of life, followed by arterial switch operation (ASO) or the Jatene procedure using the Lecompte technique on day 3 of life.

INVESTIGATIONS
Electrocardiogram showed a normal sinus rhythm with left ventricular hypertrophy by voltage criteria. A transthoracic echocardiogram (TTE) showed biventricular dilatation (left ventricle end-diastolic diameter [LVEDD] = 66 mm; indexed LVEDD [iLVEDD] = 38 mm/m², right ventricular basal diameter = 43 mm) with eccentric hypertrophy (LV mass = 206 g; LV mass index = 118 g/m²) and mildly reduced biventricular systolic function (left ventricular ejection fraction (LVEF) = 52%, tricuspid annular plane systolic excursion = 13 mm) with wall motion abnormalities of the septum and....

LEARNING OBJECTIVES
- To make a differential diagnoses in the evaluation of abnormal cardiac size and function in a D-transposition of great arteries post-ASO patient.
- To understand the role of different imaging modalities, and in particular, the role of CMR in the workup of patients with surgically corrected transposition of the great arteries.
- To recognize features of athlete’s heart and its overlap with ischemic and dilated cardiomyopathy.
Table 1. TTE Summary

| Parameter                  | Result                                      |
|----------------------------|---------------------------------------------|
| LVEF                       | 52% with RWMA                               |
| LVEDD                      | 66 mm                                       |
| Indexed LVEDD to BSA       | 38 mm/m²                                    |
| LV mass                    | 206 g                                       |
| LVMI                       | 118 g/m²                                    |
| Regional wall thickness    | 0.24                                        |
| MR vena contracta          | 5 mm                                        |
| Effective regurgitant orifice area | 0.2 cm²                                |
| Conclusions                | Dilated left ventricle with low-normal LV systolic function and RWMA. Moderate MR |

Summary of the patient’s TTE, which showed a moderately dilated left ventricle, with mildly reduced LVEF and moderate MR.

LVEDD – left ventricular end-diastolic diameter; LVEF – left ventricular ejection fraction; LVMI – left ventricular mass index; MR – mitral regurgitation; RWMA – regional wall motion abnormality; TTE – transthoracic echocardiogram.
In this case, the left coronary and right coronary arteries were closely adjacent and the surgeon was unable to translocate the coronary artery buttons separately. The single coronary button was reimplanted onto the right coronary cusp. This led to an inter-arterial course of the left coronary artery (Figure 1). In this case, where the inter-arterial course is iatrogenic and after ASO, it is less certain whether the prognosis is similar to uncorrected congenital anomalous coronary arteries. It is still, however, prone to compromised blood flow resulting from scarring and angulation. There is no guideline that addresses coronary anomalies post-ASO, but in anomalous coronary arteries, the 2018 American College of Cardiology/American Heart Association guidelines recommend a symptom-guided approach, with surgical correction in patients with left coronary arteries from the right sinus as a Class I, Level of Evidence: A recommendation when ischemia is proven on diagnostic testing, and Class II, Level of Evidence: A if there is none (2). In post-ASO cases, we recommend a prudent approach involving multidisciplinary teams when making clinical decisions on coronary reimplantation surgery.

The presence of ischemia was a key diagnostic question in our assessment. CMR can assess for ischemia in a combination of perfusion and wall motion imaging. It is also important that clinicians be cognizant of the limitations of stress CMR, especially in young patients with excellent cardiac reserve. In such cases where the clinical scenario is complex and does not fit in the clinical guidelines, we recommend a prudent approach involving multidisciplinary teams.

The last challenge was in the differentiation of dilated cardiomyopathy (DCM) from athlete’s heart. Dilated cardiomyopathy (DCM) is characterized by dilated LVEF in the absence of ischemia, valvular disease, or hypertension (3). Athlete’s heart may also have features that overlap with DCM, with chamber dilatation resulting from repetitive increased stroke volumes and pressure overload from exercise and a resulting lower resting EF (4). A study on elite cyclists showed an average left ventricle internal diameter of 60.1 ± 3.9 mm with LVEF <60% in approximately 40% of participants (5). Because of the overlapping features of DCM and athlete’s heart, the diagnosis may be difficult to ascertain. Key features in differentiating the 2 conditions are a normal diastolic function and an appropriate hyperdynamic cardiac response to exercise in athlete’s heart, which patients with DCM are rarely able to achieve (3,4). Stress-imaging modalities like echocardiography and myocardial perfusion imaging would be able to assess for these features. Although echocardiography is the standard modality to assess diastolic function, this can also be assessed via CMR. CMR, however, may have a growing role as the imaging modality of choice for patients. CMR has the added benefit of LGE assessing for fibrosis, a feature that may be present in DCM but not seen in athlete’s heart. T1 and ECV mapping may also have an additional role, especially in cases where the diagnosis is uncertain. Higher native T1, ECV, and T2 relaxation times have also been reported in patients with DCM compared with controls and athletes, with native T1 showing to be the best discriminator for both conditions (3).

In our case, the patient had no increased uptake on LGE. Additionally, he showed a hyperdynamic response to exercise with no wall motion abnormalities, and T1 and ECV mapping values were normal.
This rules out ischemic cardiomyopathy and DCM, giving the diagnosis of athlete’s heart. The effects of detraining in our patient (i.e., reduction in LV mass with no change in LVEF) were also consistent with findings in another study (6).

**FOLLOW-UP**

After detraining, a repeat echocardiogram showed a normal LV systolic function with a reduction in LV size. Because of considerations mentioned previously, a strategy of watchful waiting with advice of strictly avoiding vigorous physical activities has been used.

**CONCLUSIONS**

The multiple diagnostic considerations in this case highlight the advantages of ergometer stress CMR as a safe and comprehensive imaging modality in the assessment of a patient with complex congenital heart disease. With a noninvasive test without
radiation exposure, we have demonstrated that the patient has normal cardiac physiology and an adequate response to physical stress, clinching the diagnosis of athlete’s heart. CT angiography, with its superior spatial resolution to magnetic resonance angiography, also played a critical role in the diagnostic assessment. To our knowledge, this is the first reported case of cycle ergometer stress CMR used in this setting.

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REFERENCES

1. Sarris GE, Balmer C, Bonou P, et al. Clinical guidelines for the management of patients with transposition of the great arteries with intact ventricular septum. Eur J Cardiothorac Surg 2017; 51:e1-32.
2. Stout KK, Daniels CJ, Aboulhosn JA, et al. 2018 AHA/ACC guideline for the management of adults with congenital heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol 2019;73: e81-192.
3. Mordi I, Carrick D, Bezerra H, Tzemos N. T1 and T2 mapping for early diagnosis of dilated non-ischaemic cardiomyopathy in middle-aged patients and differentiation from normal physiological adaptation. Eur Heart J Cardiovasc Imaging 2016;17:797-803.
4. Gati S, Sharma S, Pennell D. The role of cardiovascular magnetic resonance imaging in the assessment of highly trained athletes. J Am Coll Cardiol Intv 2018;11:247-59.
5. Abergel E, Chatellier G, Hagege AA, et al. Serial left ventricular adaptations in world-class professional cyclists: implications for disease screening and follow-up. J Am Coll Cardiol 2004; 44:144–9.
6. Pedlar CR, Brown MG, Shave RE, et al. Cardiovascular response to prescribed detraining among recreational athletes. J Appl Physiol 2017;124: 813-20.

KEY WORDS athlete’s heart, cardiac magnetic resonance, stress CMR, transposition of great arteries
First Evidence of Endo-Epicardial Asynchrony of the Left Atrial Wall in Humans

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ABSTRACT

Asynchronous activation of the endo-epicardium plays an important role in persistence of atrial fibrillation. So far, endo-epicardial asynchrony has only been demonstrated in the human right atrium. Our data provides the first evidence for existence of a considerable degree of endo-epicardial asynchrony in the human left atrium. (Level of Difficulty: Advanced.) (J Am Coll Cardiol Case Rep 2020;2:745-9) © 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/).

Atrial fibrillation (AF) is regarded as the cardiovascular epidemic of the 21st century. It is a progressive disease which is associated with serious complications such as stroke, heart failure and increased mortality. However, treatment of AF is still suboptimal as mechanisms underlying AF initiation and persistence are still incompletely understood (1).

Simultaneous endo-epicardial mapping provides novel insights into the arrhythmogenic substrate underlying AF (2-4). It was recently discovered that persistence of AF is caused by asynchronous electrical activation of adjacent endo-epicardial layers, referred to as endo-epicardial asynchrony (EEA) of the right atrial (RA) wall (2). This phenomenon may even present during sinus rhythm (SR) (3). The existence of EEA is a prerequisite for transmural conduction, giving rise to so-called focal waves in the opposite layer. It is assumed that over time, enhanced by AF-induced structural remodeling, the electrical syncytium of atrial myocytes becomes disrupted and that the atrial wall is gradually transformed into layers of narrow, anatomically delineated pathways. Based on these findings, it is postulated that progression of AF transforms the atrial wall into electrical layers in which dissociated waves constantly “feed” each other (2,5).

So far, EEA has been demonstrated only in the human RA, especially in thicker parts. It is understandable that EEA occurs in thicker, trabeculated

LEARNING OBJECTIVES

- Endo-epicardial asynchrony plays an important role in the pathophysiology of atrial fibrillation and may occur in both right- and left atria.
- Simultaneous endo-epicardial mapping may provide more insights into the arrhythmogenic substrate of atrial fibrillation.
parts of the RA free wall (3,6,7). However, whether EEA is also present in the thin lateral wall of the left human atrium (LA) is unknown. The goal of the present study was to investigate if and to what extent EEA also exists in the LA in patients with AF.

METHODS

STUDY POPULATION. Patients (3 males; 73.3 ± 1.5 years of age) with paroxysmal AF undergoing cardiac surgery for coronary artery or valvular heart disease including LA appendage (LAA) amputation were investigated; clinical characteristics are provided in Table 1. The mapping protocol was approved by the institutional ethical committee (MEC2010-054).

INVESTIGATIONS AND MANAGEMENT. After the operator performed arterial cannulation, simultaneous endo-epicardial mapping was carried out using a high-density mapping device containing 2 electrode arrays of 8 × 16 electrodes (n = 256; diameter = 0.4 mm, at an interelectrode distance [IED] of 2 mm), positioned exactly opposite each other. Recordings were sampled at a rate of 1 kHz and amplified (gain: 1,000), filtered (bandwidth: 0.5 to 400 Hz), and converted from analog to digital signals (16 bits).

Before extracorporeal circulation in the patient was begun, the mapping device was introduced through the LAA incision and closed with a purse-string suture. The mapping device was positioned with its tip toward the left superior pulmonary vein in order to perform 10 s of SR mapping (Figure 1).

DATA ANALYSIS. Unipolar electrograms were analyzed semiautomatically using custom-made Python version 3.6 software (Arlington, Virginia). Local activation times were determined by marking the steepest negative slope of atrial potentials with a minimal slope of 0.05 mV/ms. Mean activation time was calculated for each patient and each layer separately. Areas of conduction delay (CD) and conduction block (CB) were defined as activation time differences of ≥7 ms and ≥12 ms, respectively, between neighboring electrodes. These cutoff values were derived from previous studies and corresponded to effective conduction velocities of 17 to <29 cm/s for CD and <17 cm/s for CB (8,9).

As shown in the right panel of Figure 1, local endo-epicardial activation time differences were determined by selecting the median of the time delays within the exact opposite electrode and its 8 surrounding electrodes. The asynchrony map shows the longest time delay for every endo-epicardial electrode pair. In accordance with prior endo-epicardial mapping studies, EEA was defined as a transmural difference in electrical activation of ≥15 ms between 2 opposite electrodes (2,3).

RESULTS

A total of 35 SR beats were analyzed. Mean total activation time of the entire endo-epicardial mapping area was 42.4 ± 9.5 ms and did not differ between both layers (epicardium: 31.2 ± 9.9 ms; and endocardium: 37.8 ± 10.3 ms; p = 0.60). Areas of CD and CB were observed in 3.2% and 6.3%, respectively, at the epicardium and 3.3% and 3.0%, respectively, at the endocardium. The lowest amount of conduction disorder (CD: 5.2%; CB: 0.3%) was observed in the patient who underwent his first AF episode only 11 days prior to surgery. Also, no EEA was present in that patient. In the 2 patients with paroxysmal AF of >6 months, the rates of EEA were 2.7% and 41.4% (degree of EEA [15 to 44 ms]), respectively. Interestingly, the patient with the highest degree of EEA (maximal: 44 ms) had paroxysmal AF for almost 5 years. Figure 2 shows color-coded activation maps of the endo-epicardium and a corresponding EEA map of 1 single SR beat from that patient.

DISCUSSION

The present data provide evidence for the existence of a significant degree of EEA in the human LA, as well, even during SR. Surprisingly, the degree of EEA in the LA was as high as 44 ms. Assuming a wall thickness of 2 or 3 mm, an EEA of 44 ms would require slow, transmural conduction velocities of 4.5 and 6.8 cm/s, respectively.

| TABLE 1 | Patient Characteristics |
|----------------|-----------------------|
| Patient I | Patient II | Patient III |
| Age, yrs | 72 | 73 | 75 |
| Sex | Male | Male | Male |
| BMI, kg/m² | 22.8 | 22.3 | 29.7 |
| Underlying heart disease | MVD | CAD | CAD |
| History of AF | PAF | PAF | PAF |
| Time since AF diagnosis, yrs | 4.8 | 0.03 | 0.54 |
| LVF | Mildly impaired | Good | Good |
| LA diameter, mm | 49 | 55 | 45 |
| LA volume, ml | 72 | 75 | 57 |
| DM | No | Yes | Yes |
| Hypertension | No | Yes | Yes |

AF = atrial fibrillation; BMI = body mass index; CAD = coronary artery disease; DM = diabetes mellitus; LA = left atrium; LVF = left ventricle function; MVD = mitral valve disease; PAF = paroxysmal atrial fibrillation.
Derakchan et al. (6) performed simultaneous endo-epicardial contact mapping of both canine atria. A total of 240 unipolar epicardial electrodes (IED = 3.1 to 6 mm) and 128 unipolar endocardial electrodes (IED = 6 to 9 mm; 64 electrodes) were inserted within the atria through an incision in the LAA. During pacing (cycle length: 250 ms) at the right atrial appendage, RA endocardial activation spread faster than RA epicardial activation (respectively: 45 ± 12 ms vs. 60 ± 19 ms; p < 0.05). However, this was not the case in the LA. Eckstein et al. (4) performed simultaneous endo-epicardial mapping (IED: 1.6 mm; 146 epicardial and 90 endocardial unipolar electrodes) of the LA free wall in goats during SR, acute AF, after 3 weeks, and after 6 months of AF. Almost no EEA was observed during SR; however, EEA did increase along with duration of AF and occurred at up to 50 ms. EEA occurred more often at thicker parts of the LA. These findings correspond to prior mapping studies examining the RA, which demonstrated that the persistence of AF is also associated with an increase in EEA and focal waves in trabeculated parts of the RA (2,8,9). Eckstein et al. (4) also observed that, with increasing duration of AF (acute AF to 6 months of AF), there was a decrease in LA wall thickness and an increase in EEA. These findings imply that the absolute thickness of the atrial wall together with the degree of electrical and structural remodeling are important for the occurrence of EEA.

**CONCLUSIONS**

Now it has been demonstrated that a considerable degree of EEA can occur in both the RA and the LA. It
can be assumed that EEA can occur anywhere in both atria. This is in line with prior epicardial mapping studies demonstrating that focal waves, which may arise due to EEA, occurred throughout both atria without predilection sites (10). Although only 3 patients are described, the highest degree of EEA was found in the patient with the longest history of AF. If this observation is confirmed in larger populations, it indicates that even during SR the degree of EEA is indeed related to AF duration and that early intervention is mandatory to prevent progression of AF. Patients with extensive remodeled atria and numerous areas of EEA may not benefit from ablative therapy. Several mapping studies and reports of hybrid procedures have shown that AF consists of a 3-dimensional arrhythmogenic substrate. In the presence of EEA, endocardial mapping alone may not provide sufficient guidance for ablative therapy (2,11). Knowledge of EEA and the ability to stage AF, based on the degree of EEA, is essential for individualized and staged AF therapy.

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REFERENCES

1. Zori-Berisso M, Lercari F, Carazza T, Domenicucci S. Epidemiology of atrial fibrillation: European perspective. Clin Epidemiol 2014;6:213-20.
2. de Groot N, van der Does L, Yaksh A, et al. Direct proof of endo-epicardial asynchrony of the atrial wall during atrial fibrillation in humans. Circ Arrhythm Electrophysiol 2016. 9 pii:e003648.
3. van der Does L, Knops P, Teuwen CP, et al. Unipolar atrial electrogram morphology from an epicardial and endocardial perspective. Heart Rhythm 2018;15:879-87.
4. Eckstein J, Maesen B, Linz D, et al. Time course and mechanisms of endo-epicardial electrical dissociation during atrial fibrillation in the goat. Cardiovasc Res 2011;89:816-24.
5. Kharbanda RK, Garcia-Izquierdo E, Bogers A, De Groot NMS. Focal activation patterns: breaking new grounds in the pathophysiology of atrial fibrillation. Expert Rev Cardiovasc Ther 2018;16:479-88.
6. Derakhchan K, Li D, Courtemanche M, et al. Method for simultaneous epicardial and endocardial mapping of in vivo canine heart: application to atrial conduction properties and arrhythmia mechanisms. J Cardiovasc Electrophysiol 2001;12:548-55.
7. Schuessler RB, Kawamoto T, Hand DE, et al. Simultaneous epicardial and endocardial activation sequence mapping in the isolated canine right atrium. Circulation 1993;88:250-63.
8. Allessie MA, de Groot NM, Houben RP, et al. Electropathological substrate of long-standing persistent atrial fibrillation in patients with structural heart disease: epicardial breakthrough. Circ Arrhythm Electrophysiol 2010;3:606-15.
9. de Groot NM, Houben RP, Smeets JL, et al. Electropathological substrate of longstanding persistent atrial fibrillation in patients with structural heart disease: epicardial breakthrough. Circulation 2010;122:1674-82.
10. Mouws E, Lanters EAH, Teuwen CP, et al. Epicardial breakthrough waves during sinus rhythm: depiction of the arrhythmogenic substrate? Circ Arrhythm Electrophysiol 2017;10 pii: e005145.
11. Glover BM, Hong KL, Baranchuk A, Bakker D, Chacko S, Bideri G. Preserved left atrial epicardial conduction in regions of endocardial “isolation. J Am Coll Cardiol EP 2018;4:557-8.

KEY WORDS atrial fibrillation, atrial remodeling, cardiac surgery, electropathology, electrophysiology, simultaneous endo-epicardial mapping
Painful left bundle branch block (LBBB) syndrome is a disorder whereby rate-related ventricular conduction aberrancy can cause disabling symptoms with significant activity limitation. Its true prevalence in the general population is unknown due to coexisting coronary artery disease (CAD) and lack of widespread awareness of its existence, but it is overall considered a rare cause of chest pain (1,2).

Since first described in 1946, a variety of treatment strategies have been utilized with variable results, suggesting a complex underlying pathophysiology. Although incompletely understood, the proposed mechanisms are probably related to significant left ventricular dyssynchronous systolic septal motion due to early septal radial inward thickening followed by late posterior inward thickening.

Selective pacing of the atrioventricular conduction axis, usually known as His bundle pacing, is currently considered the most physiological methods for maintaining intrinsic atrioventricular conduction. His bundle pacing has also been successfully employed to treat painful left bundle branch (LBB) syndrome by correction of the wide QRS complex and restoration of electrical dyssynchrony (3). Corrective His bundle pacing (HBP) is possible due to the proximal and focal nature of lesions causing intra- or infra-Hisian conduction abnormalities, resulting in complete conduction block or asynchronous conduction between longitudinally dissociated, pre-destined Purkinje fibers. The hypothesis for HBP to correct LBBB is that increased pacing output penetrates the LBBB region beyond the area of conduction block and hence normalizes LBBB by direct recruitment of the LBB (4). HBP represents an appealing strategy for the treatment of painful LBBB syndrome. However, HBP has some limitations, including knowledge of the precise location of the His bundle, which varies significantly between individual patients; the frequent occurrence of high and unstable pacing threshold; abnormal sensing; and permanent damage to the His bundle acutely or chronically. Because of these limitations, the QRS duration cannot be normalized in almost one-half of patients where HBP is achieved (5,6).

Conduction system pacing via the LBB (known as left bundle pacing [LBP]) has recently emerged as an alternative strategy for cardiac resynchronization therapy. LBP via intraseptal lead fixation can bypass conduction system pathology more distal to the leftsided His to produce near physiological activation of the heart with lower thresholds than corrective His bundle pacing. In this issue of JACC: Case Reports, Garg et al. (7) described the first 2 cases with painful LBBB syndrome successfully treated with LBP in combination with AV fusion, leading to complete alleviation of symptoms and resolution of the LBBB with remarkable narrowing of QRS.

Although this is one of the least frequent indications for LBP, the authors should be commended by their adequate patient selection, as evidenced by
their great clinical outcome and by the beautifully descriptive iconography provided in their case report. In this “Da Vinci” corner, we sought to review the anatomical determinants necessary to understand LBB pacing and the normal anatomy (and its variants) of the left bundle branch in the human heart.

**LOCATION OF THE HIS BUNDLE AS A REFERENCE FOR LBB PACING**

In 2017, Huang et al. (8) reported LBP, which is a transvenous, transseptal implantation technique resulting in LBB capture, usually with low pacing capture thresholds. With the position of the His recording as a reference, the initial site for LBP was between 0 to 15 mm below the distal tricuspid valve annulus distal (ventricular aspect) and apical to the His position in right anterior oblique (RAO) (30°) fluoroscopic view. Thus, the fluoroscopic location of the His bundle is of critical importance as it helps identify an initial tentative position to deploy the LBP lead. Precise knowledge of the location of the atrial and penetrating components of the atrioventricular conduction axis and its relation with the His position as reference during LBP is of paramount importance for successful LBP.

In our anatomical studies, we have encountered marked interindividual differences, with significant variations in the site of transition from the atrioventricular node to the bundle of His relative to the tricuspid valve annulus and the atrioventricular membranous septum. As we have emphasized in a recent publication (9), we followed the precedent of Tawara (10) when taking the site of penetration into the insulating tissues of the central fibrous body as representing the transition from the node to the bundle of His. This penetration into the fibrous tissues of the central fibrous body occurred superiorly in 58.5% of specimens, with the transition found inferiorly within the triangle of Koch in the remaining 41.5% of the hearts. Consequently, we observed that the axis penetrated on the atrial side of the hinge-line in just over one-half of the hearts, whereas in the remainder, the transition was either at the hinge-line or on its ventricular aspect. This is in keeping with our findings regarding the location of the largest His bundle deflection relative to the septal leaflet and the angiographic vertex of the triangle of Koch. These anatomical variations are of importance for the interventional electrophysiologist when assessing for the best location for lead deployment into the LBB.

**THE LBB SYSTEM**

The membranous septum is divided into atrioventricular and interventricular component at the base of the interleaflet triangle between the right and the noncoronary leaflets of the aortic valve. The length of the membranous septum is highly variable, with a mean value of 4.6 ± 1.5 mm, and a range from 1 to 9 mm. We observed that in almost three-fifths of the specimens, the interventricular component of the membranous septum was very small or nonexistent. In those cases, we found a rapid take-off of the fascicles of the LBB at the level of the hinge of the septal leaflet of the tricuspid valve.

Unlike HBP, where the target zone for effective pacing is very small, the LBB fibers, despite presenting large interindividual variations, are widely distributed as a subendocardial network, and it may be easier to reach some of the LBB areas during the intraseptal implantation technique. At the implantation of LBP, the pacing lead penetrates the ventricular septum to reach the left ventricular subendocardial trunk or ramifications of the left bundle subsequent to the branching of the axis. This part of the axis extends usually, but not always, from the inferior border of the membranous septum, sandwiched between the septum and the crest of the muscular ventricular septum. After penetrating the AV membranous septum, the conduction axis has a nonbranching component that, in 75% to 85% of cases, runs only for a short distance (1 to 3 mm) along the septal crest before giving rise to the fascicles of the left bundle (LBB) on the septal surface (Figure 1). The most anterior fibers of the LBB originate at the end of the branching portion located underneath the inferior edge of the interventricular membranous septum or—in a minority of cases—within the inferior margin of the membranous septum. Histological studies also demonstrated variations in some cases, where the His bundle distal to the central fibrous body traversed the left side of the muscular interventricular septum (IVS) between 2 and 3.5 mm below the membranous septum, or the His bundle anterior to the central fibrous body coursed to the right of the crest of the muscular IVS. As described by Massing et al. (11), in 5 hearts with "right-sided His bundles," the right bundle branch (RBB) formed a direct continuation of the His bundle, whereas in the most common setting (27 cases), the His bundle-RBB junction formed a definite obtuse angle.
The most impressive feature of the LBB anatomy was its marked variability between individuals. The origin of the LBB is broad in some and narrow in others (ranging from <1 to 14 mm) and is significantly influenced by the anatomical relationship of the His bundle to the IV septum (9,11). As it coursed down the IV S from base toward apex, the LBB widens, in some hearts abruptly, and in others more gradually. The size, number, location, configuration, and distribution of LBB subdivisions is still a matter of active debate. Some researchers consider the LBB an exclusively bifascicular structure with an anterior and a posterior ramification (12). Early electrophysiological data from Durrer et al. (13), showed that 3 distinct endocardial areas in the left ventricle are synchronously activated during the first 5 ms of cardiac excitation. These 3 islands of initial excitation may reasonably be assumed to correspond to the terminal areas of the 3 main parts of the LBB system. Although some authors described the branching of the LBB as “unpredictable,” histopathological investigations confirmed the consistent presence of 3 rather than 2 main peripheral networks comprised of a thin and elongated anterior radiation, a wider posterior one and a third radiation designated to cover the midseptal surface (9,14-16). The septal branch emerged in most cases from the common left bundle, but in some cases from the anterior, from posterior radiations, or by a complex plexus of ramification given by both the anterior and posterior fascicles. The main LBB trunk (i.e., the target of the lead to be deployed) extends inferiorly 10 to 15 mm toward the apex; therefore, it is likely that in most cases, the pacing lead penetrates the midseptal area at this level of the conduction axis and is able to excite the LBB. However, based on the complexity and variability of the LBB system topography, the transseptal lead may often times reach the midseptal branch or even a wide posterior ramification (Figure 2).

The Risk of LBB Injury and Cardiac Perforation

During LBP implantation, it is important to place the pacing lead perpendicular to the ventricular septum to avoid an excessively apical position, where the IVS becomes thicker. Following this recommendation improves the ability to rapidly advance the pacing lead helix into the left side of the IVS. Observing a unique electrocardiographic...
FIGURE 2  Anatomy and Fluoroscopy of the Left Bundle Branch

(A) A gross dissection of the human heart to reveal in simulated right anterior oblique view (RAO) the location of the compact atrioventricular (AV) node and penetrating AV bundle relative to the septal leaflet of the tricuspid valve (STV) anteriorly. In this case, the transition from the compact AV node to the penetrating AV bundle occurs inferiorly, and the length of the AV bundle implies a large His bundle recording zone. A dashed blue line marks the position of the His bundle as a reference to identify the initial site for left bundle (LB) pacing about 0 to 15 mm below the STV tricuspid valve annulus distal (ventricular) and apical to the His position. Red dashed lines indicate the schematics of the left bundle branch (LBB) on the left side of the interventricular septum.

(B) An RAO 50° fluoroscopic view of a right atrial angiography taken during an EP study to display the tricuspid valvar annulus (TVA) and the relationship between the site of recording of the largest His bundle potential (His) and the landmarks of the triangle of Koch. In this case, the His bundle was recorded superiorly at the vertex of the triangle. Pink dashed lines indicate the schematics of the LBB on the left side of the interventricular septum and the tricuspid valve annulus.

(C) Fluoroscopy with minimal RAO view obtained during the implantation of LBP. Note the different fluoroscopic position of the leads when modifying the RAO angulation. The relationship with a His pacing lead is observed. The LBP lead is deployed =1.5 cm distally and =0.5 cm more inferiorly to achieve, via transseptal deployment, pacing of the LBB. Yellow dashed lines indicate the angulation and possible location of the LBB with respect to the His bundle.
transition and an LBB potential is useful to guide the lead advancement inside the IVS while pacing. During intraseptal lead fixation, the paced electrocardiogram morphology, impedance trends, and characteristic findings of LBB capture are assessed using different pacing outputs. The presence of LBB current of injury may suggest that the tip of the lead is in close contact with the left-sided conduction system with possible penetration into the fibrous insulation of the LBB (17).

As the LBB runs subendocardially on the left ventricular septum, septal perforation is possible during LBP using this technique. Anatomic and histological information provide guidance with regard to the depth of lead penetration to avoid septal perforation into the left ventricle. There are a number of determinants that may influence the development of LBB injury during the procedure. The thickness of the IVS is not just composed of working myocardium, but one needs to consider the: 1) variable thickness of the right ventricular endocardium; 2) fatty infiltration in the elderly; 3) connective tissue surrounding the LBB; and 4) variable amount of fibrous tissue that may be linked to a patient’s conduction disorder. Moreover, the LBB thickness can be extremely variable and involve from 1 to 25 cell layers of specialized smooth myocardium conducting tissue, which is surrounded by a varying but considerable thickness of left subendocardial collagen and smooth muscle. This is illustrated in Figure 3. It is rather obvious that multiple lead deployments in this region can result in permanent RBB injury, cardiac perforation and/or damage to a septal artery.
In conclusion, in this Da Vinci Corner editorial, we have described the most common location of the His bundle to help guide the location of the LBB. In addition, we have summarized the branching patterns of the LBB and the determinants of LBB injury during LBP. We hope this editorial will be useful for the implanting physicians that seek to perform anatomy-guided LBP in the safest and most effective way possible.

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REFERENCES
1. Eichert H. Transient bundle branch block associated with tachycardia. Am Heart J 1946;31:511-8.
2. Heinsimer JA, Skelton TN, Califf RM. Rate-related left bundle branch block with chest pain and normal coronary arteriograms treated by exercise training. Am J Med Sci 1986;292:317-9.
3. Shvilkin A, Ellis ER, Gervino EV, Litvak AD, Buxton AE, Josephson ME. Painful left bundle branch block syndrome: Clinical and electrocardiographic features and further directions for evaluation and treatment. Heart Rhythm 2016;13:226-32.
4. Zhang S, Zhou X, Gold MR. Left bundle branch pacing: JACC review topic of the week. J Am Coll Cardiol 2019;74:3039-49.
5. Vilas-Gonzalez JF, Mahata I, Anter E, d’Avila A. Painful left bundle branch block syndrome treated with his bundle pacing. J Electrocardiol 2018;51:1019-22.
6. Upadhyay GA, Vijayaraman P, Nayak HM, et al. His corrective pacing or biventricular pacing for cardiac resynchronization in heart failure. J Am Coll Cardiol 2019;74:157-9.
7. Garg A, Master V, Ellenbogen KA, Padala SK. Painful left bundle branch block syndrome successfully treated with left bundle branch area pacing. J Am Coll Cardiol Case Rep 2020;2:568-71.
8. Huang W, Su L, Wu S, et al. A novel pacing strategy with low and stable output: pacing the left bundle branch immediately beyond the conduction block. Can J Cardiol 2017;33:1736 e1-3.
9. Cabrera J-A, Anderson RH, Macias Y, et al. Variable arrangement of the atrioventricular conduction axis within the triangle of Koch: implications for permanent His bundle pacing. J Am Coll Cardiol EP 2020;6:362-77.
10. Tawara S. Das reizleitungssystem des Säugetierherzens. Fischer, 1906.
11. Massing GK, James TN. Anatomical configuration of the His bundle and bundle branches in the human heart. Circulation 1976;53:609-21.
12. Rosenbaum MB, Elizari MV, Lazzari JO. Los hemibloqueos: por Mauricio B. Rosenbaum, Marcelo V. Elizari y Julio O. Lazzari. Buenos Aires: Paidos, 1968.
13. Durrer D, Van Dam RT, Freud G, Janse M, Meijler F, Arzbuecher R. Total excitation of the isolated human heart. Circulation 1970;41:899-912.
14. Uhley HN, Rivkin LM. Visualization of the left branch of the human atrioventricular bundle. Circulation 1959;20:419-21.
15. Rossi L. Sistema di conduzione trifascicolare ed emblocchi di branca sinistra. Considerazioni anatomiche ed istopatologiche. G Ital Cardiol 1971;1:55-62.
16. Demoulin JC, Kulbertus HE. Histopathological examination of concept of left hemiblock. Br Heart J 1972;34:807-14.
17. Su L, Xu T, Cai M, et al. Electrophysiological characteristics and clinical values of left bundle branch current of injury in left bundle branch pacing. J Cardiovasc Electrophysiol 2020;31:834-42.

KEY WORDS anatomy, cardiac electrophysiology, pacing
A Rare Complication of Chronic Active Epstein-Barr Virus Infection

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ABSTRACT

A 42-year-old man with a 6-month-long fever was found to have chronic active Epstein-Barr virus infection complicated by aneurysmal coronary arteries with other arteries. In adult patients with this infection, coronary aneurysms are rare but are a poor prognostic factor. (Level of Difficulty: Intermediate.) (J Am Coll Cardiol Case Rep 2020;2:756–9) © 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 42-year-old man was admitted to our hospital because of a fever lasting 6 months, anterior uveitis, hearing loss, systemic lymphadenopathy, splenomegaly, and abdominal aortic arteritis.

MEDICAL HISTORY

Epstein-Barr virus (EBV) antibody titers were as follows: viral capsid antigen immunoglobulin G (IgG), 1:1280; viral capsid antigen IgM, <1:10; early antigen IgG, 1:640; and EBV nuclear antigen, 1:80. The EBV-DNA load in peripheral blood was determined to be \(3.7 \times 10^3\) copies/10\(^6\) white blood cells. Monoclonal proliferation of EBV-infected cells was demonstrated in the peripheral blood with Southern blot analysis using EBV-terminal repeat. On the basis of these results, chronic active EBV infection (CAEBV) was diagnosed. Contrast-enhanced computed tomography (CT) showed that the coronary artery was diffusely dilated without aneurysm and that the wall of the abdominal aorta was also thickened, suggesting arteritis without aneurysm (Figure 1A). After CAEBV was diagnosed, prednisolone was administered at an initial dosage of 1 mg/kg/day and then slowly tapered depending on its effectiveness. The decreased wall thickness of the abdominal aorta was confirmed with CT (Figure 1B).

DIFFERENTIAL DIAGNOSIS

Differential diagnosis included coronary artery aneurysms associated with inflammatory disorders such as Kawasaki disease, Takayasu disease and Churg-Strauss syndrome, or connective tissue
disorders such as Marfan syndrome and Ehlers-Danlos syndrome.

INVESTIGATIONS

Two years after the diagnosis of CAEBV, an abdominal aortic aneurysm and bilateral common iliac artery (CIA) aneurysms were discovered with CT just before allogeneic bone marrow transplantation was performed as a curative treatment for CAEBV. The maximum diameter of the aortic abdominal aorta was 34 mm (Figure 1E), and the maximum diameter of the right CIA was 26 mm (Figure 1G). Owing to prolonged fever, CT examination was performed 1 month later and demonstrated a coronary artery aneurysm from the left main trunk through the left anterior descending and right coronary arteries, with a maximum diameter of 7 mm in the left main trunk and 6 mm in the right coronary artery (Figure 1C). Regarding treatment, the decision was made for close monitoring without intervention at that time. The EBV-DNA level in peripheral blood finally decreased to beneath the detection limit. Follow-up CT 6 years after diagnosis of CAEBV showed fusiform dilatation of the aneurysms, with a maximum diameter of 11 mm in the left main trunk, 7 mm in the right coronary artery (Figure 1D), 40 mm in the abdominal aorta (Figure 1F), and 40 mm in the right CIA (Figure 1H, Table 1). The patient has been followed on aspirin with close monitoring until the present time.

DISCUSSION

Coronary artery aneurysm (CAA) is classically defined as a focal dilatation of more than 1.5 times the diameter of an adjacent artery (1). The prevalence of CAA was reported to be 0.2% to 4.9% of patients undergoing coronary angiogram (2,3). Patients with CAA can be completely asymptomatic, as in our patient, but can present with a variety of symptoms, including chest pain, congestive heart failure, acute coronary syndrome, and sudden cardiac death (1). The Coronary Artery Aneurysm Registry, the largest multicenter registry, found an overall mortality rate of 15.3% and a major adverse cardiac events rate of 31% (4). However, no reports have been
published with respect to specific prognosis of patients with CAEBV complicated by CAA.

Cases of CAEBV have various symptoms, including fever, lymphadenopathy, hepatosplenomegaly, and cytopenia, which can lead to such cardiovascular complications as CAA. According to previous studies, of patients with CAEBV, a CAA develops in approximately 9% (5). Pathological studies have revealed that lymphoid infiltration is present in CAA and that these aneurysms result from lymphoid vasculitis (6).

In the present case, an abdominal aortic aneurysm and a CIA aneurysm had already been detected in addition to a CAA at the time of bone marrow transplantation, 2.5 years after disease onset. Furthermore, the aneurysms had gradually enlarged despite successful eradication of EBV-infected cells. Because coronary artery lesions, including dilation, stenosis, and calcification, have been reported to regress within several years after cord blood transplantation, allogeneic hematopoietic stem cell transplantation being performed soon after CAEBV is diagnosed might prevent aneurysms from developing (7). Although the relationships of the size of aneurysms with disease activity or prognosis remain uncertain, high EBV load, fever, and cytopenia are reported to be involved in the cardiovascular complications (7). The present case was considered to be of high risk of development of cardiac complications because of the presence of high EBV load and fever.

With respect to medical treatment for CAAs, the decision was made to administer aspirin alone to prevent coronary artery disease, because the main etiology of CAA is atherosclerosis (1). In addition, the Coronary Artery Aneurysm Registry has reported that aspirin is the preventative agent most often prescribed (4). Moreover, although a previous report has shown the efficacy of anticoagulation therapy in a specific patient with the complication of thrombus (8), the present patient had no evidence of thrombus of the coronary artery.

FOLLOW-UP

The current practice guideline does not recommend a specific approach to monitoring CAA (9). In the present case, greater attention should have been paid to monitor the size of the CAA by performing serial contrast-enhanced CT.

CONCLUSIONS

Despite the scarce evidence of CAAs in cases of CAEBV, carefully investigating cardiovascular complications, including CAAs, is important because they are poor prognostic factors.

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REFERENCES

1. Pham V, Hemptinne Q, Grinda JM, Duboc D, Varenne O, Picard F. Giant coronary aneurysms, from diagnosis to treatment: a literature review. Arch Cardiovasc Dis 2020;113:59-69.

2. Swaye PS, Fisher LD, Litwin P, et al. Aneurysmal coronary artery disease. Circulation 1983;67:134-8.

3. Tunick PA, Stater J, Kronzon I, Glassman E. Discrete atherosclerotic coronary artery aneurysms: a study of 20 patients. J Am Coll Cardiol 1990;15:279-82.

4. Nunez-Gil U, Cerrato E, Bollati M, et al. Coronary artery aneurysms, insights from the
international coronary artery aneurysm registry (CAAR). Int J Cardiol 2020;299:49-55.

5. Kimura H, Morishima T, Kanegane H, et al. Prognostic factors for chronic active Epstein-Barr virus infection. J Infect Dis 2003;187:527-33.

6. Nakagawa A, Ito M, Iwaki T, Yatabe Y, Asai J, Hayashi K. Chronic active Epstein-Barr virus infection with giant coronary aneurysms. Am J Clin Pathol 1996;105:733-6.

7. Muneuchi J, Ohga S, Ishimura M, et al. Cardiovascular complications associated with chronic active Epstein-Barr virus infection. Pediatr Cardiol 2009;30:274-81.

8. Doi T, Kataoka Y, Noguchi T, et al. Coronary artery ectasia predicts future cardiac events in patients with acute myocardial infarction. Arterioscler Thromb Vasc Biol 2017;37:2350-5.

9. Fihn SD, Gardin JM, Abrams J, et al. 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American College of Physicians, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. J Am Coll Cardiol 2012;60:e44-164.

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**KEY WORDS**

aortic artery aneurysm, chronic active Epstein-Barr virus infection, computed tomography, coronary artery aneurysm
ATGL Deficiency-Induced Triglyceride Deposit Cardiomyovasculopathy Requiring Heart Transplant
A 5-Year Follow-Up

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ABSTRACT
A young man presented with syncope. He was diagnosed with triglyceride deposit cardiomyovasculopathy and skeletal myopathy secondary to adipose triglyceride lipase (ATGL) deficiency. Despite optimal medical therapy, he required heart transplantation to treat his heart failure. Five years post-transplant, the graft function was normal with no evidence of triglyceride deposits. (Level of Difficulty: Intermediate.) (J Am Coll Cardiol Case Rep 2020;2:760–3) © 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/).

HISTORY OF PRESENTATION
A 22-year-old male presented with syncope for the first time. Since childhood, because of mild dyspnea and myalgia, he had reduced exertional capacity when compared with his peers but this had not been medically evaluated.

MEDICAL HISTORY
He had no formal medical history nor any family history. His parents were first cousins of South Asian origin.

LEARNING OBJECTIVES
- To be aware that lipid storage diseases, such as ATGL deficiency, can cause heart failure.
- To appreciate that heart transplantation is an effective cure for triglyceride cardiomyovasculopathy.

EXAMINATION
There was a pansystolic murmur in the mitral region with no signs of fluid overload. Cranial nerve examination was normal. There was wasting of the upper limb muscles with proximally distributed weakness. The lower limb weakness was distally distributed. All reflexes were absent but with normal plantar reflexes. Sensation was normal.

DIFFERENTIAL DIAGNOSIS
Multisystem involvement and parental consanguinity raised the suspicion of a recessively inherited myopathic disorder.

INVESTIGATIONS
Electrocardiogram showed poor R wave progression and Troponin I was mildly elevated. Echocardiogram...
and cardiac magnetic resonance (CMR) imaging demonstrated a severely dilated and impaired left ventricle with thinning and akinesis of the inferolateral wall, extending from the base to the apex. The left ventricular ejection fraction was 20% to 25%. All other walls were thin and hypokinetic. Late gadolinium imaging showed subendocardial enhancement in the anterolateral and inferior walls in an unusual pattern, not typical for coronary disease (Figures 1A and 1B). The coronary angiogram was normal.

Creatine kinase (CK) was 1,600 u/l (normal range 22 to 198 U/l). Electromyography confirmed prominent myopathy affecting both distal and proximal muscle fibers. Skeletal muscle and skin biopsies showed myocytes vacuolation raising the suspicion of a lipid myopathy. Exome sequencing revealed homozygosity for the c.497A>G (p.Asp166Gly) mutation in the PNPLA2 gene. This causes excessive lipid storage in myocytes (1).

**MANAGEMENT**

He was treated with optimal guideline directed medical therapy and cardiac resynchronization therapy-defibrillator. He remained stable for 18 months. In the following 12 months, he was hospitalized 4 times with decompensated heart failure. His symptoms deteriorated from New York Heart Association functional class I to IV.

He was hospitalized again due to repeated but appropriate cardiac resynchronization therapy-defibrillator shocks. Echocardiogram showed a decrease in left ventricular ejection fraction (10% to 15%). Thus, he was referred for an assessment to receive mechanical circulatory support ± heart transplant.

On arrival to the transplant center, he exhibited signs of inadequate cardiac output with renal and hepatic dysfunction requiring inotropic support. Right heart catheter study showed severely reduced cardiac index (1.3). Left ventricular endomyocardial biopsy (EMB) showed myocyte enlargement with cytoplasmic vacuolation in a lace-like pattern (Figure 2A). This confirmed the diagnosis of triglyceride deposit cardiomyovasculopathy (2) and helped to exclude other causes of heart failure.

His case was discussed at the transplant multidisciplinary meeting. Besides his mild neuromuscular weakness, he had no other comorbidities and thus he was placed on the urgent waiting list for a heart transplant. However, despite being on inotropic support, his condition deteriorated rapidly and he developed cardiogenic shock. Therefore, a biventricular assist device was implanted to maintain end-organ perfusion and bridge him to heart transplantation.
After 4 weeks, he received a heart transplant. Postoperatively, he was put on extracorporeal membranous oxygenation support for 3 days because of severe primary graft dysfunction. EMB excluded acute allograft rejection.

He had a prolonged stay in the intensive care unit of 125 days, mainly because of slow respiratory weaning. His preexisting neuromuscular weakness and being critically ill before the transplant surgery were likely to be the contributing factors.

**FOLLOW-UP**

Five years post-transplant, he continues to be followed up by neurologists. Although there is no cure for the neuromuscular condition, he does not report any deterioration.

In the transplant clinic, he denied any cardiac symptoms. His CK was raised at 2,628 U/l (normal range 22 to 198 U/l) and troponin I was 46 ng/l (normal <19 ng/l). This prompted a repeat CMR and EMB. CMR showed normal left ventricular function (left ventricular ejection fraction 62%) and no evidence of fat infiltration or fibrosis in the transplanted heart (Figures 1B and 2C). The EMB of the right ventricle did not show any triglyceride deposits nor signs of rejection.

**DISCUSSION**

Adipose triglyceride lipase (ATGL), coded by the patatin-like phospholipase domain containing 2 (PNPLA2) gene, is the enzyme responsible for the first step of triglyceride hydrolysis (3,4). Mutations in the PNPLA2 gene lead to reduced messenger RNA levels of peroxisome proliferator-activated receptors target genes (5,6). This results in the autosomal recessive disorder, neutral lipid storage disease with myopathy, where there is excessive cytoplasmic lipid accumulation in organs and tissues throughout the body (5,6).

Approximately 90 patients with neutral lipid storage disease with myopathy from a variety of ethnic groups have been clinically and genetically characterized (1–9). Patients usually present with proximal muscle weakness in their late 20s and early 30s (6,8). Some go on to have distal limb involvement (9). Serum CK levels remain elevated throughout (6,8,9). Approximately 40% of patients exhibit cardiac dysfunction which appears to be affected later in the course of the disease, usually after the age of 20 (2,3,5–9).

The extent of cardiac involvement is influenced by many factors as evidenced by siblings who carry the same ATGL mutation (3,5–9). Estrogen appears to have a protective effect demonstrated by the higher incidence of cardiac damage in male patients (3,8). Similarly, there is ethnic disparity of cardiac involvement as none of the 45 Chinese patients described by Zhang et al. (9) had a severe cardiac phenotype (9).

Only 2 cases of triglyceride deposit cardiomyovasculopathy secondary to ATGL deficiency required left ventricular assist device and later, heart transplant (2). Our case adds a third example of this and for the first time describes a 5-year follow-up after heart transplant with CMR images and EMB histology, demonstrating that the donor heart is free of triglyceride deposits.
CONCLUSIONS

We describe a very rare case of a patient with triglyceride deposit cardiomyovasculopathy secondary to ATGL deficiency. This led to advanced heart failure requiring heart transplantation. For the first time, we have demonstrated with supporting CMR and cardiac histology data that heart transplantation offers a cure for triglyceride deposit cardiomyovasculopathy, as the disease has not affected the donor heart 5 years after transplant.

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REFERENCES

1. Coassin S, Schweiger M, Branstatter AK, et al. Investigation and functional characterization of rare genetic variants in the adipose triglyceride lipase in a large healthy working population. PLoS Genet 2010;6:e1001239.
2. Hirano K, Tanaka T, Ikeda Y, et al. Genetic mutations in adipose triglyceride lipase and myocardial up-regulation of peroxisome proliferated activated receptor-γ in patients with triglyceride deposit cardiomyovascularopathy. Biochem Biophys Res Commun 2014;443:574–9.
3. Pasanisi MB, Missaglia S, Cassandrini D, et al. Severe cardiomyopathy in a young patient with complete deficiency of adipose triglyceride lipase due to a novel mutation in PNPLA2 gene. Int J Cardiol 2016;207:165–7.
4. Zimmermann R, Strauss JG, Haemmerle G, et al. Fat mobilization in adipose tissue is promoted by adipose triglyceride lipase. Science 2004;306:1383–6.
5. Fischer J, Lefèvre C, Morava E, et al. The gene encoding adipose triglyceride lipase (PNPLA2) is mutated in neutral lipid storage disease with myopathy. Nat Genet 2007;39:28–30.
6. Haemmerle G, Moustafa T, Woelkart G, et al. ATGL-mediated fat catabolism regulates cardiac mitochondrial function via PPAR-α and PGC-1. Nat Med 2011;17:1076–85.
7. Missaglia S, Tasca E, Angelini C, et al. Novel missense mutations in PNPLA2 causing late onset and clinical heterogeneity of neutral lipid storage disease with myopathy in three siblings. Mol Genet Metab 2015;115:110–7.
8. Reilich P, Horvath R, Krause S, et al. The phenotypic spectrum of neutral lipid storage myopathy due to mutations in the PNPLA2 gene. J Neurol 2011;258:1987–7.
9. Zhang W, Zhao Y, Wen B, et al. Neutral lipid storage disease with myopathy in China: a large multicentric cohort study. Orphanet J Rare Dis 2019;14:234.

KEY WORDS cardiac magnetic resonance, cardiac transplant, cardiomyopathy, chronic heart failure, genetic disorders, lipid metabolism disorders
Successful Conservative Treatment of a Large Infected Saphenous Graft Aneurysm

Usefulness of PET/CT

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ABSTRACT

We report a case of a 75-year-old man with a medical history of coronary artery bypass graft surgery and a recent graft angioplasty, who presented to our emergency department with fever. An 18F-fluorodeoxyglucose positron emission tomography demonstrated a saphenous graft infected aneurysm, which was successfully treated conservatively with antibiotic therapy. (Level of Difficulty: Beginner.) (J Am Coll Cardiol Case Rep 2020;2:764–8) © 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/).
infections, were considered. Subsequently, because of the persistence of fever despite antibiotic treatment, other causes of fever of unknown origin were considered: rheumatic polymyalgia with or without temporal arteritis, cytomegalovirus infection, tuberculosis, Q fever, antiphospholipid syndrome, infective endocarditis, and neoplastic diseases such as lymphoma. The differential diagnosis was directed according to the frequency of diseases in our population.

INVESTIGATIONS

Peripheral venous line was removed and blood cultures were drawn. One culture grew methicillin-resistant Staphylococcus aureus and antibiotics were started according to antibiogram. The patient continued to have fever. Yet, there were no clear signs of infection on physical examination, nor were there symptoms of respiratory or urinary infection or gastroenteritis. Chest radiography and urinalysis were normal. A transesophageal echocardiogram (TEE) did not document signs of infectious endocarditis. Finally, an 18F-FDG PET/CT revealed an anterior mediastinal mass of 6x4 cm involving the saphenous graft (Figures 1A and 1B).

To assess patency of the graft and the condition of the coronary arteries, a thoracic contrast CT scan was performed (Figure 2). No clear leakage point was observed, and the saphenous graft lumen could not be properly assessed. The patient therefore underwent a coronary angiography demonstrating that the saphenous graft was occluded.

MANAGEMENT

An infected saphenous graft aneurysm was suspected and antibiotic treatment was switched to rifampin and daptomycin. The fever subsided with the new antibiotic therapy; left ventricular ejection fraction was normal and the patient was asymptomatic. Following discussion with the multidisciplinary heart team, because the aneurysm was excluded from the systemic circulation and given the complexity of the surgical intervention, a medical approach was preferred over surgery.

The patient continued with antibiotics and acute phase reactants (C-reactive protein and erythrocyte sedimentation rate) and leukocytosis progressively decreased. An 18F-FDG PET/CT was repeated after 2 weeks of antibiotics and a mild reduction of 18F-FDG uptake was observed. It was decided to continue with intravenous rifampin and daptomycin for a total of 6 weeks followed by 3 months of oral antibiotic treatment with rifampin and linezolid. After this long antibiotic cycle, a new 18F-FDG PET/CT showed resolution of the infection (Figures 1C and 1D) and antibiotics were discontinued.

DISCUSSION

SVG aneurysms are a rare complication after coronary artery bypass graft surgery. Only a few case reports and small case series have been published (1–3). Operative complications and need for re-exploration after surgery have been identified as predictors of this complication (1).

The pathophysiology of these lesions is poorly understood. Conduit injury, anastomotic suture disruption, and infection of the graft may be involved in the genesis of SVG aneurysms (2). Postoperative sternal wound infection or mediastinitis contributed to most of the infected SVG aneurysms (1,3). In the case presented here, we hypothesize that conduit injury during complex angioplasty and graft stenting plus the use of triple antithrombotic therapy might cause the formation of the SVG aneurysm. Subsequently, angioplasty- or catheter-related (phlebitis) bacteremia would cause aneurysm infection. Frequently, SVG aneurysms present with ischemic symptoms secondary to graft thrombosis or distal aneurysmal embolization, or as an asymptomatic mass during chest imaging (1). In infected aneurysms, in contrast, fever and infectious symptomatology prevail, making diagnosis more difficult.

S. aureus has been the most commonly involved microorganism in infected SVG aneurysms (3). The strong virulence of this microorganism may explain this association. S. aureus bacteremia is associated with high mortality, and TEE is indicated in most patients to rule out infected endocarditis. In our patient, after TEE was negative and the site of infection remained unknown, an 18F-FDG PET/CT successfully detected the focus of infection. The clinical value of this technique in S. aureus bacteremia has been recently shown (4,5).

Once an SVG aneurysm is detected, a chest CT should be performed to determine graft patency, as well as the exact location of the aneurysm within the mediastinum to guide the surgical approach. Cardiac catheterization should also be done to assess coronary anatomy and potential distal targets for revascularization.

There is no consensus on the optimal management of SVG aneurysms. Treatment options include surgical repair and percutaneous closure with Amplatzer devices, covered stents, and arterial coiling (1). In
infected aneurysms, open surgical repair of the mycotic aneurysm and debridement with or without revascularization has been the most common management in previous cases (3). In our patient, a conservative management was decided according to 4 clinical reasons: 1) the patient was evolving well under antibiotics; 2) the saphenous graft was occluded and yet the patient had no signs of ischemia; 3) the infected aneurysm was already excluded from the systemic circulation; and 4) surgical risk was high.

In our center, daptomycin is the first-line therapy for methicillin-resistant *S. aureus* bacteremia (6). Rifampin is bactericidal against *S. aureus*, achieves

![PET/CT Images Before and After Antibiotic Treatment](image-url)

**FIGURE 1** PET/CT Images Before and After Antibiotic Treatment

(A) A huge mass surrounding the saphenous graft with intense 18F-FDG uptake (SUVmax 15.8) (arrow). (B) Three months after oral antibiotherapy, a complete resolution of the infection with absence of FDG uptake can be seen. Note: a physiological uptake of the myocardium is seen in B and D. 18F-FDG = 18F-fluorodeoxyglucose; PET/CT = positron emission tomography/computed tomography; SUVmax = maximum standardized uptake value.
high intracellular levels, is one of the few antimicrobial agents that can penetrate biofilms, and it has been commonly used adjunctively to treat *S. aureus* infections (7). Thus, we first used parenteral antibiotic therapy with daptomycin; thereafter, we used prolonged oral antibiotic combination of linezolid plus rifampin (6). It is pertinent to emphasize that in our case PET/CT was useful both in the location of the infectious focus and to monitor the therapeutic response. The possibility of using 18F-FDG PET/CT as a tool to monitor the response to the antibiotic treatment in patients with graft infections has already been suggested (8).

**FOLLOW-UP**

After 6 months of follow-up, the patient is doing well, without fever or any type of infectious or ischemic symptoms.

**CONCLUSIONS**

In selected cases, infection of SVG aneurysms can be treated conservatively with prolonged antibiotic therapy. 18F-FDG PET/CT is a useful technique in the diagnosis of this complication and in monitoring the response to antibiotic therapy.

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REFERENCES

1. Smer A, Alla V, Chandraprakasam S, Abuzaid A, Saurav A, Holmberg J. Saphenous venous graft pseudoaneurysm: a review of the literature. J Card Surg 2015;30:70.e3.

2. Ramirez FD, Hibbert B, Simard T, et al. Natural history and management of aortocoronary saphenous vein graft aneurysms: a systematic review of published cases. Circulation 2012;126:2248–56.

3. Lin TW, Chang CH, Lin PY. Early development of saphenous vein graft infected pseudoaneurysm caused by perioperative Enterobacter cloacae bacteremia. Kaohsiung J Med Sci 2017;33:637–8.

4. Ekhar S, Vupputuri A, Nair RC, Palaniswamy SS, Natarajan KU. Coronary stent infection successfully diagnosed with FDG-PET CT. Can J Cardiol 2015;32:1575.e1–1575.e3.

5. Brandenstiid MB, Pedersen C, Rosemvinge FS, Hantlund-Carsen PF, Hess S. Clinical value of FDG-PET/CT in bacteremia of unknown origin with catalase-negative gram-positive cocci or Staphylococcus aureus. Eur J Nucl Med Mol Imaging 2019;46:1351–8.

6. Styriewski ME, Corey GR. New treatments for methicillin-resistant Staphylococcus aureus. Curr Opin Crit Care 2009;15:403–12.

7. Arnaiz de Las Revillas F, Fernandez-Sampedro M, Arnaiz-García AM, et al. Daptomycin treatment in Gram-positive vascular graft infections. Int J Infect Dis 2018;68:69–73.

8. García-Arribas D, Vilacosta I, Ortega Candí A, et al. Usefulness of positron emission tomography/computed tomography in patients with valve-tube graft infection. Heart 2018;104:1447–54.

KEY WORDS complication, coronary artery bypass, endocarditis, nuclear medicine, percutaneous coronary intervention, positron emission tomography
Immunoglobulin G4-Related Multiple Giant Coronary Artery Aneurysms and a Single Left Gastric Artery Aneurysm

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ABSTRACT

Coronary artery aneurysm (CAA) is potentially life-threatening. We describe a case of multiple giant CAAs and a single left gastric artery aneurysm caused by immunoglobulin G4-related disease (IgG4-RD). Our case highlights the significance of assessing IgG4-RD in the diagnosis of CAA and screening for other concurrent cardiovascular involvements. (Level of Difficulty: Intermediate.) (J Am Coll Cardiol Case Rep 2020;2:769–74) © 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 giant coronary artery aneurysm (CAA) measuring more than 50 mm in diameter is extremely rare; however, potentially serious sequelae may occur (1). The diagnosis and management of giant CAAs remain challenging.

HISTORY OF PRESENTATION

A 77-year-old man was referred to our hospital for the evaluation of a suspected mediastinal mass that was incidentally detected on chest radiography (Figure 1). His vital signs were stable. All physical and laboratory examination results and the electrocardiogram were unremarkable.

LEARNING OBJECTIVES

- To understand radiological findings in coronary and abdominal artery involvements associated with IgG4-RD.
- To review the causes of CAAs.

MEDICAL HISTORY

The patient had a history of ischemic stroke, diabetes, hypertension, hyperlipidemia, and smoking. He underwent subtotal gastrectomy for a gastric ulcer at 45 years of age and coronary angiography for angina at 49 years of age.

DIFFERENTIAL DIAGNOSIS

We initially suspected atherosclerotic-related CAAs, postintervention coronary pseudoaneurysms, or inflammatory and infectious diseases.

INVESTIGATIONS

Echocardiography revealed 2 huge masses around the heart (Figure 2). Contrast-enhanced computed tomography (CT) revealed multiple CAAs severely compressing the cardiac chambers (Figure 3). In addition to a left gastric artery aneurysm (LGAA), we...
also identified a severe mural calcification in the main coronary arteries without systemic arterial sclerosis. Coronary CT angiography further characterized multiple CAs involving the main coronary arteries (Figure 4). Axial and coronal CT scans demonstrated 2 giant CAs of the proximal and distal right coronary artery (RCA), with the major axes measuring 6.5 × 7.5 cm and 4.8 × 3.5 cm, respectively. Moreover, we detected a proximal RCA with a large lumen and irregular mural thrombus lining; the distal RCA had a circumferential mural calcification and a false lumen filled with mural thrombus. The other CAs of the proximal left anterior descending and left circumflex arteries with a whole false lumen were filled with a mural thrombus and circumferential mural calcification.

MANAGEMENT

Owing to the increased risk of an aneurysmal rupture or the thrombotic occlusion of the CAs, proximal and distal RCA aneurysmectomy with simultaneous coronary artery bypass grafting (using a saphenous vein graft) was performed (Figure 5A). The resected aneurysms were filled with a massive organized thrombus (Figure 5B). Pathological examination of the resected aneurysmal wall revealed lymph follicles of the adventitia and storiform fibrosis amid a prominent lymphoplasmacytic infiltrate, mainly in the adventitia, concomitant with the destruction of the normal structures of the majority of the media. Immunostaining revealed numerous immunoglobulin G4 (IgG4)-positive plasma cells (Figures 5C and 5D); the average number of IgG4-positive plasma cells was 629/high-power field (range: 234 to 1,043/high-power field). The IgG4/IgG ratio was 97%, which suggested IgG4-related coronary periarteritis. The serum IgG4 level was elevated at 353 mg/dl (normal range: 4 to 108 mg/dl). These findings fulfilled all comprehensive diagnostic criteria for immunoglobulin G4-related disease (IgG4-RD) because of the clinical exclusion of all other disorders that may mimic IgG4-RD, including malignancies and inflammatory, infectious, and autoimmune diseases.

DISCUSSION

IgG4-RD is a systemic immune-mediated fibroinflammatory disease with multiorgan involvement (2); coronary artery involvement presents with various clinical phenotypes, including inflammatory pseudotumors, fibrotic diffuse thickening, and coronary artery stenosis. Multidetector row CT can clearly characterize the perivascular tissue and be useful for the diagnosis of IgG4-RD (3). Typically, coronary artery involvements are characterized by periarterial fibrosclerotic thickening without atherosclerotic changes (e.g., calcification). However, the strong association between IgG4-RD and atherosclerotic coronary artery disease is gaining considerable attention (4). Chronic inflammation, secondary to IgG4-RD, may be involved in the development and progression of atherosclerotic coronary artery disease (5). Epidemiologically, IgG4-RD is common in middle-aged to elderly men with multiple risk factors of atherosclerosis. Thus, IgG4-related CAs must be clinically differentiated from atherosclerotic-related CAs. In the present case, coronary artery calcifications were severe despite the less-severe systemic arteriosclerosis. These mismatched findings might be key to the consideration of this rare entity. IgG4-RD can simultaneously affect large and/or medium vessels; this frequently occurs in the infrarenal segment of the abdominal aorta (6,7). To the best of our knowledge, the present report is the first on IgG4-RD-associated LGAA. Segmental arterial mediolysis (SAM), which occurs in the middle to advanced ages, is

**ABBREVIATIONS AND ACRONYMS**

CAA = coronary artery aneurysm
CT = computed tomography
LGAA = left gastric artery aneurysm
IgG = immunoglobulin G
IgG4-RD = immunoglobulin G4-related disease
RCA = right coronary artery
SAM = segmental arterial mediolysis

**FIGURE 1 Chest Radiograph**

A convex contour of the right cardiac border is observed (arrowheads).
a life-threatening, nonatherosclerotic, and noninflammatory vasculopathy. It often causes intra-abdominal bleeding resulting from the formation and rupture of aneurysms in the abdominal arteries, and requires prompt treatment by vascular embolization or surgical resection (8). In addition to the superior mesenteric, hepatic, celiac, and splenic arteries, the left gastric artery is also affected. The CT findings for LGAA are similar between IgG4-RD and SAM. Thus, it is important to distinguish between the 2 because although they are similar in terms of the age of onset and radiological findings, they differ in the requisite treatment approaches. IgG4-RD and SAM can also be differentiated based on the histopathological findings (9).

Although corticosteroid therapy is the gold standard treatment for IgG4-related cardiovascular involvements, its effectiveness for luminal dilated lesions is controversial (6,7); there are concerns regarding acute progression or rupture of the existing CAAs and the development of new aortic aneurysmal lesions after therapy. Thus, care must be taken with the indication or timing and the dose of the corticosteroid treatment for CAAs or LGAA. Rituximab is considered a second option in maintenance therapy after steroid tapering or in high-risk patients with steroid intolerance (6). Immuno-modulators, such as cyclophosphamide, may be an additional treatment option (10). In some cases, long-term spontaneous remission was achieved without an aggressive drug treatment for IgG4-RD (11). Further investigation is necessary to devise proper treatment strategies for patients with IgG4-RD. Our patient refused the aforementioned drug treatments and received close monitoring with outpatient follow-up.

**FOLLOW-UP**

The postoperative course was uneventful. With no medical treatment, the remaining coronary artery lesions showed no exacerbation. Spontaneous regression of the LGAA was observed at the 6-month follow-up (Figure 6). He remained clinically stable with a 48-month follow-up. Although the serum IgG4 levels remained elevated (584 mg/dl), other serological inflammatory biomarkers were within the normal range: erythrocyte sedimentation rate, 12 mm/h (reference: 0 to 15 mm/h) and C-reactive protein level, 0.01 mg/dl (reference: 0 to 0.30 mg/dl). The serum complement levels, including those of C3, C4, and CH50, were within the normal range.

**CONCLUSIONS**

We described a case of multiple giant CAAs and a single LGAA resulting from IgG4-RD. Clinicians...
FIGURE 3  Contrast-Enhanced Computed Tomography

(A,B) Coronal and (C) axial images. Computed tomography images show multiple CAAs (arrowheads) severely compressing the cardiac chambers, with severe mural calcification in the main coronary arteries (dashed arrows) and a single LGAA (arrow), with a maximum diameter of 18 mm in the lesser curvature of the postoperative stomach. CAA = coronary artery aneurysm; LGAA = left gastric artery aneurysm; RA = right atrium; RV = right ventricle.

FIGURE 4  Coronary Computed Tomography Angiography

(A) Coronal and (B) axial images. (C) Curved planar reconstruction and (D) volume-rendering reconstruction. The extracoronary luminal lesion appears in green. Two giant CAAs of the proximal and distal RCA (arrowheads) and other CAAs of the proximal LAD and LCX (arrows) are visible. Ao = aorta; CAA = coronary artery aneurysm; LAD = left anterior descending artery; LCX = left circumflex artery; RCA = right coronary artery.
**FIGURE 5** Intraoperative and Pathological Findings

(A) Surgeons’ intraoperative view of the RCA aneurysms. (B) Resected aneurysms. (C) Photomicrograph with hematoxylin and eosin staining (scale bar: 50 μm). (D) Photomicrograph with immunostaining for immunoglobulin G4 (scale bar: 50 μm). RCA = right coronary artery.

**FIGURE 6** Follow-Up Contrast-Enhanced Computed Tomography Image

(A) Coronal and (B) axial images. Spontaneous regression of the left gastric artery aneurysm observed at the 6-month follow-up (arrows).
should be aware of this new clinicopathological entity, considering the possibility of this disease as a differential diagnosis of CAA in adults. Radiological screening for any other concurrent cardiovascular involvements is warranted.

**REFERENCES**

1. Crawley PD, Mahlow WJ, Huntsinger DR, Afniwala S, Wortham DC. Giant coronary artery aneurysms: review and update. Tex Heart Inst J 2014;41:603-8.

2. Kamisawa T, Zen Y, Pillai S, Stone JH. IgG4-related disease. Lancet 2015;385:1460-71.

3. Oyama-Manabe N, Yabusaki S, Manabe O, Kato F, Kanno-Okada H, Kudo K. IgG4-related cardiovascular disease from the aorta to the coronary arteries: multidetector CT and PET/CT. Radiographics 2018;38:1934-48.

4. Inokuchi G, Hayakawa M, Kishimoto T, Makino Y, Iwase H. A suspected case of coronary periarteritis due to IgG4-related disease as a cause of ischemic heart disease. Forensic Sci Med Pathol 2014;10:103-8.

5. Sakamoto A, Ishizaka N, Saito K, et al. Serum levels of IgG4 and soluble interleukin-2 receptor in patients with coronary artery disease. Clin Chim Acta 2012;413:577-81.

6. Perugino CA, Wallace ZS, Meyersohn N, Oliveira G, Stone JR, Stone JH. Large vessel involvement by IgG4-related disease. Medicine (Baltimore) 2016;95:e3344.

7. Ozawa M, Fujinaga Y, Asano J, et al. Clinical features of IgG4-related periaortitis/periarteritis based on the analysis of 179 patients with IgG4-related disease: a case-control study. Arthritis Res Ther 2017;19:223.

8. Tabassum A, Sasani S, Majid AJ, Henderson C, Merrett ND. Segmental arterial mediolysis of left gastric artery: a case report and review of pathology. BMC Clin Pathol 2013;13:26.

9. Skeik N, Olson SL, Hari G, Pavia ML. Segmental arterial mediolysis (SAM): systematic review and analysis of 143 cases. Vasc Med 2019;24:549-63.

10. Yunyun F, Yu C, Panpan Z, et al. Efficacy of cyclophosphamide treatment for immunoglobulin G4-related disease with addition of glucocorticoids. Sci Rep 2017;7:6195.

**KEY WORDS** coronary artery aneurysm, coronary artery calcification, immunoglobulin G4-related disease, left gastric artery aneurysm

**APPENDIX** For supplemental videos, please see the online version of this paper.
A novel frameshift variant was identified in APOB that segregates in a dominant manner with low levels of low-density lipoprotein cholesterol. Affected family members show no apparent clinical complications. There is no consensus regarding clinical management, and the long-term consequences of low levels of low-density lipoprotein cholesterol remain unknown. (Level of Difficulty: Advanced.) (J Am Coll Cardiol Case Rep 2020;2:775–9) © 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 20-year-old Caucasian male patient presented to his primary care provider with complaints of palpitations. His 12-lead electrocardiogram was normal. A lipid profile revealed a low-density lipoprotein cholesterol (LDL-C) level of 8 mg/dl. The patient was referred to the Michigan Medicine Lipid Disorders Clinic for evaluation. His physical examination was notable for a weight 64 kg, height 180 cm, and body mass index 19.5 kg/m². The remainder of his physical examination was unremarkable, including no evidence of hepatomegaly, peripheral neuropathy, or retinopathy. A lipoprotein metabolism profile (Mayo Clinic, Rochester, Minnesota) revealed total cholesterol 77 mg/dl, LDL-C 15 mg/dl, high-density lipoprotein cholesterol 48 mg/dl, triglycerides 32 mg/dl, and apolipoprotein B (ApoB) 15 mg/dl. Thyroid-stimulating hormone level, comprehensive metabolic panel, and complete blood count were normal.
PAST MEDICAL HISTORY

The patient’s childhood development was normal, with no reported history of failure to thrive; no symptoms of malabsorption; and no neurological, hepatic, or visual abnormalities. There was no history of chronic or acute infections, recent hospitalizations, or inflammatory disease.

DIFFERENTIAL DIAGNOSIS

Causes of very low levels of LDL-C are listed in Table 1. Based on the history and available data, the etiology of this patient’s very low LDL-C was hypothesized to be genetic (1,2). Genetic conditions causing very low LDL-C levels have varied etiologies and clinical presentations (3). They are characterized by plasma levels of total cholesterol, LDL-C, and apoB <5th percentile, with typical LDL-C values between 20 and 50 mg/dl (4). Homozygous or biallelic pathogenic mutations in genes encoding key proteins in lipoprotein metabolism and synthesis cause abetalipoproteinemia, homozygous familial hypobetalipoproteinemia (FHBL), and chylomicron retention disease. These diseases typically present with prominent multiorgan system phenotypes identified in infancy or youth, including failure to thrive, steatorrhea, and fat-soluble vitamin

| Table 1 Differential Diagnosis of Low LDL-C |
|---------------------------------------------|
| **Affected Gene**                           |
| **Mode of Inheritance**                     |
| Primary causes                              |
| Abetalipoproteinemia                        | MTTP | Recessive |
| Familial combined hypolipoproteinemia       | ANGPT3 | Recessive |
| Chylomicron retention disease               | MTTP | Recessive |
| Familial hypobetalipoproteinemia            | APOB | Co-Dominant |
| Familial hypolipoproteinemia                | PCSK9 | Co-Dominant |
| Acquired/secondary causes                   |
| Chronic parenchymal liver disease           | –    | –          |
| Intestinal fat malabsorption syndromes      | –    | –          |
| Exocrine pancreatic deficiency              | –    | –          |
| Cystic fibrosis                             | –    | –          |
| Chronic pancreatitis                        | –    | –          |
| Hyperthyroidism                             | –    | –          |
| Moderate to severe hypertriglyceridemia     | –    | –          |
| Malignancy                                  | –    | –          |
| Sepsis                                      | –    | –          |
| Chronic infection                           | –    | –          |
| Medication effects                          | –    | –          |

This figure presents the stepwise process for clinical management for patients presenting with low levels of low-density lipoprotein cholesterol (LDL-C), low apolipoprotein B (apoB), and co-dominant inheritance. This figure was modified from Tarugi and Averna (2) and modified from Hartz et al. (1). CVD = cardiovascular disease.
deficiencies often with retinopathy, neuropathy, or coagulopathy (4).

This patient lacked any of the multiorgan system dysfunction of abetalipoproteinemia, homozygous FHBL, or chylomicron retention disease despite having an LDL-C <5th percentile. Thus, other genetic causes of low LDL-C, which typically have little or no clinical manifestations, were considered (Figure 1). These included heterozygous or homozygous familial hypolipoproteinemia due to mutations in PCSK9 and heterozygous FHBL due to mutations in APOB (Figure 1)(2). Heterozygous FHBL is the most common cause of LDL-C <5th percentile, with an estimated prevalence of APOB-related FHBL of 1 in 1,000 to 3,000 (4,5). However, this patient presented with an LDL-C of 8 mg/dl, which is much lower than typical for heterozygous FHBL, thereby confounding the clinical picture. Contrarily, patients with homozygous or compound heterozygous FHBL have LDL-C levels and clinical conditions similar to the severe recessive disorders (i.e., abetalipoproteinemia).

INVESTIGATIONS

Cascade screening for low levels of LDL-C was performed for first- and second-degree relatives. Next, the index patient and 7 family members (Table 2, Figure 2) enrolled into the Cardiovascular Health Improvement Project, a longitudinal biorepository (HUM00052866). Saliva samples were collected, coded, and linked to electronic health records, and DNA was isolated. High-coverage whole genome sequencing (30x) was performed by Psomagen, Inc. (Rockville, Maryland). Supplemental Table 1 and the Supplemental Material provide a summary of genetic sequencing data and methods.

WHOLE GENOME SEQUENCING. Of the rare (not present in gnomAD [6] or 1000 Genomes European reference populations [7] or minor allele frequency <1%) high-impact polymorphisms (variant effect predictor annotations as transcript ablation, splice acceptor or donor, stop gained, frameshift, and stop or start lost) identified in the 8 samples, only 1 (APOB p.Val853fs) followed the dominant inheritance pattern with the low LDL-C status (Table 3, Figure 3).

Inheritance with low LDL-C. None of these 7 mutations fell into genes known to affect lipid metabolism (Table 3, Figure 3).

The identified APOB frameshift variant was not present in any of the public databases, and we were not able to find any publications or case reports in the published data. Thus, we believe that this particular variant is novel. There are multiple previously published mutations in APOB shown to cause low LDL-C levels, but also observed in conjunction with adverse liver effects including hepatic steatosis and hepatocellular carcinoma (1,4,8). The LDL-C levels seen for the affected cases (undetectable and between 8 and 19 mg/dl) are significantly lower (T-statistic for the difference in mean = 7.58, 2-tailed p = 3.0 × 10^-8) than the average LDL-C level of heterozygous APOB loss-of-function (LoF) mutation carriers in the HUNT (9) biobank (mean LDL-C for APOB LoF carriers = 56 mg/dl)

| Family Member | Low-LDL Case | Total Cholesterol (mg/dl) | LDL-C (mg/dl) | Triglycerides (mg/dl) | HDL-C (mg/dl) | APOB p.Val853fs |
|---------------|--------------|---------------------------|---------------|----------------------|--------------|----------------|
| Control       | Not tested   | —                         | —             | —                    | —            | Noncarrier     |
| Case          | Yes          | 84                        | 19            | 32                   | 59           | LoF carrier    |
| Control       | No           | 199                       | 102           | 132                  | 71           | Noncarrier     |
| Index case    | Yes          | 86                        | 8             | 29                   | 72           | LoF carrier    |
| Case          | Yes          | 88                        | 12            | 16                   | 73           | LoF carrier    |
| Case          | Yes          | 88                        | Undetectable | 20                   | 55           | LoF carrier    |
| Case          | Yes          | 73                        | 13            | 25                   | 55           | LoF carrier    |

*Particle sizes were measured and interpreted as normal (R.B.).

HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; LoF = loss of function.

FIGURE 2 Family Pedigree

This figure presents the family pedigree. Abbreviations as in Figure 1.
The extreme LDL-C phenotype (LDL-C values <10 mg/dl) observed could be attributable to an uncharacterized property of this particular mutant ApoB protein or an unidentified genetic cause, including an unknown genetic variant or the possibility of a polygenic burden for low LDL-C levels.

**MANAGEMENT**

Patients with heterozygous *APOB*-related FHBL have been reported to have elevated levels of liver enzymes. Decreased secretion of mutated apoB from the liver results in reduced hepatic triglyceride export, which can lead to the development of hepatic steatosis, oral fat intolerance, and intestinal fat malabsorption (4,10). There have also been reports of patients with *APOB*-related FHBL developing cirrhosis and hepatocellular carcinoma (4,8,11). Thus, despite having normal liver function, it was recommended that the index patient and affected family members obtain liver ultrasounds and have liver enzymes measured as part of routine medical care. Additional testing including retinal examinations and serum fat-soluble vitamin levels (e.g., vitamin A) as well as formal testing for peripheral neuropathy was recommended. The patient was counseled that offspring should have lipid profiles by age 2 years, and should consult with a lipid specialist if LDL-C is <5th percentile (3).

**TABLE 3** Rare Mutations That Segregate With Disease and Are Predicted to Have an Impact on the Protein

| CHR | POS (hg38) | rsID   | REF/ALT | Annotation (Most Severe) | Gene  | Missense Prediction SIFT/PolyPhen or Consequence |
|-----|------------|--------|---------|---------------------------|-------|-------------------------------------------------|
| 1   | 23375929   | rs35758282 | A/C     | Missense                  | MAP3K21| Deleterious/possibly damaging                   |
| 1   | 240493250  | rs142343894 | G/C     | Missense                  | GREM2 | Tolerated/benign                                |
| 1   | 248038821  | rs138290082 | C/T     | Missense                  | OR2L2 | Deleterious/probably damaging                   |
| 2   | 21023572   | CT/C    | Frameshift | APOB                     |       | Loss-of-function                               |
| 3   | 37222434   | rs62001874 | C/T     | Missense                  | CEBPZ | Tolerated/benign                                |
| 3   | 193363301  | rs201387347 | C/T     | Missense                  | ATP13A5| Tolerated/benign                                |
| 6   | 43339661   | rs145629243 | G/A     | Missense                  | ZNF318| Deleterious/probably damaging                   |
| 6   | 43450828   | rs768837940 | C/T     | Missense                  | DLK2  | Deleterious/benign                               |

(Figure 4). The extreme LDL-C phenotype (LDL-C values <10 mg/dl) observed could be attributable to an uncharacterized property of this particular mutant ApoB protein or an unidentified genetic cause, including an unknown genetic variant or the possibility of a polygenic burden for low LDL-C levels.

**FIGURE 3** Description of the Sequence Data Analysis

LOF mutations n = 1,409
(VEP annotation as HIGH impact:
transcript ablation, Splice acceptor or donor, stop gained, frameshift, and stop or start lost)

With low prevalence in the general European population n = 293
(Not present or with MAF<1% in the gnomAD database and 1000 Genomes project Europeans)

Dominant mode of inheritance n = 1
Recessive mode of inheritance n = 0

Moderate impact mutations n = 17,319
(VEP annotation as MODERATE impact:
missense, inframe insertion and deletion, and protein altering)

With low prevalence in the general European population n = 3,058
(Not present or with MAF<1% in the gnomAD database and 1000 Genomes project Europeans)

Dominant mode of inheritance n = 7
Recessive mode of inheritance n = 0

This figure presents a flow chart of the analyses identifying a loss of function (LoF) and moderate impact mutations. MAF = minor allele frequency; VEP = variant effect predictor.
DISCUSSION OF HETEROZYGOUS APOB-RELATED FHBL

The novel finding is that the identified APOB LoF variant carriers have significantly lower LDL-C levels compared with levels of the carriers from the HUNT study. Moreover, the index patient and affected family members were without known adverse clinical complications. Hepatic steatosis and elevation of liver enzymes are the main clinical manifestations (4); however, the current screening approaches, liver ultrasound and fibroscan, lack sensitivity, and subclinical disease can progress. Genetic testing is important for risk-stratifying patients into groups requiring long-term and routine follow-up, such as those with APOB LoF compared with PCSK9 LoF variant carriers, the latter of which typically do not have any adverse clinical manifestations.

FOLLOW-UP

The index patient and affected cases were not clinically followed after the management plan was discussed due to the proximity of residence to clinic location.

CONCLUSIONS

This case report is reflective of a family with normal development without known adverse clinical complications despite very low levels of LDL-C. Given the finding of an APOB LoF as the cause for the low LDL-C, routine screening for liver disease and other associated complications should be pursued long-term. Importantly, this patient and affected family members had normal development with very low LDL-C levels, and will likely gain protection against atherosclerotic cardiovascular disease.

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REFERENCES

1. Hartz J, Hegele RA, Wilson DP. Low LDL cholesterol—friend or foe? J Clin Lipidol 2019;13:367-73.
2. Tarugi P, Averna M. Hypobetalipoproteinemia: genetics, biochemistry, and clinical spectrum. Adv Clin Chem 2011;54:81-107.
3. Lee J, Hegele RA. Abetalipoproteinemia and homozygous hypobetalipoproteinemia: a framework for diagnosis and management. J Inherit Metab Dis 2014;37:333-9.
4. Welty FK. Hypobetalipoproteinemia and abetalipoproteinemia. Curr Opin Lipidol 2014;25:161-8.
5. Burnett JR, Bell DA, Hooper AJ, Hegele RA. Clinical utility gene card for: Abetalipoproteinemia—update 2014. Eur J Hum Genet 2015;23:890.
6. Karczewski KJ, Franciosi LC, Tiao G, et al. Variation across 141,456 human exomes and genomes reveals the spectrum of loss-of-function intolerance across human protein-coding genes. bioRxiv 2019;531210.
7. Auton A, Brooks LD, Durbin RM, et al. A global reference for human genetic variation. Nature 2015;526:68-74.
8. Celalu AB, Pirrucello JP, Noto D, et al. A novel APOB mutation identified by exome sequencing cosegregates with steatosis, liver cancer, and hypcholesterolemia. Arterioscler Thromb Vasc Biol 2013;33:2021-5.
9. Krookstad S, Langhammer A, Hveem K, et al. Cohort profile: the HUNT study, Norway. Int J Epidemiol 2013;42:969-77.
10. Mouzaki M, Shah A, Arce-Clachar AC, Hardy J, Bramlage K, Xanthakis SA. Extremely low levels of low-density lipoprotein potentially suggestive of familial hypobetalipoproteinemia: A separate phenotype of NAFLD? J Clin Lipidol 2019;13:425-31.
11. Tanoli T, Yue P, Yablonsky D, Schonfeld G. Fatty liver in familial hypobetalipoproteinemia: roles of the APOB defects, intra-abdominal adipose tissue, and insulin sensitivity. J Lipid Res 2004;45:941-7.

KEY WORDS: apolipoprotein B loss-of-function, hypobetalipoproteinemia, low-density lipoprotein cholesterol

APPENDIX For supplemental methods and a supplemental table, please see the online version of this paper.
His Bundle Pacing in Amiodarone-Induced Complete Heart Block, QT Prolongation, and Torsade de Pointes

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ABSTRACT

A woman with ischemic cardiomyopathy presented with recurrent syncope. Electrocardiogram showed complete heart block and torsade de pointes (TdP) secondary to amiodarone, recently started for paroxysmal atrial fibrillation. We describe a novel application of His bundle pacing that suppressed TdP and corrected the underlying left bundle branch block. (Level of Difficulty: Intermediate.) (J Am Coll Cardiol Case Rep 2020;2:780–4) © 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/).

A 78-year-old woman was admitted following recurrent syncope. Prior to this admission, she was just discharged 1 day prior after a 6-day admission for decompensated heart failure in the setting of atrial fibrillation with rapid ventricular response. A total of 2,250 mg of amiodarone was given during the previous hospitalization before she was discharged on oral amiodarone 200 mg twice a day. Her other medications were: atorvastatin 40 mg every night, apixaban 2.5 mg twice daily, furosemide 40 mg every morning, potassium chloride slow release 600 mg every morning, and omeprazole 20 mg every morning.

Upon arrival to emergency department, her blood pressure was 181/77 mm Hg and she had an irregular pulse of 56 beats/min. Physical examination revealed no signs of heart failure.

LEARNING OBJECTIVES

- To make a differential diagnosis of causes of recurrent syncope episodes in a patient with paroxysmal atrial fibrillation started on amiodarone with background history of ischemic cardiomyopathy.
- To recognize one of the subacute amiodarone side effects affecting the cardiovascular system, which include complete heart block, prolonged QTc, and recurrent TdP. In this setting, ventricular pacing from conventional sites was arrhythmogenic whereas pacing at the His bundle region suppressed TdP.

MEDICAL HISTORY

The patient’s medical history included hypertension, ischemic cardiomyopathy with left ventricular ejection function (LVEF) of 38%, New York Heart Association functional class II, left bundle branch...
block with QRS complex duration of 155 ms and paroxysmal atrial fibrillation with CHA\textsubscript{2}DS\textsubscript{2}-VASc score of 6.

**DIFFERENTIAL DIAGNOSIS**

Differential diagnosis included significant post-atrial fibrillation conversion pause, ventricular tachycardia in the setting of ischemic cardiomyopathy, or TdP in the setting of long QTc secondary to amiodarone.

**INVESTIGATIONS**

Her electrocardiogram (Figure 1) on this admission showed complete heart block with slow ventricular escape rhythm and long QT (QTc: 710 ms). Each ventricular escape beat was followed by late coupled premature ventricular ectopics of varying morphology. Serum potassium and magnesium were normal at 4.1 and 1.48 mmol/l, respectively. Liver and renal function tests were normal. Serial serum troponin level was not elevated. Telemetry showed multiple episodes of non-sustained TdP (associated with symptoms of pre-syncope) (Figure 2). Coronary angiogram did not show any significant obstructive lesion. Transthoracic echocardiography, specifically LVEF assessment, was unchanged from before.

The most likely explanation for her recurrent syncope was nonsustained TdP in the setting of long QTc secondary to amiodarone.

**MANAGEMENT**

As the patient had a background of broad left bundle branch block with significant cardiomyopathy, as well as an urgent need for pacing for recurrent episodes of TdP, a decision was made to implant a cardiac resynchronization therapy defibrillator (device: Compia MRI CRT-D Sure Scan; right atrial lead: CapSure Fix Novus 5076/52 cm; right ventricular [RV] lead: Sprint SC DF4 6935M/62 cm; all Medtronic, Minneapolis, Minnesota).

During the procedure, pacing from the RV apical lead and left ventricular (LV) lead (Medtronic Attain Performa Advanced Quadripolar lead 4298/88 cm) positioned at the posterolateral coronary sinus (CS) branch invariably induced nonsustained TdP (Figure 3). Pacing-induced nonsustained TdP also occurred at other sites of CS branches. Thus, the LV lead was not placed. In view of this, we proceeded to perform His bundle pacing by placing a lumenless bipolar pace/sense lead (Medtronic 3830/69 cm Select Secure) using C315 His sheath (Medtronic). Nonselective pacing at the His bundle region did not induce TdP (Figure 4) with a satisfactory pacing threshold (1.0 V at 1.0 ms). The QTc (calculated using Bazett formula) at baseline (on admission) was 710 ms compared with QTc during RV pacing of 560 ms as well as QTc during nonselective His bundle pacing of 529 ms. QTc during LV pacing was not measured, as pacing at LV invariably induced TdP.
FIGURE 2  Telemetry Showed Complete Heart Block, Slow Ventricular Escape Rhythm With Long QT Followed by Spontaneous Initiation and Termination of Nonsustained Torsade de Pointes

Telemetry electrocardiogram showed 2 continuous tracings and each tracing **from top to bottom** showed electrocardiogram lead II, plethysmography waveform, and respiratory waveform.

FIGURE 3  Electrocardiogram Strip Showed Left Ventricular Pacing-Induced Torsade de Pointes

Electrocardiogram leads configuration from **top to bottom**: I, II, III, and V1.
DISCUSSION

Amiodarone is a class III antiarrhythmic agent with well-documented long-term side effects involving multiple systems, including but not limited to pulmonary toxicity, thyroid dysfunction, and liver injury. Subacute amiodarone syndrome, however, is rare and affects mainly the liver (1-5) rather than heart. Sequeira et al. (6) were the first to describe the association of intravenous amiodarone-induced third-degree atrioventricular block and extreme QT interval prolongation generating TdP in a patient with paroxysmal atrial fibrillation (6). In our case, amiodarone was initially administered intravenously and the patient was already on oral amiodarone when she presented with TdP. This was in contrast with the case of Sequeira et al. (6), in which TdP happened during administration of intravenous amiodarone. Another interesting observation in our case was that pacing from both ventricles induced non-sustained TdP whereas non-selective His bundle pacing was not arrhythmogenic.

In general, amiodarone has low proarrhythmic effect both in normal and heart failure patients despite QT prolongation due to its fast phase III repolarization, a low incidence on dispersion of repolarization, a lower potential to induce early after depolarization, and a weak effect on reverse frequency dependence (7,8). However, the proarrhythmic effect of amiodarone has been well described (7,8). In our case, the proarrhythmic effect of amiodarone was likely exacerbated by low repolarization reserve in this patient. However, the patient declined genetic testing for long QT syndrome.

Conventional pacing at the RV apex and epicardial LV through the CS vasculature triggered TdP (Figure 3). This would have precluded the use of temporary RV pacing, which may have been attempted in most centers without access to urgent electrophysiological service. Pacing at the His bundle region, however, managed to suppress the premature ventricular complexes and TdP. A plausible explanation is a lowering of the dispersion of repolarization by pacing at the His bundle region and relative shortening of QT interval.

FOLLOW-UP

Subsequent follow-up (up to 12 months) showed no ventricular arrhythmia event, stable nonselective His bundle pacing threshold, as well as RV lead parameters. There was no recurrent hospitalization. Her effort tolerance improved markedly to New York Heart Association functional class I. Repeat transthoracic echocardiography showed LVEF had improved from 38% to 45%.
CONCLUSIONS

We describe a case of subacute amiodarone side effect resulting in complete heart block, prolonged QTc, and recurrent TdP. In this setting, ventricular pacing from conventional sites (RV apex and coronary sinus) was arrhythmogenic, whereas pacing at the His bundle region suppressed TdP. To the best of our knowledge, this is the first case reporting on the novel application of His bundle pacing in the context of amiodarone-induced TdP.

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REFERENCES

1. Rhodes A, Eastwood JB, Smith SA. Early acute hepatitis with parenteral amiodarone: a toxic effect of the vehicle? Gut 1993;34:565-6.
2. Ng XR, Wee LY, Chadachan V. Acute amiodarone syndrome after a single intravenous amiodarone bolus. Singapore Med J 2012;53:e225-7.
3. Pye M, Northcote RJ, Cobbe SM. Acute hepatitis after parenteral amiodarone administration. Br Heart J 1988;59:690-1.
4. Lupon-Roses J, Simo-Canonge R, Lu-Cortez L, Permanyer-Miralda G, Allende-Monclus H. Probable early acute hepatitis with parenteral amiodarone. Clin Cardiol 1986;9:223-5.
5. Stevenson RN, Nayani TH, Davies JR. Acute hepatic dysfunction following parenteral amiodarone administration. Postgrad Med J 1989;65:707-8.
6. Sequeira OR, Aquino NJ, Gomez NB, et al. Amiodarone-induced third degree atrioventricular block and extreme QT prolongation generating torsade des pointes in paroxysmal atrial fibrillation. J Atr Fibrillation 2016;9:1502.
7. Milberg P, Ramtin S, Monnig G, et al. Comparison of the in vitro electrophysiologic and proarrhythmic effects of amiodarone and sotalol in a rabbit model of acute atrioventricular block. J Cardiovasc Pharmacol 2004;44:278-86.
8. Meierhenrich R, Helguera ME, Kidwell GA, Tebbe U. Influence of amiodarone on QT dispersion in patients with life-threatening ventricular arrhythmias and clinical outcome. Int J Cardiol 1997;60:289-94.

KEY WORDS: amiodarone, atrial fibrillation, cardiac pacemaker, cardiomyopathy, complete heart block, His bundle pacing.
A 48-year-old man presented with rapidly progressive heart failure and monoclonal gammopathy of uncertain significance. No specific cause was detected on endomyocardial biopsy. As the heart failure worsened, he also developed progressive skeletal myopathy. This provided the clue to the diagnosis, and cardiac function recovered rapidly with cause-directed therapy. (Level of Difficulty: Intermediate.) (J Am Coll Cardiol Case Rep 2020;2:785–9)

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significance can cause inflammatory/myocarditis, but due to the extent of these findings infiltrative heart disease was discussed even though there was no myocardial hypertrophy (Figure 1). Cardiac biopsy demonstrated mild fibrosis and myocyte hypertrophy, but no signs of amyloid or other causes of infiltrative disease (Figure 2). Supplementary work-up revealed an immunoglobulin G lambda monoclonal band in the serum (1 g/l). The proportion of plasma cells in the bone marrow was 1% to 3%, which is consistent with a diagnosis of monoclonal gammopathy of uncertain significance (MGUS).

It was noted that the patient had an abnormal gait, and he complained of having trouble walking fully upright, but magnetic resonance imaging showed no pathology in the spinal cord, spinal nerve roots, or spine. On neurological examination, we observed fasciculations, proximal muscular atrophy, and axial and proximal muscle weakness. The sensory examination was normal. Tendon reflexes were brisk and the plantar response normal. Blood levels of creatine kinase were normal. The cerebrospinal fluid was normal apart from a slightly elevated protein level. A computed tomography scan revealed no thoracic, abdominal, or pelvic malignancy. The electromyogram and muscle biopsies showed signs of myopathy.

**DIFFERENTIAL DIAGNOSIS**

The combination of myopathy and heart failure was suggestive of inherited muscle disease. We performed a genetic work-up that included a large panel of genes known to cause myopathy and cardiomyopathy (see the overview of genes sequenced in the Supplemental Appendix), without discovering a genetic cause of the patient’s disease. Monoclonal gammopathy of uncertain significance can cause cardiac amyloid light-chain amyloidosis through the deposition of free light chains. Due to high suspicion of infiltrative disease, we repeated endomyocardial biopsy, but again, there was no sign of amyloid. On renewed examination of deltoid and vastus skeletal muscle biopsies, however, we found abundant sarcoplasmic nemaline rods consistent with sporadic late-onset nemaline myopathy (SLONM) (Figure 3). On first look, these inclusions had not been recognized for what they were.

**MANAGEMENT**

Approximately 2 years after first being diagnosed with heart failure, the patient was in New York Heart Association functional class IV with dyspnea at rest despite optimal pharmacological treatment for heart failure. His hemodynamics were severely compromised (Table 1, Videos 3 and 4). He had pronounced axial and proximal muscle weakness and atrophy, dysphagia, and dropped head. He had difficulties walking unaided and rising from a chair. We regarded MGUS-associated SLONM as the likely cause of his myopathy and heart failure but considered him too ill to tolerate high-dose chemotherapy with autologous stem-cell support. Instead, we decided to initiate front-line therapy for MGUS to provide disease control. Shortly before admission for the initiation of therapy for MGUS, the patient developed atrial flutter with an average ventricular rate of approximately 110 beats/min. He received ablation therapy for atrial flutter, after which we began treatment as in plasma cell disease with bortezomib, lenalidomide, and dexamethasone. The monoclonal component could not be detected after start of treatment.

**TABLE 1 Clinical and Hemodynamic Variables**

|                      | NYHA functional class | Blood pressure, mm Hg | Heart rate, beats/min | NT-proBNP, pg/l | LV internal diameter, cm | LV septum thickness, cm | LVEF, % | Right heart catheterization | Cardiac output, l/min | Mixed venous oxygen saturation, % |
|----------------------|-----------------------|-----------------------|-----------------------|-----------------|--------------------------|-------------------------|--------|----------------------------|----------------------|-------------------------------|
|                      | On First Admission    | 18 Months Later        | Before Start of Specific Therapy* | 2 Months After the Initiation of Therapy |                      |                         |        | Right atrial pressure, mm Hg |                        |                                |
|                      | IV                    | III                   | IV                    | IV              |                          |                         |        | 7                           | 18                   |                                |
|                      | 156/116               | 145/100               | 117/96                | 115/85          |                          |                         |        | MPAP, mm Hg                 | 38                   | 47                            |
|                      | 106                   | 90                    | 110                   | 74              |                          |                         |        | PCWP, mm Hg                 | 24                   | 34                            |
|                      | 5.6                   | 5.8                   | 5.6                   | 5.8             | 1.0                      | 1.1                     |        | 40                          | 40                   | 18                            |
|                      | 5.6                   | 5.8                   | 5.6                   | 5.8             |                          |                         |        | 5.9                         | 3.8                  | 6.3                           |
|                      |                          |                       |                       |                  |                          |                         |        | Mixed venous oxygen saturation, % | 63                   | 43                            |

*—Bortezomib, lenalidomide, and dexamethasone. †—Measured by echocardiography. ‡—Measured by cardiac magnetic resonance imaging.

LV = left ventricle; LVEF = left ventricular ejection fraction; MPAP = mean pulmonary arterial pressure; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association; PCWP = pulmonary capillary wedge pressure.

**ABBREVIATIONS AND ACRONYMS**

MGUS = monoclonal gammopathy of uncertain significance

SLONM = sporadic late-onset nemaline myopathy

**NGMS**

MAY 2020:785

Progressive Heart Failure, Myopathy, and MGUS

Broch et al

N-terminal pro-

JACC: CASE REPORTS, VOL. 2, NO. 5, 2020

There were pathological values on native T1 left ventricular dilation and mild systolic dysfunction. There were pathological values on native T1 mapping and extensive late gadolinium enhancement in the midwall and subepicardial layers of the left ventricle. The enhancement pattern could suggest inflammation/myocarditis, but due to the extent of these findings infiltrative heart disease was discussed even though there was no myocardial hypertrophy (Figure 1). Cardiac biopsy demonstrated mild fibrosis and myocyte hypertrophy, but no signs of amyloid or other causes of infiltrative disease (Figure 2). Supplementary work-up revealed an immunoglobulin G lambda monoclonal band in the serum (1 g/l). The proportion of plasma cells in the bone marrow was 1% to 3%, which is consistent with a diagnosis of monoclonal gammopathy of uncertain significance (MGUS).

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|----------------------|-----------------------|-----------------------|-----------------------|-----------------|--------------------------|-------------------------|--------|----------------------------|----------------------|-------------------------------|
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|                      | 106                   | 90                    | 110                   | 74              |                          |                         |        | PCWP, mm Hg                 | 24                   | 34                            |
|                      | 5.6                   | 5.8                   | 5.6                   | 5.8             | 1.0                      | 1.1                     |        | 40                          | 40                   | 18                            |
|                      | 5.6                   | 5.8                   | 5.6                   | 5.8             |                          |                         |        | 5.9                         | 3.8                  | 6.3                           |
|                      |                          |                       |                       |                  |                          |                         |        | Mixed venous oxygen saturation, % | 63                   | 43                            |

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LV = left ventricle; LVEF = left ventricular ejection fraction; MPAP = mean pulmonary arterial pressure; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association; PCWP = pulmonary capillary wedge pressure.
FOLLOW-UP

After the initiation of therapy, the patient rapidly recovered. Two months later, his left ventricular function had normalized (Videos 5 and 6), and he was in New York Heart Association functional class I (Table 1). On physical testing, he had improved muscle strength, but persistent weakness of the proximal and axial muscles. He was deemed fit to tolerate high-dose chemotherapy with autologous stem-cell support, which we recently performed without severe side effects.

DISCUSSION

Skeletal myopathy and cardiomyopathy coexist in several hereditary disorders including mitochondrialopathies, storage diseases, and diseases caused by mutations in genes encoding structural proteins (1). A family history of myopathy or cardiomyopathy and either early-onset or slowly progressive disease supports the diagnosis of hereditary myopathy with cardiomyopathy. In this case, we could not find a genetic cause, and the coexistence of MGUS eventually led us to look for a different explanation. MGUS is a premalignant disease caused by the monoclonal expansion of a plasma cell. It carries a 1% yearly risk of progressing to multiple myeloma, lymphoma, amyloid light-chain amyloidosis, macroglobulinemia, lymphocytic leukemia, or plasmacytoma (2). MGUS is known to cause cardiac amyloid light-chain amyloidosis through the deposition of free light chains (3), but it is also associated with the rare myopathy SLONM (4).

Nemaline myopathy is usually an early-onset, inherited disease caused by mutations in genes encoding myocyte structural proteins. The rare sporadic late-onset variety has been associated with MGUS. In a few cases, concomitant heart failure has been reported (4). In SLONM, the MGUS presumably causes myopathy through interaction between the monoclonal immunoglobulins and the sarcomeric proteins of the myocytes (4). Presumably, the same mechanism is responsible for the heart failure, but notably, we did not find nemaline bodies on endomyocardial biopsy.

In case series, successful treatment of MGUS has led to recovery from the myopathy (4,5), and in 2 single cases, simultaneous recovery from heart failure has been reported (6,7). In the latter cases, SLONM with MGUS preceded the onset of heart failure. In our patient, on the other hand, heart failure preceded the onset of symptomatic myopathy by several months. SLONM with MGUS should therefore be considered in the diagnostic evaluation not only in progressive myopathy, but also in unexplained heart failure. Importantly, skeletal muscle, biopsy, but not endomyocardial biopsy, was diagnostic in our case. By the time treatment for MGUS was initiated, our patient had severe, end-stage heart failure, which nevertheless improved rapidly. Notably, the left ventricular function recovered more rapidly than skeletal muscle function, suggesting that the pathophysiologic mechanism of heart failure in SLONM with MGUS is different from that in the skeletal muscles. This is supported by the fact that nemaline bodies were not detected in 2 separate sets of endomyocardial biopsies in our patient.

FIGURE 1 CMR Imaging

Two-chamber long-axis (A) and short-axis (B) views showing midwall and subepicardial late gadolinium enhancement (arrows).
FIGURE 2  Endomyocardial Biopsy

(A) Light micrograph from a hematoxylin and eosin–stained section. There is focal loss of muscle elements and repair by fibrosis (upper left). (B,C) Electron micrograph showing normal myocytes (B) and focal Z-disc streaming (C). No sarcoplasmic rods were observed.

FIGURE 3  Muscle Biopsy (Vastus Lateralis)

(A) Light micrograph from a hematoxylin and eosin–stained section showing chronic myopathy. (B) Gomori trichrome. There is extensive deposition of cytoplasmic granular material: nemaline rods. (C, D) Electron microscopy. Multiple sarcoplasmic nemaline rods can be observed.
CONCLUSIONS

Our case highlights a rare cause of heart failure amenable to cause-directed therapy. SLONM is a disease that primarily affects skeletal muscle, but can also cause heart failure. Our case illustrates the potential for recovery from severe heart failure with treatment directed at plasma cells in SLONM with MGUS.

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REFERENCES

1. Arbustini E, Di Toro A, Giuliani L, Favalli V, Narula N, Grasso M. Cardiac phenotypes in hereditary muscle disorders: JACC State-of-the-Art Review. J Am Coll Cardiol 2018;72:2485-506.
2. Kyle RA, Larson DR, Therneau TM, et al. Long-term follow-up of monoclonal gammopathy of undetermined significance. N Engl J Med 2018;378:241-9.
3. Falk RH, Alexander KM, Liao R, Dorbala S. AL (light-chain) cardiac amyloidosis: a review of diagnosis and therapy. J Am Coll Cardiol 2016;68:1323-41.
4. Schnitzler LJ, Schrekenbach T, Nadaj-Pakleza A, et al. Sporadic late-onset nemaline myopathy: clinico-pathological characteristics and review of 76 cases. Orphanet J Rare Dis 2017;12:86.
5. Voermans NC, Benveniste O, Minnema MC, et al. Sporadic late-onset nemaline myopathy with MGUS: long-term follow-up after melphalan and SCT. Neurology 2014;83:2133-9.
6. Belhomme N, Maamar A, Le Gallou T, et al. Rare myopathy associated to MGUS, causing heart failure and responding to chemotherapy. Ann Hematol 2017;96:695-6.
7. Kotchetkov R, Dyszkiewicz-Korpanty A, Kukreti V. Chemotherapy with stem cell transplantation is more effective than immunotherapy in sporadic late onset nemaline myopathy with monoclonal gammopathy. Bone Marrow Transplant 2018;53:895-9.

KEY WORDS: cardiomyopathy, chronic heart failure, echocardiography, imaging, right-sided catheterization

APPENDIX For supplemental videos and an overview of the genes sequenced, please see the online version of this paper.
SPURIOUSLY ELEVATED CARDIAC TROTONIN
IN THE SETTING OF ATYPICAL CHEST PAIN
PRESENTATION
A DIAGNOSTIC CONUNDRUM

Kamal M. Kassem, MD,a Mahboob Ali, MD,b Naseem Ghazanfari, MD,b Mohamed Effat, MDb

ABSTRACT

A 47-year-old woman presented with atypical chest pain and a troponin level of 30.15 ng/dl. A detailed diagnostic work-up did not detect an acute myocardial infarction but revealed the presence of heterophile antibodies. Laboratory values need to be interpreted in the context of the clinical picture when test results do not correspond to clinical findings. (Level of Difficulty: Beginner.) (J Am Coll Cardiol Case Rep 2020;2:790–5) © 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/).

HISTORY OF PRESENTATION

A 47-year-old African American woman with a medical history of hypertension and nonobstructive coronary artery disease presented to the hospital with left-sided chest pain and a sensation of heaviness and numbness in her left arm that lasted for 12 h. She reported having experienced similar episodes of intermittent chest pain associated with left arm numbness over the previous 5 months. The pain was described as a stabbing sensation, lasting for a few seconds to minutes and occurring both at rest and with activity. It was not associated with nausea, vomiting, or diaphoresis. Vital signs on admission revealed blood pressure of 170/92 mm Hg, heart rate of 65 beats/min, respiratory rate of 22 breaths/min, and oxygen saturation of 100% on room air. Physical examination, including a comprehensive cardiovascular examination, was unremarkable except for the presence of an apical S4.

LEARNING OBJECTIVES

- To recognize the spurious causes of hypotroponinemia.
- To incorporate the clinical context when analyzing diagnostic data.

The patient had presented in a similar fashion to an outside facility in Georgia 5 months before this presentation. At that time, she reportedly underwent left-sided heart catheterization (LHC) that showed nonobstructive coronary artery disease (~30% left circumflex lesion). She subsequently moved to our city and started working in a plasma donor center.
The patient ran out of her antihypertensive medications after moving to our area.

**DIFFERENTIAL DIAGNOSIS**

Her presentation was concerning for several possibilities, including acute coronary syndrome (ACS), acute aortic dissection, and acute pulmonary embolism. ACS was initially thought to be the most likely cause because her chest pain occurred at rest and was associated with left arm numbness.

**INVESTIGATIONS**

The initial work-up in the emergency department included a 12-lead electrocardiogram (ECG) (Figure 1), a complete metabolic panel, and a complete blood count; all were unremarkable. A serum troponin I level was drawn and was found to be elevated at a strikingly high 30.15 ng/dl (normal: <0.04 ng/dl). This was the conventional Access AccuTnI+ troponin I assay (Beckman Coulter, Brea, California; referred to here as the Beckman assay) and not a high-sensitivity troponin assay. Additional biomarker test results included a creatine kinase (CK) level of 120 U/l (normal: 30 to 223 U/l) and a lactate dehydrogenase level of 205 IU/l (normal: 110 to 270 IU/l). The second troponin I value was 32.21 ng/dl, and the third was 31.52 ng/dl, which represented an insignificant change.

Despite the normal 12-lead ECG, the marked elevation of serum troponin made the diagnosis of ACS high on our differential diagnosis. Therefore, the patient underwent an urgent LHC, which revealed only tortuous coronary arteries, consistent with hypertensive heart disease with no evidence of significant coronary obstruction or dissection (Figure 2).

The unremarkable results of the LHC led to further evaluation for noncoronary causes of myocardial necrosis (Table 1). Chest computed tomography angiography excluded aortic aneurysm and dissection. However, it did show a trivial pericardial effusion. An echocardiogram revealed mild left ventricular hypertrophy and mild global hypokinesis with a left ventricular ejection fraction of ~45% to 50%, possibly resulting from myocarditis or hypertensive cardiomyopathy secondary to her long-standing uncontrolled hypertension. The working diagnosis at that point shifted toward myocarditis versus other rare causes of troponin elevation. On hospital day 5, she underwent an endomyocardial biopsy, which revealed normal histologic findings. Subsequently, cardiac magnetic resonance revealed...
low normal left ventricular systolic function with no regional wall motion abnormalities or findings to suggest inflammation or infiltration. There was a diffusion defect on the lateral side, likely representing microstructural anisotropy caused by myocyte hypertrophy, but no myocardial edema by T2-weighted imaging (Figures 3A to 3D). Various other laboratory tests, including inflammatory markers and autoimmune serological examinations, were obtained (Table 2), but none initially yielded further diagnostic information.

At that point, an interfering substance with our facility’s troponin I assay was suspected. We sent samples of troponin T and CK-MB for testing in an outside laboratory, but both were reported to be within normal limits. Meanwhile, we contacted the laboratory at the hospital in Georgia where the patient had initially presented with chest pain 5 months earlier. There, the troponin I value had been normal. We then aimed to investigate the type of troponin I used in our laboratory. Our facility uses the Beckman assay. The assay used for troponin I testing in Georgia was found to be the Architect i2000SR (Abbott, Abbott Park, Illinois; referred to here as Architect 2000). We located a nearby center where the Architect 2000 assay was also being used. We then rechecked troponin I at our facility and the outside laboratory using the same sample. Troponin I was found to be within normal range with the Architect 2000 assay at the outside laboratory and was markedly elevated, at 30 ng/dl, with the Beckman assay at our facility. Subsequent serological testing confirmed the presence of a human antimurine antibody (HAMA) that reacted with the murine antibody used in the Beckman troponin assay.

**DISCUSSION**

This case demonstrates an example of falsely elevated cardiac troponin (cTn) related to the presence of heterophile antibodies. Cardiac biomarkers
play a pivotal role in the diagnosis of myocardial injury and infarction, and their presence and degree of elevation have been associated with high rates of adverse cardiovascular outcomes in various clinical settings (1,2). Nonspecific biomarkers such as aspartate aminotransferase, lactate dehydrogenase, and CK were initially replaced by the more specific MB fraction of CK. However, on iterative revisions of the definition of myocardial infarction, it has become widely acceptable to use cTn as the biomarker of choice because of its higher sensitivity and tissue specificity. The Fourth Universal Definition of Myocardial Infarction (2018) proposed the following criteria (3,4): the term acute myocardial infarction should be used when there is clinical evidence of myocardial ischemia and detection of a rise and/or fall of cTn values above the 99th percentile upper reference limit with at least 1 of the following: 1) ischemic ECG changes; 2) development of Q waves; 3) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with ischemia; or 4) identification of a coronary thrombus by angiography or autopsy. Along with cTnI, we concomitantly measured the aforementioned biomarkers, and in retrospect, the normal level of CK-MB should have cast serious doubts about the validity of the elevated cTn and altered the course of our diagnostic work-up. The markedly elevated cTn prompted an urgent proceeding with cardiac catheterization, even before performing an echocardiogram. However, invasive procedures carry certain risks and should be reserved for cases with clear indications and appropriate use criteria.

It is not uncommon for patients with non-ST-segment elevation myocardial infarction to have normal ECGs or nonspecific ST-T change. An ischemia cascade typically begins with myocardial

| Test                  | Value               |
|-----------------------|---------------------|
| Creatine kinase       | 120 U/l             |
| Lactate dehydrogenase | Negative            |
| Sedimentation rate    | 3 mm/h              |
| C-reactive protein    | 1.8 mg/l            |
| Rheumatoid factor     | <10.0 U/ml (negative) |
| Antinuclear antibody  | Negative            |
| TSH                   | 0.33 mIU/l (normal) |
| HIV antibody          | Negative            |
| Hepatitis C antibody  | Negative            |
| D dimer               | 0.75 mg/l (positive) |

HIV = human immunodeficiency virus; TSH = thyroid-stimulating hormone.
hypoperfusion, and cardiac biomarkers often rise in a gradual fashion, peaking around the first 24 to 48 h. However, there are several limitations to using cardiac biomarkers in clinical practice, including cases in which cTn can be elevated in non-ACS conditions. These are further divided into non-ACS cardiac and noncardiac causes (Table 1). Thus, the clinical diagnosis of acute myocardial infarction requires a comprehensive assessment of symptoms and ECG findings, in addition to the presence of cardiac biomarker abnormalities with a typical rise and fall pattern.

A scarcely reported problem is related to spuriously elevated cTn, which either can represent a technical issue with the development of commercially available assays or can signal the presence of interfering substances, including heterophilic and antianimal antibodies. The detection of cTn on such assays uses an immunoassay mechanism that is inherently subject to erroneous results in the presence of interfering antibodies. Troponin immunoassays often use a pair of monoclonal antibodies (capture and label antibodies) directed at 2 binding sites (sandwich) for troponin detection (Figure 4). The capture antibody initially binds to any troponin in the sample. The label antibody is added after a wash phase and binds to the captured troponin, thereby providing a quantifiable signal. The Beckman assay uses a pair of antibodies lying next to each other and directed against epitopes in the heart-specific and stable region of the troponin molecule close to the NH2 terminus. The heterophile antibodies can form links with antibodies used in Beckman assays, thus mimicking the cTn antigen for which the assay was designed and giving rise to spuriously high troponin levels. Conversely, the Architect 2000 assay incorporates 1 antibody directed toward the heart-specific region close to the NH2 terminus and another antibody directed against epitopes in the stable part closer to the COOH terminus (5).

Detectable levels of heterophile antibodies can be associated with exposure to a variety of antigens, including the following: transfused blood components; vaccinations; viral infections such as cytomegalovirus, human immunodeficiency virus, and viral hepatitis; and even dietary antigens. Additionally, heterophile antibody activity has been observed in leukemia and rheumatoid arthritis. This is of particular importance because in some conditions the antibodies may be present only transiently in low levels, thus resulting in erroneous negative conclusions because of saturation of the assay antibody, or in very high levels, as in our case, resulting in falsely elevated values. The presence of such antibodies can otherwise be clinically silent, with an incidence ranging between 9% and 40% in the general population in some reports and anywhere from 1% to 80% in other series (6–8). HAMA is probably the most common antianimal antibody, and its presence can be iatrogenic (immunized after treatment or imaging with agents containing mouse antibody) or non-iatrogenic (8).

Heterophile antibody interference challenges most, if not all, cTn immunoassays. However, as in our case, antibodies that interfere with 1 assay may not affect another. The exact mechanism of such discordance remains elusive. Similar cases have been found in published reports, both for troponin elevation and for erroneous elevation of CK-MB, beta-human chorionic gonadotropin, thyroid-stimulating hormone, and carcinoembryonic antigen, all using the “sandwich” mechanism for detection of serum proteins (9,10). There are modern high-sensitivity assays that incorporate heterophilic antibody blocking tubes, thereby removing the antibody and reducing the chance of interference (11). However, some degrees of interference can still occur in these assays. Such tubes should be used in patients when the clinical picture does not correlate with the cTnI or cTnT elevation or when no cause for such elevation is obvious.

Notwithstanding the lack of evidence, we suspect that our patient’s exposure to blood products in the plasma donor center may have led to the development of HAMA antibodies.

FOLLOW-UP

In follow-up, the patient continued to report recurrent episodes of atypical left-sided chest and arm discomfort. She received a diagnosis of carpal tunnel syndrome and underwent tendon release surgery. On
one of her presentations, the cTnI level was checked and again was found to be extremely elevated at 143 ng/dl. Because there was no other evidence of myocardial infarction, this finding was attributed to her heterophile antibodies.

CONCLUSIONS

The clinician’s suspicion remains key to the recognition of erroneous results, whereas laboratory confirmation should carefully be pursued in judicious ways. Ultimately, the diagnosis of falsely elevated cTn can be made on the basis of discordance between the clinical and laboratory findings (in our case, persistently elevated cTn against a background of nonspecific chest pain, nondiagnostic ECG, and lack of imaging and tissue evidence of myonecrosis and inflammation). In our case, we had to perform an extensive work-up because of a markedly, yet falsely, elevated cTn level. Heuristically driven clinical decision making led to delayed recognition of an epiphenomenon and an unnecessary cascade of diagnostic testing. The main practical lesson learned here is that laboratory values should be interpreted within the framework of the clinical picture, to avoid unnecessary diagnostic testing and prolonged hospital stay.

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REFERENCES

1. Apple FS, Murakami MM, Pearce LA, et al. Predictive value of cardiac troponin I and T for subsequent death in end stage renal disease. Circulation 2002;106:2941-5.
2. Giannitsis E, Müller-Bardorff M, Kurowski V, et al. Independent prognostic value of cardiac troponin T in patients with confirmed pulmonary embolism. Circulation 2000;102:211-7.
3. Jaffe AS, Ravkilde J, Roberts R, et al. It’s time for a change to a troponin standard. Circulation 2000;102:1216-20.
4. Thygesen K, Alpert JS, Jaffe AS, et al. Fourth universal definition of myocardial infarction (2018). J Am Coll Cardiol 2018;72:2231-64.
5. James S, Flodin M, Johnston N, Lindahl B, Venge P. The antibody configurations of cardiac troponin I assays may determine their clinical performance. Clin Chem 2006;52:832-7.
6. Thompson RJ, Jackson AP, Langlois N. Circulating antibodies to mouse monoclonal immunoglobulins in normal subjects- incidence, species specificity, and effects on a two-site assay for creatine kinase-MB isoenzyme. Clin Chem 1986;32:476-81.
7. Boscato LM, Stuart MC. Incidence and specificity of interference in two-site immunoassays. Clin Chem 1986;32:1491-5.
8. Kricka LJ. Human anti-animal antibody interferences in immunological assays. Clin Chem 1999;45:942-56.
9. Primus FJ, Kelley EA, Hansen HJ, Goldenberg DM. "Sandwich"-type immunoassay of carcinoembryonic antigen in patients receiving murine monoclonal antibodies for diagnosis and therapy. Clin Chem 1988;34:261-4.
10. Mair J, Lindahl B, Müller C, et al. What to do when you question cardiac troponin values. Eur Heart J Acute Cardiovasc Care 2018;7:577-86.
11. Kim WJ, Laterza OF, Hock KG, et al. Performance of a revised cardiac troponin method that minimizes interference from heterophile antibodies. Clin Chem 2002;48:1028-34.

KEY WORDS cardiac magnetic resonance, computed tomography, electrocardiogram, heterophile antibodies, left-sided catheterization, troponin
Appropriate Implantable Cardioverter-Defibrillator Therapies Delivered 5 Years After End of Service

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ABSTRACT

We present the case of a 57-year-old man with a primary prevention internal cardioverter-defibrillator for severe non-ischemic cardiomyopathy. At the time of elective replacement indicator, systolic function had fully recovered, and his generator was not changed. Nearly 5 years post-elective replacement indicator he received appropriate internal cardioverter-defibrillator therapies during a myocardial infarction. (Level of Difficulty: Intermediate.) (J Am Coll Cardiol Case Rep 2020;2:796–801) © 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 implantable cardioverter-defibrillator (ICD) is a key strategy for primary and secondary prevention of sudden death in patients with severe cardiomyopathy and in patients with previous sustained ventricular tachyarrhythmias without a reversible cause. Normalization of left ventricular systolic function after implantation of an ICD for primary prevention in the absence of any documented tachyarrhythmias or pacing indication raises uncertainty at the time of pulse generator elective replacement indicator (ERI), given that the original indication for device implantation is no longer present (1-4). On the basis of the manufacturer’s recommendation, standard practice is to perform pulse generator change for ICDs and pacemakers within 3 months of...

LEARNING OBJECTIVES

- To review the uncertainty surrounding optimal management of patients with a primary prevention implantable cardioverter-defibrillator without documented tachyarrhythmias or pacing and full recovery of left ventricular systolic function at the time of pulse generator elective replacement indicator.
- To understand factors that affect current drain and battery depletion in implantable cardioverter-defibrillators.
- To recognize the potential transitioning of ventricular arrhythmia substrate from non-ischemic to ischemic.

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reaching ERI, also known as the recommended replacement time (ERT) or elective replacement time (ERT). This replacement should be done before the device reaches its end of life (EOL), also termed end of service (EOS), to prevent inadequate and erratic therapies or lack of therapies resulting from battery depletion (5,6). The determination of ERI is device specific, largely recommended by manufacturers in the absence of definitive publications or industry standards. Understandably, studies reporting on device performance beyond the 3 months after ERI while these devices remain in situ are lacking. In this case report, we discuss delivery of appropriate ICD therapy nearly 5 years after ERI.

HISTORY OF PRESENTATION

A 57-year-old man presented to the emergency department in 2017 with acute chest pain episodes occurring at rest followed by a syncopal episode at home. He had a dual-chamber ICD device in situ for primary prevention of sudden cardiac death in the setting of nonischemic cardiomyopathy, and he presented 4.5 years after his ICD had reached ERI. His admission vital signs and hemodynamics were stable, and physical examination was unremarkable.

PAST MEDICAL HISTORY

The patient was initially found to have heart failure when he presented with congestive symptoms in 2005 on a background of hypertension, hyperlipidemia, and type 2 diabetes mellitus. A transthoracic echocardiogram showed a severely reduced left ventricular ejection fraction (LVEF) of 20% (improving to 25%) with a dilated left ventricle and global hypokinesis. Cardiac catheterization showed nonobstructive coronary disease, and cardiac output was 2 l/min with a cardiac index of 0.8 l/min/m² (by thermodilution). Endomyocardial biopsy revealed nonspecific findings. While in the hospital, he was observed to have intermittent Mobitz type II second degree atrioventricular (AV) block on telemetry. The nonischemic cardiomyopathy was managed according to guideline-directed medical therapy. Given the occurrence of intermittent Mobitz II AV block, a dual-chamber Medtronic ICD (Medtronic, Minneapolis, Minnesota) for primary prevention against sudden cardiac death was implanted without waiting for at least 3 months of guideline-directed medical therapy during his hospitalization; the device was programmed to minimize right ventricular pacing. LVEF subsequently improved to 50% to 55% in 2010 and to 65% in 2012 when his ICD generator reached ERI, in keeping with the expected longevity. A decision was therefore made not to replace the ICD generator, primarily driven by the patient’s own reluctance to have the generator change. He had never had any therapies from his device since implantation to 2012, was paced in the right ventricle <1% of the time, and had atrial pacing of 7.8% at the time of the ERI. The lack of any significant ventricular pacing suggested that his previous intermittent AV conduction disease may have been part of his acute cardiomyopathy, which subsequently resolved. He did not come for any cardiology follow-up visits between 2012 and 2017.

DIFFERENTIAL DIAGNOSIS

The initial broad differential diagnoses of syncope and chest pain included acute coronary syndrome, cardiac tachyarrhythmias or bradyarrhythmias, and pulmonary embolism.

INVESTIGATIONS

Admission electrocardiograms revealed normal sinus rhythm with dynamic ST-segment elevation in lead V₁ and subtle ST-segment elevation in leads V₂ and V₃, as well as a normal corrected QT interval (Figure 1, top panel). Telemetry showed polymorphic nonsustained ventricular tachycardia (NSVT) episodes. There was a minor troponin I elevation that peaked at 0.17 ng/ml (normal: <0.04 ng/ml), but other routine blood tests, including electrolytes and B-type natriuretic peptide, were within normal limits. Given episodes of rest chest pain, anteroseptal wall ST-segment changes, polymorphic NSVT episodes, and minor troponin rise, he was diagnosed with acute coronary syndrome. He underwent coronary angiography, which showed a normal left main stem, severe middle to distal left anterior descending artery (LAD) stenosis (90%), mild left circumflex artery stenosis (10% to 30%), and mild right coronary artery stenosis (10% to 30%) with right dominance (Figure 2, Videos 1 and 2). The LAD stenosis was successfully revascularized with 3 drug-eluting stents.

Soon after coronary reperfusion, he developed a ventricular tachyarrhythmia storm. He received multiple shock therapies from the ICD, eventually...
**FIGURE 1** Admission ECG and Telemetry

(Top) One of the admission electrocardiograms (ECGs) showing ST-segment elevation in lead V1 and subtle ST-segment elevation in leads V2 and V3.  
(Bottom) Telemetry strip showing onset of 1 of the polymorphic ventricular tachycardia (VT) runs during coronary care unit admission.

**FIGURE 2** Coronary Angiogram Showing Severe LAD Stenosis as the Culprit of the Acute Coronary Syndrome, and Mild Stenosis in the RCA

LAD — left anterior descending artery; RCA — right coronary artery.
followed by an episode during which the device did not intervene, and external defibrillation was required (see telemetry strip of onset of polymorphic VT at the bottom of Figure 1). ICD interrogation showed battery voltage of 2.58, with ERI reached 4.5 years ago, and revealed that he had ventricular arrhythmia during the syncopal episode at home that led to the hospitalization. The device had registered 13 sustained episodes of ventricular tachycardia (VT) or ventricular fibrillation (VF) after ERI, including 7 within 48 h of the current hospitalization and multiple NSVT episodes, with the ICD shocking him appropriately and successfully terminating the first 6 of the 7 recent VT or VF episodes (Table 1). The seventh episode during hospitalization was treated with external defibrillation (Figure 3). Further interrogation of his device after it failed to deliver therapy revealed abnormally high pacing impedance (>3,000 Ω) and shock impedance (>200 Ω). Of note, the ICD was not interrogated at first opportunity despite his presentation with syncope because it was presumed to be EOL because it had been nearly 5 years since ERI. An echocardiogram revealed normal LVEF of 65% with no significant valvular disease.

**MANAGEMENT**

Cardiac catheterization in combination with LAD stent placement was undertaken. Given the likelihood that the substrate for arrhythmia risk had changed from initially nonischemic to now ischemic, he underwent an ICD pulse generator change for secondary prevention before discharge. He received a new Medtronic device with satisfactory parameters using the existing leads. The patient had a Medtronic Spring Fidelis ICD lead in situ with potential for recall. However, good lead parameters were observed during generator change (R-wave sensing: 14.8 mV; threshold: 0.7 V; impedance: 471 Ω), and fluoroscopy and cine acquisition revealed no conductor abnormalities or physical damage to the lead, so it was left in place. He also began standard secondary prevention therapy for ischemic heart disease, dual antiplatelet therapy, and sotalol 80 mg twice daily to prevent further arrhythmias, in case the VT or VF episodes were not entirely driven by the acute coronary syndrome.

**DISCUSSION**

Our patient had successful appropriate discharging of ICD therapies nearly 5 years after the device had reached ERI. A publication search did not reveal any prior reports of successful therapies by ICD this long after reaching ERI. It remains unclear why the device still had the electrical capacity to deliver therapies after such a long period.

Factors that affect current drain and battery depletion include pacing percentage, pacing rate, programmed output voltage, pulse width, lead impedance, number of ICD shocks, energy levels of shocks, and capacitor maintenance. The batteries commonly used in contemporary pacemakers and ICD are lithium iodine, lithium silver vanadium oxide, and lithium manganese oxide. Two commonly used battery depletion indicators determining the ERI are battery cell impedance elevation above a given threshold (usually >15,000 to 20,000 Ω) and battery voltage drop below a given threshold, depending on the type of battery and manufacturer (6). Ampere hour also has been shown to be a predictor of ERI (7). Some studies have suggested that these variables may not reliably predict ERI, whereas others have suggested that the 3-month window from ERI to EOL may be too conservative (8). Device interrogation in our patient showed presumably inappropriate pacing and shock impedance elevation despite documented lead integrity at the time of generator change probably as a result of generator battery depletion. Event #13 with VF detected for 1 min had no therapies delivered, presumably because of the inability to charge secondary to battery depletion.

This case report raises some interesting clinical conundrums. There has been much debate about what to do when patients with a primary prevention

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**TABLE 1 VA Episodes Retrieved From the Implantable Cardioverter-Defibrillator Since it Reached ERI in 2012**

| VA Event Number | Date and Time | VA Cycle Length, ms | Last Therapy and Therapy Success Duration | Therapy Type |
|-----------------|---------------|---------------------|------------------------------------------|--------------|
| 13              | Jan 03 14:14:35 | VF 150s | VF Rx x 1 | Yes | 1.0 min |
| 12              | Jan 03 13:34:22 | VF 210 | VF Rx x 1 | Yes | 18 s |
| 11              | Jan 03 09:36:15 | VF 140 | VF Rx x 1 | Yes | 18 s |
| 10              | Jan 03 04:13:39 | VF 140 | VF Rx x 1 | Yes | 17 s |
| 9               | Jan 03 04:00:57 | VF 140 | VF Rx x 1 | Yes | 17 s |
| 8               | Jan 02 21:15:04 | VF 170 | VF Rx x 1 | Yes | 18 s |
| 7               | Jan 02 07:19:05 | VF 140 | VF Rx x 1 | Yes | 20 s |
| 6               | Nov 03 04:15:30 | FVT | 390 | No Rx delivered | --- | 55 s |
| 5               | May 18 07:51:17 | VF 240 | No Rx delivered | --- | 4 s |
| 4               | Mar 15 10:57:12 | VF 190 | No Rx delivered | --- | 11 s |
| 3               | Jul 01 14:32:38 | VF 160 | VF Rx x 1 | Yes | 6 s |
| 2               | Jul 01 14:31:50 | VF 170 | No Rx delivered | --- | 10 s |
| 1               | Jul 01 14:31:03 | VF 200 | VF Rx x 1 | Yes | 7 s |

*The table depicts VA episodes during the last device interrogation in January 2017. It bears evidence of successful treatment of these VA episodes as shown by "Yes" in column 6. ERI = elective replacement interval; FVT = fast ventricular tachycardia; Rx = therapy; VA = ventricular arrhythmia; VF = ventricular fibrillation.*
ICD for nonischemic cardiomyopathy reach ERI with sustained normalization of ventricular ejection fraction and no significant tachyarrhythmias or bradyarrhythmias requiring therapies. A few studies have suggested that at the time of ERI, patients with partially recovered left ventricular systolic function (LVEF of 36% to 49%) and fully recovered left ventricular systolic function (LVEF ≥50%) after primary prevention ICD implantation have a relatively low risk of ventricular tachyarrhythmias, heart failure admissions, and mortality when compared with patients with LVEF ≤35% (1,4). Although some studies have shown no appropriate ICD therapies or an extremely low risk of ventricular arrhythmias in patients with completely normalized LVEF (≥50%) prospectively during follow-up (1), the majority of studies showed a persistent residual risk of ventricular arrhythmias requiring appropriate ICD therapies in patients with LVEF >35% who no longer met primary prevention ICD indications, albeit at a significantly lower rate compared with LVEF ≤35% (4). However, in this latter group of patients with LVEF >35%, ventricular arrhythmia outcomes in a subset of patients with LVEF ≥50% at time of generator change were not separately reported. Therefore, we currently have no robust data to recommend whether patients with fully recovered LVEF and no previous appropriate tachycardia or bradycardia therapies should or should not undergo ICD generator at time of ERI. The MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial With Cardiac Resynchronization Therapy) substudy suggested that in view of the risk of inappropriate ICD therapies, those patients with normalized ejection fractions could be considered for downgrade from a cardiac resynchronization therapy (CRT) defibrillator to a CRT pacemaker at the time of battery depletion if no ventricular arrhythmia episodes have occurred (1). However, a potential continuous benefit from ICDs in patients with recovered LVEF has been highlighted in primary prevention recipients with improved LVEF without a previous history of appropriate ICD therapy at generator change (3). Comparable risks of all-cause mortality between improved and unimproved left ventricular systolic function have been observed, with benefit from ICD largely preserved (9). In addition, a joint task force report on the appropriate use criteria for ICD and CRT by the American College of Cardiology Foundation, Heart Rhythm Society, American Heart Association, American Society of Echocardiography, Heart Failure Society of America, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Computed Tomography, and Society for Cardiovascular Magnetic Resonance suggested that it may be appropriate for patients with primary prevention ICD and no clinically relevant ventricular arrhythmias and normalized LVEF of ≥50% at time of ERI to proceed with the generator replacements (2). Cardiac implantable electronic device generator changes carry periprocedural and short- to medium-term risks (10). The REPLACE registry (Implantable Cardiac
Pulse Generator Replacement Registry) data showed that pacemaker and ICD pulse generator change are not benign procedures, with a risk of complications as high as 4.0% in patients without an upgrade and 15.3% with an upgrade or lead revision and higher for ICDs compared with pacemakers (10).

On the basis of contemporary evidence, risk reversion at the time of generator change in patients with recovered LVEF is likely to be important. The risk of undergoing a potentially risky ICD generator change with possibly no palpable benefit and its potential inappropriate shocks should be weighed against the residual risk of malignant arrhythmias and sudden cardiac death in the context of comorbidities and life expectancy, in a careful, shared decision-making process between the implanting physician and the patient. As demonstrated by our patient, normalization of LVEF with no prior tachycardia therapies did not absolve him from a future risk of ventricular arrhythmias related to a new disorder.

**FOLLOW-UP**

Periodic device interrogations, with the most recent occurring 19 months after his myocardial infarction, revealed only 1 episode of NSVT, which lasted 11 beats at 187 beats/min without any associated symptoms. He has had no issues identified with the Sprint Fidelis ICD lead, which is being monitored closely with the Lead Integrity Alert algorithm through the currently implanted device. His LVEF remains preserved at 60%.

**CONCLUSIONS**

We have reported on a case of an ICD delivering appropriate tachycardia therapies nearly 5 years after reaching ERI and no generator change as a result of recovered LVEF in the patient. Given that uncertainty remains about what to do with patients who have ICDs for primary prevention and whose cardiomyopathy resolves by the time of ERI, prospective clinical trials comparing outcomes in patients with full LVEF recovery who did not undergo generator change versus those who did at the time of ERI may help decipher this clinical equipoise.

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**REFERENCES**

1. Rouwald MH, Solomon SD, Foster E, et al. Left ventricular ejection fraction normalization in cardiac resynchronization therapy and risk of ventricular arrhythmias and clinical outcomes: results from the Multicenter Automatic Defibrillator Implantation Trial With Cardiac Resynchronization Therapy (MADIT-CRT) trial. Circulation 2014;130:2278-86.

2. Russo AM, Stainback RF, Bailey SR, et al. ACCF/HRS/AHA/ASE/HFSA/SCAI/SCCT/SCMR 2013 appropriate use criteria for implantable cardioverter-defibrillators and cardiac resynchronization therapy: a report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, Heart Rhythm Society, American Heart Association, American Society of Echocardiography, Heart Failure Society of America, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Computed Tomography, and Society for Cardiovascular Magnetic Resonance. J Am Coll Cardiol 2013;61:1318-68.

3. Madhavan M, Waks JW, Friedman PA, et al. Outcomes after implantable cardioverter-defibrillator generator replacement for primary prevention of sudden cardiac death. Circ Arrhythm Electrophysiol 2016;9:e003283.

4. Smer A, Saurav A, Azzouz MS, et al. Meta-analysis of risk of ventricular arrhythmias after improvement in left ventricular ejection fraction during follow-up in patients with primary prevention implantable cardioverter-defibrillators. Am J Cardiol 2017;120:279-86.

5. Barold SS, Schoenfeld MH. Pacemaker elective replacement indicators: latched or unlatched? Pacing Clin Electrophysiol 1989;12:990-5.

6. Untereker DF, Schmidt CL, Juni G, Tamirisa PA, Hossick-Schott J, Viste M. Power sources and capacitance for pacemakers and implantable cardioverter defibrillators. In: Ellenbogen KA, Wilkoff BL, Kay GN, Lau CP, Auricchio A, editors. Clinical Cardiac Pacing, Defibrillation, and Resynchronization Therapy. 5th edition. Philadelphia, PA: Elsevier, 2017:251-69.

7. Ellis CR, Dickerman DI, Orton JM, et al. Ampere hour as a predictor of cardiac resynchronization defibrillator pulse generator battery longevity: a multicenter study. Pacing Clin Electrophysiol 2016;39:658-68.

8. Aarons D, Mower M, Veltri E. Use of the elective replacement indicator in predicting time of automatic implantable cardioverter-defibrillator battery depletion. Pacing Clin Electrophysiol 1989;12:1724-8.

9. Adabag S, Patton KK, Buxton AE, et al. Association of implantable cardioverter defibrillators with survival in patients with and without improved ejection fraction: secondary analysis of the Sudden Cardiac Death in Heart Failure trial. JAMA Cardiol 2017;2:767-74.

10. Poole JE, Gleva MJ, Mela T, et al. Complication rates associated with pacemaker or implantable cardioverter-defibrillator generator replacements and upgrade procedures: results from the REPLACE registry. Circulation 2010;122:1553-61.

**KEY WORDS** cardiomyopathy, elective replacement indicator, implantable cardioverter-defibrillator, ventricular arrhythmias

**APPENDIX** For supplemental videos, please see the online version of this paper.
We describe a case of fulminant eosinophilic myocarditis as the first presentation of eosinophilic granulomatosis with polyangiitis, promptly managed with extracorporeal membrane oxygenation. This case highlights the multidisciplinary work involving all health care professionals in the acute management of these patients and discusses it from an educational point of view. (Level of Difficulty: Intermediate.) (J Am Coll Cardiol Case Rep 2020;2:802-8)

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A 22-year-old Caucasian man presented to the emergency department with mild chest discomfort and constitutional symptoms (i.e., nausea, vomiting, and anorexia) for the past 5 days. His history was notable for mild persistent asthma, allergic rhinitis, and previous smoking (5 pack-years).

The patient denied any past or current history of drug use. Other than sinus tachycardia at 126 beats/min, the physical examination was unremarkable. He was afebrile, with a normal breathing rate, blood pressure of 100/79 mm Hg, clear chest sounds, nontender abdomen, and no peripheral edema.

On laboratory work-up there was a normal hemoglobin level (14.5 g/dl), leukocytosis (24.0 × 10^9/l) with marked eosinophilia (11.7 × 10^9/l; i.e., 48%), and heightened C-reactive protein (19.9 mg/dl) and
erythrocyte sedimentation rate (28 mm/h). Liver enzymes, creatine kinase, and lactate dehydrogenase were elevated (aspartate aminotransferase: 119 IU/l; alanine aminotransferase: 50 IU/l; creatine kinase: 1042 IU/l; and lactate dehydrogenase: 986 IU/l), and mild acute kidney injury was present (serum creatinine, 1.45 mg/dl). Both high-sensitivity-cardiac troponin T and N-terminal pro-B-type natriuretic peptide were markedly increased (i.e., 2,500 ng/l and 18,795 pg/ml, respectively). A brief panel of autoantibodies was unremarkable. Electrocardiography (Figure 1A) was notable for inferolateral ST-segment depression and chest radiography (Figure 1B) showed bilateral interstitial lung infiltrates. Transthoracic echocardiography (TTE) (Figure 1C) revealed severe left ventricular systolic dysfunction (left ventricular ejection fraction [LVEF] <30%) secondary to global hypokinesis, a restrictive filling pattern, and pericardial thickening without effusion; right ventricular and valvular function was preserved. Given all the above, an eosinophil-associated disease with myocardial involvement was highly suspected (Table 1). On additional workup, chest and paranasal sinus computed tomography (CT) scans were performed and showed bilateral ground-glass lung infiltrates (Figure 2A) and maxillary and ethmoidal sinus opacifications, respectively.

**MANAGEMENT**

Despite clinical stability at presentation, the patient showed rapid clinical deterioration within the first hours, noted by acute heart failure, type 1 respiratory failure, and Acute Kidney Injury Network stage 3 oliguric acute kidney injury, and he was admitted to the cardiac intensive care unit on an emergency basis. Sedation, invasive ventilation, and intravenous (IV) inotropes were started. Repeat TTE revealed altered cardiac standstill (Figure 1D, Video 1). Despite these measures, clinical deterioration resumed with refractory cardiogenic shock, ultimately requiring venoarterial extracorporeal membrane oxygenation (ECMO) at 14 h after emergency department admission. Coronary angiography was not performed immediately because acute coronary syndrome was highly unlikely and emergent hemodynamic support was needed.

Given the fulminating presentation, it was decided to perform an endomyocardial biopsy (EMB) for diagnostic work-up. After viral replication was excluded on cardiac biopsy, 1 mg/kg IV methylprednisolone and broad-spectrum antibiotics were started. Over the next few days, TTE revealed progressive improvement in cardiac function, and ECMO was discontinued on day 7, while the patient was weaned from both the ventilator and inotropes. During this period, no arrhythmic events were documented.

On hospital day 10, the patient was transferred to the cardiology ward, where further work-up was performed. Results of autoimmune screening, including antinuclear antibodies and cytoplasmic and perinuclear antineutrophil cytoplasmic antibodies, were negative. EMB later revealed severe myocardial necrosis with myocyte damage and a diffuse eosinophilic inflammatory infiltrate (Figures 3A and 3B). Accordingly, eosinophilic granulomatosis with polyangiitis (EGPA) was confirmed, with 4 out of 6 criteria (1) present: 1) asthma; 2) eosinophilia >10%; 3) primary hypereosinophilic syndrome (HES) and 4) eosinophilic granulomatosis with polyangiitis (formerly Churg-Strauss syndrome) (Figures 3A and 3B). Accordingly, eosinophilic granulomatosis with polyangiitis (EGPA) was confirmed, with 4 out of 6 criteria (1) present: 1) asthma; 2) eosinophilia >10%; 3) primary hypereosinophilic syndrome (HES) and 4) eosinophilic granulomatosis with polyangiitis (formerly Churg-Strauss syndrome) (Figures 3A and 3B).
extravascular eosinophils on EMB; and 4) paranasal sinusitis (Table 2). Re-evaluation chest CT was performed (Figure 2B), revealing resolution of lung infiltrates and further confirming the diagnosis (i.e., nonfixed fleeting lung infiltrates—5 out of 6 criteria).

Furthermore, cardiac magnetic resonance (CMR) was remarkable for left ventricular widespread subendocardial late gadolinium enhancement (LGE) (Figures 4A and 4B). CT angiography, performed once clinical stability was achieved, revealed no epicardial coronary artery disease.

During the hospital stay, management was adjusted to EGPA-directed treatment with oral corticosteroid and twice monthly IV cyclophosphamide, in addition to up-titration of guideline-directed medical therapy (GDMT) for heart failure with reduced ejection fraction (HFrEF) and cardiac rehabilitation. Despite these measures, LVEF did not fully recover and plateaued at 34% on TTE serial evaluation. Given these findings and the widespread LGE on CMR, the heart team decided to insert an implantable cardioverter-defibrillator after 35 days of GDMT. On hospital day 45, the patient was doing well and was discharged on 40 mg oral prednisolone and twice monthly IV cyclophosphamide pulse for 6 months in addition to HFrEF GDMT.
DISCUSSION

Formerly known as Churg-Strauss syndrome, EGPA is a rare systemic necrotizing vasculitis involving small to medium-sized vessels and is associated with asthma and with blood and tissue eosinophilia. According to the American College of Rheumatology, the presence of 4 or more criteria (Table 2) establishes the diagnosis with a sensitivity of 85% and a specificity of 99.7% (1).

FIGURE 2 Comparison of Admission and Re-Evaluation Chest CT

(A) Bilateral ground-glass lung infiltrates. (B) Resolution of lung infiltrates. CT = computed tomography.

FIGURE 3 Eosinophilic Myocarditis on EMB (H&E, 400×)

(A) Severe myocardial necrosis (asterisk) with destruction of myocytes and adjacent normal myocardium (arrow). (B and C) Perivascular spaces with mixed inflammatory infiltrate consisting almost entirely of eosinophils (arrows). (C) Interstitial spaces with edema and eosinophils (arrows). EMB = endomyocardial biopsy; H&E = hematoxylin and eosin.
EGPA is one of the most common systemic vasculitides to involve the heart, which is typically associated with eosinophilia and a negative antineutrophil cytoplasmic antibody work-up. It often leads to myocarditis and acute heart failure, coronary vasculitis, and myocardial infarction, as well as ventricular arrhythmias and sudden cardiac death. However, a significant proportion of patients will be asymptomatic or have an insidious, rather than fulminant, presentation (1). Cardiac imaging plays a pivotal role in the detection of myocardial, pericardial, or valvular involvement, although findings are often nonspecific. TTE should be promptly performed, whereas CMR may further refine the diagnosis and determine the extent of myocardial necrosis. However, definitive diagnosis is exclusively established by EMB (3,4). Invasive coronary angiography (or CT angiography in selected patients) should be performed to rule out coronary disease (5). In this case, and although arguable, the heart team decided not to perform coronary angiography immediately because an alternative diagnosis seemed very likely (i.e., myocarditis).

This patient presented with rapidly progressive fulminant myocarditis with a need for emergent hemodynamic support. ECMO, an extracorporeal life support technique able to provide cardiopulmonary bypass, may be lifesaving in refractory cardiogenic shock. Venoarterial peripheral ECMO is of utmost value in supporting a compromised heart until a definitive diagnosis is made and cause-specific treatment is initiated, whenever possible. The optimal timing for implementation is not uniformly established and must rely on an informed individualized heart team decision (6). Standard operating procedure must include early contact with the ECMO tertiary referral center with expertise in the management of the critically ill patient (Figure 5). Indeed, this case of EGPA-related fulminant eosinophilic myocarditis emphasizes the crucial role of such timing and the successful role of ECMO as a bridge-to-recovery strategy.

EMB is recommended early in the work-up of unexplained new-onset or recent (<2 weeks) heart failure and hemodynamic deterioration (Class I, Level of Evidence: B) because it may lead to treatment decisions based on histopathological findings that may substantially improve prognosis (3,4). Indeed, cardiac involvement in EGPA further worsens the prognosis and is the cause of death in roughly one-half of the

**TABLE 2 EGPA Diagnostic Criteria**

1. History of asthma
2. Eosinophilia (>10% of leukocytes on differential white cell count)
3. Mononeuropathy (including monoplex or polyneuropathy)
4. Migratory or transient pulmonary infiltrates
5. Paranasal sinus abnormality
6. Biopsy showing a blood vessel with extravascular eosinophils

Reprinted with permission from Masi et al. (1).

EGPA = eosinophilic granulomatosis with polyangiitis.

**FIGURE 4 CMR Findings**

(A and B) Widespread subendocardial late gadolinium enhancement (arrows) on cardiac magnetic resonance (CMR).
patients. However, survival significantly improves with appropriate immunosuppression. It is recommended to use a combination of glucocorticoids and either cyclophosphamide or rituximab for remission induction in patients with organ or life-threatening disease (2). The Five Factor Score (FFS) is the most commonly used prognostic tool, and it is helpful for selecting patients who may benefit from immunosuppressive agents (i.e., cyclophosphamide) (FFS 1).

Finally, in this particular case we decided to insert a subcutaneous implantable cardioverter-defibrillator before discharge, despite the general recommendation to wait until 3 months of HFrEF GDMT are completed. The rationale for this decision included the absence of patients with acute myocarditis in the clinical trials that support this recommendation and the extensive LGE that made reverse remodeling unlikely. A wearable defibrillator vest could have been a valid alternative, but unfortunately it is not available at our center.

**FOLLOW-UP**

At 1-year follow-up, the patient is doing well, in New York Heart Association functional class I. He has resumed his work as a barber, and no vasculitis relapse has been documented. He is currently taking prednisolone 10 mg and HFrEF GDMT (bisoprolol: 10 mg daily; ramipril: 10 mg daily; and spironolactone: 25 mg daily). Nonetheless, his LVEF remained severely depressed (34%) on TTE re-evaluation. Thus far, he has had no heart failure hospitalizations or implantable cardioverter-defibrillator-related events.

**CONCLUSIONS**

We report a rare case of rapidly progressing vasculitis in a patient who presented with fulminant myocardial involvement. Multidisciplinary teams are paramount to improve the prognosis of such rare yet life-threatening conditions. Early ECMO implementation and EMB were key strategic decisions for a successful outcome.

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REFERENCES

1. Masi AT, Hunder GG, Lie JT, et al. The American College of Rheumatology 1990 criteria for the classification of Churg-Strauss syndrome (allergic granulomatosis and angiitis). Arthritis Rheum 1990;33:1094–100.

2. Yates M, Watts RA, Bajema IM, et al. EULAR/ERA-EDTA recommendations for the management of ANCA-associated vasculitis. Ann Rheum Dis 2016;75:1583–94.

3. Cooper LT, Baughman KL, Feldman AM, et al. The role of endomyocardial biopsy in the management of cardiovascular disease: a scientific statement from the American Heart Association, the American College of Cardiology, and the European Society of Cardiology. Endorsed by the Heart Failure Society of America and theHeart Failure Association of the European Society of Cardiology. J Am Coll Cardiol 2007;50:1914–31.

4. Caforio AL, Pankuweit S, Arbustini E, et al. Current state of knowledge on aetiology, diagnosis, management, and therapy of myocarditis: a position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. Eur Heart J 2013;34:2636–48. 2648a–d.

5. Caforio ALP, Adler Y, Agostini C, et al. Diagnosis and management of myocardial involvement in systemic immune-mediated diseases: a position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Disease. Eur Heart J 2017;38:2649–62.

6. Rao P, Khalpey Z, Smith R, Burkhoff D, Kociol RD. Venoarterial extracorporeal membrane oxygenation for cardiogenic shock and cardiac arrest. Circ Heart Fail 2018;11:e004905.

7. Guillevin L, Lhote F, Gayraud M, et al. Prognostic factors in polyarteritis nodosa and Churg-Strauss syndrome. A prospective study in 342 patients. Medicine (Baltimore) 1996;75:17–28.

KEY WORDS acute heart failure, autoimmune, cardiac assist devices, Churg-Strauss syndrome, heart team

APPENDIX For a supplemental video, please see the online version of this paper.
Apical Sparing Pattern of Longitudinal Strain and Positive Bone Scintigraphy in Metastatic Myocardial Calcification

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ABSTRACT

An apical sparing pattern of longitudinal strain and positive radionuclide bone scintigraphy are believed to be specific for the diagnosis of transthyretin cardiac amyloidosis. We report on a young woman with apical sparing of longitudinal strain and positive bone scintigraphy who was found to have metastatic myocardial calcification at autopsy. (Level of Difficulty: Intermediate.) (J Am Coll Cardiol Case Rep 2020;2:809–13) © 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 35-year-old African-American woman was admitted to the hospital with syncope. She was getting out of a car when she had an acute onset of palpitations and diaphoresis followed by loss of consciousness and implantable cardioverter-defibrillator (ICD) shock. She regained consciousness after a brief period of confusion and presented to the emergency department.

On physical examination, the patient’s temperature was 98.7°F, heart rate 97 beats/min, blood pressure 99/67 mm Hg, respirations 16 breaths/min, oxygen saturation 98% on room air, and body mass index 31 kg/m². Cardiovascular physical examination revealed an irregularly irregular rhythm, no murmurs or gallops, jugular venous pulsation at 8 cm of water, and trace lower extremity edema. ICD pocket appearance was within normal limits.

LEARNING OBJECTIVES

- To create a differential diagnosis for restrictive cardiomyopathy using multimodality cardiac imaging.
- To recognize the clinical presentation of metastatic myocardial calcification.

MEDICAL HISTORY

The patient’s pertinent medical history included end-stage renal disease due to pre-eclampsia, 2 failed renal allografts due to antibody-mediated rejection, anuria...
with ongoing peritoneal dialysis (with 9 total years of treatment), paroxysmal atrial fibrillation, presumed hypertrophic cardiomyopathy with placement of a primary prevention ICD 12 years ago, history of ICD shocks for ventricular tachycardia, multiple miscarriages, and bilateral pulmonary emboli.

Medications included amiodarone 100 mg twice daily, midodrine 20 mg three times daily, fluudrocortisone 0.1 mg twice daily, warfarin 3 mg daily, atorvastatin 40 mg daily, levothyroxine 250 μg daily, prednisone 5 mg daily, sevelamer 1,600 mg 3 times daily, and calcitriol 0.5 μg 3 times weekly. For peritoneal dialysis, she alternated between 2.5% and 4.25% dextrose baths using 2 L exchanges over 8.5 h of total cycler therapy time.

INITIAL TEST RESULTS

Laboratory evaluations revealed the following: troponin I 0.12 ng/ml, N-terminal pro-B-type natriuretic peptide 250,200 pg/ml, creatinine level 16.39 mg/dl, calcium 10.8 mg/dl, phosphorus 6.5 mg/dl, intact parathyroid hormone 998 pg/ml, and reduced urea clearance with Kt/V_urea of 1.22 (K, dialyzer clearance of urea; t, dialysis time; V_urea, volume of distribution of urea).

An electrocardiogram showed atrial fibrillation with low-voltage QRS and an intraventricular conduction delay (Figure 1). A transthoracic echocardiogram revealed a small, crescent-shaped left ventricular (LV) cavity with LV ejection fraction of 55% to 60% (Videos 1 and 2). Severe concentric hypertrophy was seen with a diastolic interventricular septal thickness of 2.1 cm and a posterior wall thickness of 1.8 cm. Mitral annular velocities were reduced (average e’ 0.06 m/s) with a single e’ waveform, and the mitral inflow Doppler profile was consistent with restrictive physiology (deceleration time 121 ms) (Figure 2). In addition, an apical sparing pattern of longitudinal strain (LS) was noted (Figure 3). There was no valvular or annular calcification, or pericardial effusion. Device interrogation confirmed sustained ventricular tachycardia with appropriate device therapy.

DIFFERENTIAL DIAGNOSIS

The imaging findings of low-voltage QRS, increased LV wall thickness, restrictive Doppler echocardiography, and apical sparing pattern of LS are suspicious for an infiltrative cardiomyopathy, particularly cardiac amyloidosis. Although wild-type transthyretin cardiac amyloidosis affects older individuals, light chain amyloidosis and hereditary transthyretin cardiac amyloidosis are diagnostic possibilities in this case. Cardiac sarcoidosis is another diagnostic consideration, especially in the

![FIGURE 1 Electrocardiography](image)

Electrocardiogram showed atrial fibrillation with low voltage in the limb leads and an intraventricular conduction delay.

ABBREVIATIONS AND ACRONYMS

ICD = implantable cardioverter-defibrillator
LV = left ventricular
LS = longitudinal strain

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setting of frequent ventricular arrhythmias and the patient’s race. Other causes of LV hypertrophy include hypertensive heart disease, hypertrophic cardiomyopathy, Fabry disease, and metabolic disease (i.e., Friedreich ataxia).

INVESTIGATIONS AND MANAGEMENT

Due to clinical suspicion for cardiac amyloidosis, the patient underwent technetium pyrophosphate bone scintigraphy. This procedure revealed grade 3 myocardial uptake, consistent with the diagnosis of transthyretin cardiac amyloidosis (Figure 4). Serum protein electrophoresis did show an immunoglobulin G kappa monoclonal protein, although this was believed to be nonspecific in the setting of renal failure. Cardiac magnetic resonance imaging was not pursued due to renal failure and the inability to administer gadolinium contrast. Confirmatory endomyocardial biopsy was aborted after the operator was unable to obtain venous access to the heart despite significant effort. Unfortunately, the patient experienced a pulseless electrical activity cardiac arrest during the hospital stay and died.

At autopsy, the patient was found to have multi-organ widespread calcium deposition, findings consistent with metastatic calcification. The severity of calcium deposition was most extensive in the heart. On gross examination, the heart was rigid and heavy (640 g; normal range 250 to 300 g). A white, firm, waxy infiltration was identified, most obvious in the LV wall (Figure 5A). On microscopic examination, the myocardium showed interstitial fibrosis and extensive calcium deposition. The calcification exhibited a chicken-wire pattern, a finding consistent with primary calcium deposition as opposed to secondary dystrophic calcification after myocardial injury (e.g., myocardial infarction) (Figure 5B). Congo Red staining was negative for amyloidosis.

DISCUSSION

Extraskeletal calcium deposition is common in patients on maintenance dialysis, with mitral annular calcification and aortic valve sclerosis being the most common sites of cardiac calcification (1). Massive myocardial calcification is a rare autopsy finding, although it is more common in anuric patients receiving long-term peritoneal dialysis and concomitant warfarin therapy. Sudden cardiac death is common in the setting of metastatic myocardial calcification (2–6). Although most cases are diagnosed at autopsy, dual-energy chest radiography and chest computed tomography imaging have both shown utility for diagnosis (2,7). In our patient, abnormal myocardial attenuation was seen on noncontrast computed tomography scans as early as 7 years before her death.

Our case details the electrocardiographic and echocardiographic findings of metastatic myocardial calcification, which overlap significantly with those seen in cardiac amyloidosis. These include low-voltage QRS, increased LV wall thickness, low mitral annular tissue Doppler velocities, and a restrictive diastolic filling pattern. Importantly, our patient had an apical sparing pattern of LS with relative apical LS of 1.0, calculated as (average LS of apical segments)/(average LS of basal segments + average LS of mid-segments) (8). Relative apical LS >1.0 has been reported to have high diagnostic accuracy for cardiac amyloidosis among patients with increased LV wall thickness (8). Alternative causes of an apical sparing pattern have not been well characterized. To our knowledge, this report is the first of an apical sparing pattern of LS in metastatic myocardial calcification.

The study patient had also tested markedly positive on radionuclide bone scintigraphy. A large multicenter study found >99% sensitivity and 82% specificity of radionuclide bone scintigraphy for transthyretin cardiac amyloidosis, with light chain cardiac amyloidosis patients accounting for nearly all of the false-positive findings (9). In our patient, the markedly positive test result was likely due to high myocardial calcium content. The diagnostic
There was diffusely increased radiotracer uptake throughout the myocardium of the right and left ventricles, with no uptake in the apex. This corresponded to a visual score of 3, indicating myocardial uptake greater than bone.
performance of radionuclide bone scintigraphy for cardiac amyloidosis in dialysis patients is not known, and clinicians should be aware that positive radionuclide bone scintigraphy in this population may indicate primary myocardial calcification and not transthyretin cardiac amyloidosis. This is particularly important as radionuclide bone scintigraphy increasingly takes on a primary role in the diagnostic algorithm for cardiac amyloidosis in general practice and clinical trial settings.

CONCLUSIONS

Metastatic myocardial calcification presents in dialysis patients as a restrictive cardiomyopathy with high cardiac arrhythmia burden. Cardiac imaging findings may mimic those of transthyretin cardiac amyloidosis and include apical sparing of longitudinal strain and high-grade myocardial uptake on radionuclide bone scintigraphy. Clinicians should maintain a high index of suspicion for metastatic myocardial calcification in the appropriate clinical context.

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REFERENCES

1. Kerr DNS. Hypercalcemia and metastatic calcification. Cardiovasc Res 1997;36:293–7.
2. Matsui M, Okayama S, Takitsume A, et al. Heart failure associated with metastatic myocardial calcification in a hemodialysis patient with progressive calcification of the hand. Cardiorenal Med 2012;2:251–5.
3. Isotalo PA, Halli A, Green M, Tang A, Lach B, Veinot JP. Metastatic calcification of the cardiac conduction system with heart block: an underreported entity in chronic renal failure patients. J Forensic Sci 2000;45:1335–8.
4. Cao V, Brickner L. Myocardial calcification in a patient with end-stage renal disease. J Hosp Med 2009;4:E16.
5. Na JY. A heart of stone: an autopsy case of massive myocardial calcification. Forensic Sci Med Pathol 2018;14:102–5.
6. Okada M, Kyakuno M, Imamura J, Nakamura T, Takahara S. An autopsy case of sudden death in renal transplant recipient. Clin Transplant 2002;16 Suppl 8:58–61.
7. Sanders C, Frank MS, Rostand SG, Rutsky EA, Barnes GT, Fraser RG. Metastatic calcification of the heart and lungs in end-stage renal disease: detection and quantification by dual-energy digital chest radiography. AJR Am J Roentgenol 1987;149:881–2.
8. Phelan D, Collier P, Thavendiranathan P, et al. Relative apical sparing of longitudinal strain using two-dimensional speckle-tracking echocardiography is both sensitive and specific for the diagnosis of cardiac amyloidosis. Heart 2012;98:1442–8.
9. Gillmore JD, Maurer MS, Falk RH, et al. Nonbiopsy diagnosis of cardiac transthyretin amyloidosis. Circulation 2016;133:2404–12.

KEY WORDS cardiomyopathy, echocardiography, nuclear medicine, restrictive

APPENDIX For supplemental videos, see the online version of this paper.
Late Presentation of Pulmonary Artery-Left Atrial Appendage Fistula Formation After Left Atrial Appendage Device Closure

Wayne H. Miller, MD, Sandhya Dhruvakumar, MD, Mina C. Owlia, MD, Greg R. D’Onofrio, MD, David Hsi, MD

ABSTRACT

Atrial fibrillation is the most common arrhythmia in clinical practice with indication for anticoagulation in those patients whose annual risk for thromboembolism is >2%. Left atrial appendage closure is growing as an alternative to anticoagulation. We present a case of pulmonary artery-left atrial appendage fistula seen after left atrial appendage closure. (Level of Difficulty: Intermediate.) (J Am Coll Cardiol Case Rep 2020;2:814–8) © 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/).

An 85-year-old woman with paroxysmal atrial fibrillation was evaluated for left atrial appendage closure (LAAC). She was deemed to be a good candidate because of her history of repetitive traumatic falls while on anticoagulation. She was scheduled for percutaneous LAAC with a Boston Scientific WATCHMAN device (Boston Scientific, Marlborough, Massachusetts).

Intraoperative transesophageal echocardiography (TEE) showed no LAA thrombus or pericardial effusion at baseline. Transseptal puncture using a Brockenbrough 1 needle (Medtronic, Minneapolis, Minnesota) under intracardiac echocardiography, TEE, and fluoroscopic guidance was performed. Measurements of the LAA ostium were obtained by TEE at 0°, 45°, 90°, and 135°. The greatest ostial diameter measured 24 mm. A 27-mm WATCHMAN device was deployed using standard techniques. Postoperative TEE images showed the WATCHMAN device to be in good position. There was no paradoxic leak visualized at a Nyquist limit of 30 cm/s and no evidence of communication between the LAA and pulmonary artery (PA) (Figure 1). Overall left and right ventricular systolic function remained normal. A small de novo post-procedural septal defect was visualized at the site of transseptal puncture. No new pericardial effusion was appreciated. The LAA was engaged only once, and the device was implanted on the first attempt. She had an uneventful recovery. Postoperative TEE images showed no evidence of new pericardial

LEARNING OBJECTIVES

- To appreciate that LAA-pulmonary artery fistula formation is a rare but potentially fatal complication of LAAC closure.
- To better understand the anatomical relationship between the LAA and pulmonary artery utilizing multimodality imaging.

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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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effusion. Although she was at risk for bleeding, she was also at significantly increased risk for stroke. The decision was made for the patient to complete 45 days of anticoagulation to prevent on-device thrombus formation as per the PROTECT AF (WATCHMAN Left Atrial Appendage System for Embolic PROTECTion in Patients With Atrial Fibrillation) trial protocol.

On postoperative day 45, she returned for follow-up TEE, which showed the 27-mm WATCHMAN device to still be in good position. However, there were 2 peridevice leaks now present, both with vena contracta <5 mm. Images also showed that a fistulous track formed between the LAA and the main PA (Figure 2, Video 1).

**DIFFERENTIAL DIAGNOSIS**

Along with LAA-PA fistula, other possible causes for the abnormal findings seen by TEE could include migration of the device, with the fabric no longer creating a complete seal around the ostium of the LAA with resultant peridevice leak, and LAA-pulmonary vein fistula.

**INVESTIGATION**

Computed tomography angiography (CTA) with pulmonary artery mapping was performed to better understand the anatomical relationship between the LAA and nearby vascular structures (Figures 3 and 4). Images showed the WATCHMAN device to be in good position without evidence of any anchor wire fracture or perforation of the wall. The maximum diameter at the shoulder of the LAA was 24 mm. The LAA-PA fistula was not identified, although contrast could be seen within the LAA.

**MANAGEMENT**

Despite the abnormal TEE findings at postoperative day 45, the patient remained asymptomatic. Treatment options included percutaneous placement of
coils within the LAA, surgical repair, or continued medical management with close follow-up. She was felt to be too frail for open-heart surgery, and there was concern that the placement of coils may increase the size of the peridevice leaks, prolonging her need for anticoagulation. The decision was made to continue with medical therapy and close observation. Apixaban (5 mg bid) was stopped and she was

FIGURE 3 Computed Tomography Angiography of the WATCHMAN Device and Surrounding Structures

Pulmonary artery and WATCHMAN device computed tomography angiography. All 10 Watchman anchor wires were intact. There was no pericardial effusion.
**FIGURE 4** Computed Tomography Angiography With 3D Image Rendering of the WATCHMAN Device and Surrounding Structures

Computed tomography angiography 3-dimensional rendering of the main pulmonary artery, WATCHMAN device, and its anchor wires. The contact point of the LAA and main pulmonary artery (MPA) can be appreciated. AO = aorta; LV = left ventricle; RV = right ventricle; other abbreviations as in Figure 2.

**FIGURE 5** Postoperative Transesophageal Echocardiography: 4 Months

Transesophageal echocardiography images 4 months post-LAA closure showing diminished PA-LAA fistula. Paradevice leak was no longer appreciated. Abbreviations as in Figure 2.
prescribed aspirin (81 mg daily) and clopidogrel (75 mg daily).

A follow-up TEE was performed 4 months postoperatively that showed the peridevice leaks were no longer present and the fistulous tract had greatly diminished in size (Figure 5, Video 2). Doppler gradient across the orifice measured 1 mm Hg. Shunt ratio was normal, at 1.0. Bubble study showed no bubbles within the left atrium or the LAA. As there was no evidence of peridevice leak, it was decided to stop antplatelet therapy.

**DISCUSSION**

Although complications are rare, the LAAC procedure is not entirely without risk (1,2). Cases of delayed PA perforation, tamponade, and LAA-great cardiac vein fistula formation caused by implantable LAAC devices have been reported previously (3–8). This has led to greater interest in the spatial relationship between the LAA and other nearby structures such as the left upper pulmonary vein, left circumflex artery, and pulmonary artery (9,10). Halkin et al. (9) studied 100 patients with atrial fibrillation who underwent cardiac-gated CTA of the left atrium. They identified 3 types of LAA-PA anatomical relationships: 1) no contact (type 1); 2) proximal contact (type 2; within 15 mm of the ostium of the LAA); and 3) distal contact (type 3). Proximal contact occurred in 28% of observed patients and was the location where fixation components of most LAAC devices were positioned (9). TEE images show that this patient likely has a type 2 LAAC-PA anatomical relationship and that the fistulous tract formed within 15 mm of the ostium of the LAA.

**FOLLOW-UP**

The patient remains hemodynamically stable. She completed 5 months of dual antiplatelet therapy and is now taking aspirin 81 mg daily. We plan to perform repeat TEE in 1 to 3 months.

**CONCLUSIONS**

To our knowledge, this is the first case in which a LAA-PA fistula formed, tamponade did not ensue, surgical intervention was not performed, and follow-up TEE showed evidence of progressive tract closure. We felt that it was prudent to stop the anticoagulation after the initial recognition of the LAA-PA fistula, given the concern for possible hemopericardium and her high bleeding risk. Pulmonary CTA was very helpful in documenting the integrity of the WATCHMAN device, lack of pericardial effusion, and device stability. Cardiac surgery or percutaneous coil for the LAA-PA fistula occlusion would have carried not insignificant risk for this elderly and frail patient.

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**REFERENCES**

1. Boersma LV, Schmidt B, Betts TR, et al., E WoLuTion investigators. Implant success and safety of the left atrial appendage closure with the WATCHMAN device: peri-procedural outcomes from the EWOLUTION registry. Eur Heart J 2016; 37:2465–74.
2. Tzikas A, Shahir S, Gafoor S, et al. Left atrial appendage occlusion for stroke prevention in atrial fibrillation: multicentre experience with the Amplatz cardiac plug. EuroIntervention 2016;11: 1170–9.
3. Vemulapalli S, Hurwitz Koweek LM, Kiefer TL, Jackson KP, Piccini JP. Left atrial appendage closure devices to topographic neighboring structures using standardized imaging by cardiac computed tomography angiography. Clin Cardiol 2019;42:264–9.
4. Yaqubi T, Iyer S, Siddiqui W, Deneen A. A rare case of left atrial appendage to pulmonary vein fistula post watchman device placement. J Am Coll Cardiol 2019;73:2906.
5. Sepahpour A, Ng MK, Storey P, McGuire MA. Death from pulmonary artery erosion complicating implantation of percutaneous left atrial appendage occlusion device. Heart Rhythm 2013; 10:1810–1.
6. Bianchi G, Solinas M, Gasbarri T, et al. Pulmonary artery perforation by plug anchoring system after percutaneous closure of left appendage. Ann Thorac Surg 2016;96:e3–5.
7. Hanawawa K, Brunei M, Saenger J, et al. Close proximity between pulmonary artery and left atrial appendage leading to perforation of the artery, tamponade and death after appendage closure using cardiac plug device. Int J Cardiol 2014;175: e35–6.
8. Suwalski G, Wojnowski A, Mizerski J, Gryszyk L. Delayed pulmonary artery perforation with left atrial appendage occlude hooks. Ann Thorac Surg 2016;101:e37–9.
9. Halkin A, Cohen C, Rosso R, et al. Left atrial appendage and pulmonary artery anatomic relationship by cardiac-gated computed tomography: implications for late pulmonary artery perforation by left atrial appendage closure devices. Heart Rhythm 2016;13:2064–9.
10. Linder S, Behnes M, Wenke A, et al. Relation of left atrial appendage closure devices to topographic neighboring structures using standardized imaging by cardiac computed tomography angiography. Clin Cardiol 2019;42:264–9.

**KEY WORDS**

3-dimensional imaging, anticoagulation, complication, echocardiography, postoperative, pulmonary circulation, stroke

**APPENDIX** For supplemental videos, please see the online version of this paper.
Tropical Endomyocardial Fibrosis

Joanne S. Sutter, MD, Tisha M. Suboc, MD, Anupama K. Rao, MD

ABSTRACT

Tropical endomyocardial fibrosis is a common cause of restrictive cardiomyopathy worldwide, but is relatively rare in developed countries. We present a case of tropical endomyocardial fibrosis with right ventricular involvement initially mistaken as Ebstein's anomaly. We highlight the need for timely and accurate diagnosis to ensure appropriate management. (Level of Difficulty: Intermediate.) (J Am Coll Cardiol Case Rep 2020;2:819–22) © 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-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

A 42-year-old male immigrant from Kerala, India, with a reported history of Ebstein's anomaly status post-bioprosthetic tricuspid valve replacement presented to cardiology clinic with shortness of breath and abdominal distention. A transthoracic echocardiogram (TTE) demonstrated a normally functioning bioprosthetic tricuspid valve with marked right atrial dilation and prominent right ventricular (RV) apical hypertrophy (Figure 1A, Video 1). Contrast-enhanced echocardiography revealed patchy enhancement of the hypertrophied regions, suggesting vascularity (Figure 1B, Video 2).

PAST MEDICAL HISTORY

Past medical history was notable for reported Ebstein's anomaly diagnosed 1 year earlier. He initially presented with exertional dyspnea and was found to be in atrial fibrillation. TTE at that time reportedly demonstrated massive right atrial enlargement and an apically displaced septal leaflet of the tricuspid valve along with concomitant tricuspid regurgitation concerning for Ebstein's anomaly (Video 3). He underwent tricuspid valve replacement with a bioprosthetic valve but had persistent symptoms.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis for marked RV apical hypertrophy includes variants of Yamaguchi's disease (or apical hypertrophy), Ebstein's anomaly, Loeffer's endocarditis, endomyocardial fibrosis (EMF), and cardiac involvement of Behcet's disease.

INVESTIGATIONS

Cardiac magnetic resonance (CMR) was obtained and demonstrated obliteration of the RV apex with marked apical hypertrophy (Videos 4, 5, and 6). The RV apex was isointense on black-blood fat-suppression imaging, suggesting that the mass was composed of myocardium (Figure 2A). On late gadolinium enhancement (LGE) imaging, there was diffuse patchy enhancement of the entire RV apex, suggesting

LEARNING OBJECTIVES

- To recognize the clinical presentation of EMF.
- To review the imaging modalities and respective findings for EMF.
- To understand the medical and surgical management options for EMF.
diffuse myocardial fibrosis (Figure 2B). Review of the operative report from his tricuspid valve replacement was notable for “extensive calcification of the RV outflow tract as well as moderator bands with restriction of the anterior and septal leaflets” of the tricuspid valve. His original TTE prior to surgery was reviewed and demonstrated a normally attached septal leaflet of the tricuspid valve without actually meeting diagnostic criteria for Ebstein’s anomaly. Based on the distinct surgical and imaging findings as well as the unique demographic portfolio, the patient was diagnosed with tropical EMF.

**MANAGEMENT**

The patient’s persistent symptoms were attributed to the underlying EMF and resultant restrictive physiology leading to symptoms of right heart failure. Owing to his recent surgical intervention, the patient’s symptoms were managed medically with diuretics.

**DISCUSSION**

EMF is believed to be one of the most common causes of restrictive cardiomyopathy in the world, with an estimated global prevalence of 10 to 12 million in 2008. Most cases tend to arise in tropical equatorial regions of Africa, South America, and Asia, including the state of Kerala in India, where our patient was from. EMF tends to affect people with low socioeconomic status with a bimodal incidence in the second and fourth decades of life (1–3).

There are many theorized etiologies for EMF, but the exact cause and mechanism remain unclear. Several infectious organisms have been implicated and appear to elicit an exaggerated immune response. An inflammatory cascade of cytokines is triggered and activates eosinophils, cardiac mast cells, and fibroblasts, which in turn results in collagen deposition within the endomyocardium. Fibrosis extends to the atroventricular valve with resultant scarring and dysfunction (1,4). It is not known why one ventricle may be affected over the other, or why some patients get biventricular disease and others do not. Eosinophilia has been inconsistently detected in the early stages of the disease process, along with higher levels of autoimmune antibodies, such as anti-myosin antibodies (4).

Genetics are a potential factor due to ethnic clustering, but it is difficult to tease out the confounding shared environmental exposures that are thought to play a role in the development of EMF (3). Cerium is an element found in higher concentrations in the soil of tropical regions such as Kerala, and can cause subendocardial fibrosis in animal models. Cassava is a tuber with high rates of consumptions in regions with high incidence of EMF, including Kerala. When inadequately prepared, cassava is known to liberate hydrogen cyanide from the gut. Malnutrition impacts the liver’s ability to detoxify the cyanide, making the affected individual more susceptible to the toxic effects. In animal models, cassava has been demonstrated to cause EMF (1).

Further supporting this theory is the decrease in EMF incidence coinciding with decreased cassava consumption following industrialization of afflicted regions (4).

The progression of EMF begins with a pancarditis and progresses to fibrotic hypertrophy of one or both ventricles, with biventricular hypertrophy being most common (1,4). Interestingly, predominant RV hypertrophy is the most common presentation in Kerala, India (3), as was the case in our patient. The disease process is often hallmarkd by the development of massive ascites. Initially thought to be related to heart failure, the ascites is actually an exudative process and lymphocyte-predominant, indicating an inflammatory process. This is supported by the absence of concomitant pedal edema (4,6).

The diagnosis of EMF is made primarily by echocardiography. Findings include apical obliteration of the affected ventricle, fibrotic plaques, atrioventricular valve dysfunction, and ipsilateral atrial enlargement. Specific criteria have been outlined, with 2 major criteria or 1 major and 2 minor criteria required to make the diagnosis (3). Our patient met 3 major criteria (obliteration of the RV apex, thrombus without severe ventricular dysfunction, atrioventricular valve dysfunction due to adhesion of the valvular apparatus to the ventricular wall) and 3 minor criteria (thin endomyocardial patches localized to one ventricular wall, enlarged atrium with normal-size ventricle, enhanced density of the moderator band).

CMR will often demonstrate patchy fibrosis on LGE imaging sequences. First-pass perfusion sequences demonstrate perfusion of the hypertrophied areas (Supplemental Figure 1). The affected ventricle will typically appear isointense on T2-weighted imaging, indicating a lack of inflammation seen in the chronic phase (4,7,8) (Supplemental Figure 2).

Surgical resection of the fibrotic endomyocardium is the mainstay of treatment, with replacement of any affected valves at the time of surgery (9). Immediate post-surgical mortality remains high at 30%, but 10-year survival following surgical intervention has been reported as high as 70% in some studies.
Heart failure symptoms are managed with diuretic therapy. Spironolactone has been recommended for its known antifibrotic properties, though evidence supporting its use in EMF specifically remains limited (8).

Prognosis for patients with EMF is overall poor, with initial observational studies estimating a life expectancy at diagnosis of 2 years (2,3,5). This was often attributed to late presentation and lack of viable treatment options. However, with advances in surgical intervention, prognosis has improved, with recent data estimating 90% survival at 3 years (10). Causes of death are most often related to progressive heart failure, acute thromboembolism, complications of cirrhosis from right heart failure, and fatal arrhythmias.
FOLLOW UP

Our patient was referred to a specialized transplant program for consideration of advanced heart failure therapies.

CONCLUSIONS

Although EMF remains relatively uncommon, the number of cases encountered in the United States is increasing with immigration of populations from endemic areas. The diagnosis of EMF can be made by echocardiographic findings alone, though history and CMR can be helpful in distinguishing the disease entity from other processes on the differential. The overall prognosis remains poor and treatment options remain limited, with surgical endocardectomy being the only viable strategy for improving survival. Prompt and accurate diagnosis with appropriate referral to experienced surgical centers gives patients the best chance at improving their quality, and quantity, of life.

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REFERENCES

1. Mocumbi AO, Yacoub S, Yacoub MH. Neglected tropical cardiomyopathies: II. Endomyocardial fibrosis: myocardial disease. Heart 2008;94: 384-90.
2. Tharakan J, Bohora S. Current perspective on endomyocardial fibrosis. Curr Sci 2009;97: 405-10.
3. Mocumbi AO, Ferreira MB, Sidi D, Yacoub MH. A population study of endomyocardial fibrosis in a rural area of Mozambique. N Engl J Med 2008;359: 43-9.
4. Grimaldi A, Mocumbi AO, Freers J, et al. Tropical Endomyocardial Fibrosis. Circulation 2016;133: 2503-15.
5. Gupta PN, Valiaithan M5, Balakrishnan KG, Kartha CC, Ghosh MK. Clinical course of endomyocardial fibrosis. Heart 1989;62:450-4.
6. Marijon E, Hausse AO, Ferreira B. Typical clinical aspect of endomyocardial fibrosis. Int J Cardiol 2006;112:259-60.
7. Dato I. How to recognize endomyocardial fibrosis? J Cardiovasc Med (Hagerstown) 2015;16: 547-51.
8. Beaton A, Mocumbi AO. Diagnosis and management of endomyocardial fibrosis. Cardiol Clin 2017;35:87-98.
9. Mocumbi AO, Sidi D, Vouhe P, Yacoub M. An innovative technique for the relief of right ventricular trabecular cavity obliteration in endomyocardial fibrosis. J Thorac Cardiovasc Surg 2007;134:1070-2.
10. Schneider U, Jenni R, Turina J, Turina M, Hess OM. Long-term follow up of patients with endomyocardial fibrosis: effects of surgery. Heart 1998;79:362-7.

KEY WORDS cardiac magnetic resonance, cardiomyopathy, fibrosis, restrictive, right ventricle

APPENDIX For supplemental figures and videos, please see the online version of this paper.
**ABSTRACT**

A 74-year-old man returned to the clinic for follow-up of residual nonculprit lesions after reperfused acute inferior ST-segment elevation myocardial infarction. Stress cardiac magnetic resonance perfusion imaging demonstrated a severe perfusion defect in the anterior wall. Surprisingly, subsequent invasive assessment did not reveal hemodynamically significant obstruction in the nonculprit vessels. *(Level of Difficulty: Beginners.)* (J Am Coll Cardiol Case Rep 2020;2:823–4) © 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/).

Approximately 50% of patients presenting with ST-segment elevation myocardial infarction have residual lesions in nonculprit vessels after revascularization of the culprit artery *(1)*. If left unattended, these nonculprit lesions confer unfavorable prognosis *(2)*. Several strategies are available for treatment of the nonculprit lesions. Among these strategies, staged revascularization supported by measurements of fractional flow reserve is a frequently used option. An alternative strategy for management of the nonculprit lesions is noninvasive detection of ischemia using cardiac magnetic resonance (CMR) imaging.

We present the case of a 74-year-old male patient who presented with an inferior ST-segment elevation myocardial infarction. The patient was rushed to emergency angiography, which revealed a thrombotic occlusion of the right coronary artery *(Figure 1A, Video 1)* and intermediate stenosis of the left anterior descending artery *(Figures 1B and 1C, Videos 2 and 3)*. The culprit was successfully treated through implantation of 2 drug-eluting stents *(Video 4)*. The patient returned to our clinic 1 month after discharge for follow-up of the lesion in the left anterior descending artery. Although the patient was asymptomatic, CMR revealed a transmural stress perfusion defect in 1 segment anterior mid *(Figure 1E, Video 5)*, with normokinesia on cine imaging *(Figure 1D, Video 6)* and no contrast enhancement on the late gadolinium enhancement image *(Figure 1F)*, opposite to an infarction of the inferior wall. Surprisingly, subsequent angiography did not reveal a significant nonculprit stenosis and fractional flow reserve in the left anterior descending artery was measured to be 0.94. However, after careful re-evaluation of the angiogram, we noted a chronic total occlusion of the second diagonal branch with a tapered proximal cap and anterograde filling of the distal segment through micro channels or bridging collaterals *(Figures 1B and 1C)*. After discussion among our team, it was decided not to attempt revascularization because of the high lesion complexity and limited area of ischemia.

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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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This case beautifully underscores the value of CMR in the management of ST-segment elevation myocardial infarction patients with multivessel disease. Not only does CMR provide vital information on cardiac function and infarct size, it also allows to identify ischemia in nonculprit vascular territories, even when this eludes us during invasive assessment.

**REFERENCES**

1. Sorajja P, Gersh BJ, Cox DA, et al. Impact of multivessel disease on reperfusion success and clinical outcomes in patients undergoing primary percutaneous coronary intervention for acute myocardial infarction. Eur Heart J 2007;28: 1709–16.

2. Pasceri V, Patti G, Pelliccia F, et al. Complete revascularization during primary percutaneous coronary intervention reduces death and myocardial infarction in patients with multivessel disease: meta-analysis and meta-regression of randomized trials. J Am Coll Cardiol Intv 2018;11:833–43.

**ABBREVIATIONS AND ACRONYMS**

CMR = cardiac magnetic resonance

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**KEY WORDS**

cardiac magnetic resonance, fractional flow reserve, multivessel disease, myocardial ischemia, perfusion, ST-segment elevation myocardial infarction

**APPENDIX** For supplemental videos, see the online version of this paper.
Diastolic Coronary Artery Compression in Constrictive Pericarditis

Georgios Christopoulos, MD,a John M. Stulak, MD,b Jae K. Oh, MD,a Abhiram Prasad, MDa

ABSTRACT

Phasic coronary artery compression during diastole is a rare phenomenon. We describe a case of diastolic coronary artery compression which was caused by constrictive pericarditis. (Level of Difficulty: Beginner.)

A 54-year-old male was referred to the authors’ institution with a 1-year history of worsening shortness of breath and lower limb swelling. His medical history was significant for recurrent episodes of idiopathic pericarditis that began 4 years previously and were treated with non steroidal anti-inflammatory agents, colchicine, and prednisone. He showed no evidence of metastatic malignancy, uremia, tuberculosis, or chronic bacterial infection. On examination, the jugular venous pressure was elevated with a rapid “Y” descent, a pericardial knock, peripheral edema, and ascites. Chest radiography demonstrated cardiomegaly with prominence of the left cardiac border but no calcifications (Figure 1A). Transthoracic echocardiography showed ventricular interdependence, respiratory variation of the mitral inflow, annulus reversus, and expiratory end-diastolic hepatic venous flow reversals, which was diagnostic for constrictive pericarditis (Supplemental Figure 1). Cardiac magnetic resonance imaging demonstrated mild (3-mm) pericardial thickening anterior to the right ventricle (Figure 1B, arrows) and no regional wall motion abnormalities. The patient was referred for pericardectomy. Preoperative coronary angiography showed no atherosclerotic lesions, but there were discrete regions of diastolic compression of the mid left anterior descending artery; and diagonal, ramus, and distal left circumflex arteries (Figures 1C and 1D, arrows, Video 1). During surgery, it was noted that the pericardium was thick, with transverse cylindrical cords of scar which compressed the underlying epicardium (Figures 1E and 1F). Surgical pathology revealed non-calcific fibrous thickening and minimal non-granulomatous lymphoplasmacytic infiltrate, consistent with constrictive pericarditis. The patient had an uneventful postoperative course. On 6-month follow-up, his symptoms of shortness of breath and edema had completely resolved, and repeated echocardiography showed no evidence of constrictive physiology. Diastolic coronary artery compression is a rare phenomenon (1–7), unlike systolic myocardial bridging of arteries with an intramural course. Diastolic external compression usually occurs from localized pericardial thickening during cardiac relaxation and enlargement. It has also been reported in association with left atrial enlargement and following coronary artery bypass grafting and heart transplantation (4–7). Myocardial ischemia is a theoretical concern which likely resolves after...
correction of the structural cause of the compression (such as pericardiectomy). In the present patient, ischemia prior to surgery was not investigated because the clinical presentation was that of heart failure without anginal symptoms, and definitive therapy with pericardiectomy was planned.

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FIGURE 1 Chest Radiography Shows Cardiomegaly but no Calcifications

(A) Chest radiography shows cardiomegaly but no calcifications. (B, white arrows) Cardiac magnetic resonance demonstrates increased pericardial thickening. (C) Coronary angiography shows normal coronary anatomy in systole but phasic compression of multiple coronary arteries during diastole (D, yellow arrowheads). During pericardiectomy, thick cylindrical cords of pericardium were visualized (E and F, white arrows).
REFERENCES

1. Goldberg E, Stein J, Berger M, Berdoff RL. Diastolic segmental coronary artery obliteration in constrictive pericarditis. Cathet Cardiovasc Diagn 1981;7:197–202.

2. Nasser M, Madonna R, Cevik C. Segmental diastolic compression of circumflex coronary artery secondary to pericardial constriction: an uncommon cause of angina pectoris. J Invasive Cardiol 2012;24:E90–2.

3. Angelini P, Leachman RD, Autrey A. Atypical phasic coronary artery narrowing. Cathet Cardiovasc Diagn 1986;12:39–43.

4. Varghese V, Sanghvi K. Diastolic compression of the left anterior descending artery. J Invasive Cardiol 2018;30:E52–3.

5. Garg RK, Anderson AS, Jolly N. Diastolic coronary artery compression in a cardiac transplant recipient: treatment with a stent. Catheter Cardiovasc Interv 2005;65:271–5.

6. Roberto ES, Agarwal A. Phasic compression of left circumflex coronary artery during atrial systole. Tex Heart Inst J 2017;44:131–4.

7. Chokshi SK, Meyers SN. Diastolic segmental compression of saphenous vein bypass graft. Am Heart J 1989;118:402–4.

KEY WORDS constrictive pericarditis, coronary angiography

APPENDIX For a supplemental figure and video, please see the online version of this paper.
A 49-year-old female presented to the emergency room with complaints of a chronic cough, 3 days of progressive dyspnea, and new-onset orthopnea. Her vital signs were unremarkable. A chest X-ray revealed vascular congestion suggestive of pulmonary edema. A transthoracic echocardiogram demonstrated a large echogenic mass in the left atrium measuring 5.5 × 4.3 cm. The stalk and origin of the tumor were not clearly visualized. Additionally, the mass prolapsed across the mitral annulus causing severe mitral stenosis with a mean pressure gradient of 22 mm Hg (Video 1). The patient was taken to the operating room. The left atrium was opened and 2 well-circumscribed masses were identified (Supplemental Figure). One mass had a stalk originating from the lateral wall and the second mass had a separate stalk in the medial wall. Both masses, including the stalks and bases, were resected completely and sent to pathology for further evaluation (Supplemental Figure). The patient recovered well. Histopathologic evaluation revealed low-grade leiomyosarcomas. She was referred to an oncologist and decision was made for surveillance given that further imaging did not show any residual lesion. She was contacted 4 months after surgery and has no evidence of recurrence.

Primary cardiac leiomyosarcomas are rare and even fewer synchronous lesions have been reported. The incidence of primary cardiac tumors is 0.02%, and primary cardiac leiomyosarcomas represent <0.25% of all cardiac tumors (1,2). Although complete resection is not always feasible, surgical intervention is required for definitive tissue diagnosis, symptomatic relief, and prevention of related sequela such as embolic events. Synchronous cardiac leiomyosarcoma are rarely present in available reports. Although more than 1 tumor is unusual, this should be taken into preoperative consideration and resection of all tumors confers better outcomes.
REFERENCES

1. Reynen K. Frequency of primary tumors of the heart. Am J Cardiol 1996;77:107.

2. Nakashima K, Inatsu H, Kitamura K. Primary cardiac leiomyosarcoma: a 27-month survival with surgery and chemotherapy. Intern Med 2017;56:2145-9.

APPENDIX For a supplemental video and figure, please see the online version of this paper.
A previously healthy man presented with inferior myocardial infarction and recent upper respiratory tract infection. Bacteremia was detected and treated; however, the patient developed refractory polymorphic ventricular tachycardia storm and shock. Clinical autopsy revealed the diagnosis of isolated bacterial myocarditis. (Level of Difficulty: Beginner.) (J Am Coll Cardiol Case Rep 2020;2:830–1) © 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 61-year-old previously healthy man presented to a community hospital with transient loss of consciousness and acute chest discomfort. He had upper respiratory tract infection for 2 weeks with subjective fever and rigors for 1 day. The patient was apyrexic and initial physical examination was normal. Serum leukocyte count and chest radiograph were normal, and 12-lead electrocardiogram demonstrated inferior ST-segment elevation myocardial infarction. There were no stigmata of endocarditis or signs of aortic dissection. Intravenous thrombolysis was administered, and he was transferred to a tertiary care hospital.

Coronary angiography demonstrated occlusion of the distal left-dominant posterior descending artery, without other significant lesions, and angioplasty was not possible because of small vessel size. Transthoracic echocardiography showed left ventricular apical-inferior hypokinesis and no valve lesions. Cranial computed tomography identified a small cerebellar hemorrhage. The patient was clinically stable and transferred to cardiac intensive care unit for medical management. Approximately 24 h later there was onset of polymorphic ventricular tachycardia storm and profound shock. Admission blood cultures grew methicillin-sensitive Staphylococcus aureus and intravenous antibiotics were administered. Despite maximum supportive therapy the patient died 48 h following admission.

Autopsy revealed acute bacterial myocarditis (BM) with multifocal suppuration of the lower interventricular septum and inferior ventricles. The cardiac valves were unremarkable. Intramyocardial abscesses contained gram-positive cocci (methicillin-sensitive S. aureus) (Figure 1A). The posterior descending artery exhibited acute bacterial vasculitis and adjacent abscess (Figure 1B). Additional findings included microabscesses in the brain and spinal cord.

Endocarditis is the most common cardiac manifestation of bacterial infection in developed countries. Perivalvular extension with abscess formation is a recognized complication, but isolated BM is exceptionally rare (1).
BM presenting with myocardial infarction has been reported; however, this case is notable because of the absence of immunocompromise. The incidence of isolated BM in modern practice is unknown and most reports come from old autopsy series (1). Complications of BM include myocardial rupture, arrhythmia, sepsis, and shock (1). Treatment consists of supportive care, antimicrobial therapy, and source control. Surgical intervention is not well described and may be ineffective with multifocal involvement. Use of venoarterial extracorporeal membrane oxygenation in BM has not been reported. Often, as in this case, definitive diagnosis relies on autopsy findings.

Despite modern clinical tools autopsy reveals new diagnoses or diagnostic errors in approximately 30% of cases (2). Autopsy remains an invaluable tool for quality control, education, and advancement of medical science. Unfortunately, use of autopsy has declined significantly. We highlight the ongoing utility of autopsy to establish diagnosis and provide closure to patients’ family members and clinical teams.

**FIGURE 1** Bacterial Myocarditis Hematoxylin-Eosin Micrographs

(A) Myocardial microabscesses with clusters of gram-positive cocci (original magnification ×20). (B) Posterior descending artery with acute bacterial vasculitis (top arrow) and adjacent abscess (bottom arrow) (original magnification ×4).

**REFERENCES**

1. Wasi F, Shuter J. Primary bacterial infection of the myocardium. Front Biosci 2003;8: 228-31.

2. De cock KM, Zielinski-Gutiérrez E, Lucas SB. Learning from the dead. N Engl J Med 2019;381: 1889-91.
Unexpected or Nonsuspected?
A Rare Cause of Recovered Left Ventricular Ejection Fraction After ECMO

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ABSTRACT

Acute heart failure represents a challenge, especially in infrequent etiologies. We present the clinical case of a young woman diagnosed with acute heart failure and cardiogenic shock. Pheochromocytoma was identified as a reversible etiology. The surgical treatment led to a complete recovery of cardiac function. (Level of Difficulty: Beginner.) (J Am Coll Cardiol Case Rep 2020;2:832–4) © 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/).

A 24-year-old woman without relevant past medical history presented to the emergency room after 6 days of flu-like symptoms. In the last 24 h, she also presented dyspnea, hot flashes, and palpitations. The physical examination was relevant for hypertension and tachycardia. The electrocardiogram showed supraventricular tachycardia that was treated with adenosine and labetalol returning to sinus rhythm. Two hours later, she had signs of peripheral hypoperfusion and low oxygen saturation. Laboratory tests were performed, and hypothyroidism, pneumonia, and pulmonary embolism were ruled out. The transthoracic echocardiography showed ejection fraction (EF) 20%, left atrial dilatation, and global hyperkinesia. The patient was transferred to the intensive care unit with cardiogenic shock after a cardiac arrest and developed multiorgan dysfunction; she required vasopressor, inotropic, and venoarterial extracorporeal membrane oxygenation support for 5 days. Her medical condition improved, but her blood pressure was difficult to control. A new echocardiography showed improvement of left ventricular EF to 60%, and cardiac magnetic resonance imaging ruled out myocarditis. The 24-h urine methanephrines tested positive, and the abdominal contrast magnetic resonance showed a left adrenal gland lesion compatible with pheochromocytoma (Figures 1A and 1B). The metaiodo-benzyl-guanidine scintigraphy showed signs of left adrenal gland neuroendocrine tumor (Figures 1C and 1D). The patient underwent radical left adrenalectomy and histopathology.
confirmed the diagnosis of pheochromocytoma. The patient improved her medical condition: after surgery she did not require antihypertensive medication, and was completely asymptomatic. During the follow-up period, she did not present heart failure manifestations, and the N-terminal pro-B-type natriuretic peptide and EF returned to normal values.

Cardiomyopathy induced by pheochromocytoma represents a barely recognized entity. It has diverse clinical manifestations: Takotsubo syndrome, myocarditis, and dilated cardiomyopathy. The clinical presentation is variable: hypertension is the most frequent (65%), and the classical triad (headache, palpitations, and diaphoresis) is described in 4% (1). There are few reports of patients who present cardiogenic shock (2), but the predominance of multiorgan failure over catecholamine excess symptoms is frequently described (1). In this case, dobutamine could contribute to the evolution because of its potential to induce shock in patients with pheochromocytoma (2). The pheochromocytoma resection is associated with improvement of ventricular function in 96% of cases. The lack of intervention is related to an increase in mortality (33%), heart transplant (11%), and serious adverse events (44%) (1).

Pheochromocytoma-induced cardiomyopathy represents a potentially reversible disease. The diagnosis implies an early suspicion in cases of heart failure without clear etiology, even in the absence of classical symptoms of catecholamine excessive stimulation. Pheochromocytoma resection can prevent progression to irreversible cardiac remodeling and adverse outcomes.

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**FIGURE 1** Adrenal Mass: Pheochromocytoma

(A and B) Abdominal contrast magnetic resonance showed a left adrenal gland lesion. (C and D) The metaiodo-benzyl-guanidine scintigraphy showed signs of left adrenal gland neuroendocrine tumor.

**ABBREVIATIONS AND ACRONYMS**

EF = ejection fraction
REFERENCES

1. Zhang R, Gupta D, Albert SG. Pheochromocytoma as a reversible cause of cardiomyopathy: analysis and review of the literature. Int J Cardiol 2017;249:319-23.

2. Pereira-da-Silva T, Abreu J, Ramos R, et al. Unexpected triggers for pheochromocytoma-induced recurrent heart failure. Int Arch Med 2014;7:30.

KEY WORDS acute heart failure, cardiomyopathy, ejection fraction
A Rare Case of Epicardial Lead Strangulation of Left Ventricular Inflow

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ABSTRACT

This is an unusual case of left atrioventricular groove strangulation by an abandoned epicardial pacing lead associated with mild left ventricular inflow obstruction, left atrial enlargement, and new atrial tachycardia that resolved with surgical lead removal. (Level of Difficulty: Intermediate.) (J Am Coll Cardiol Case Rep 2020;2:835–6) © 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/).

A 14-year-old female born with complete heart block secondary to maternal lupus underwent dual-chamber epicardial pacemaker implantation at age 11 months. Atrial and ventricular leads were placed through a limited lower sternotomy incision (the atrial lead was placed at the atrial-caval junction). Her postoperative course was complicated by post-pericardiotomy syndrome. At 9 years of age, she was noted to have a prominent posterior ridge above the mitral valve without obstruction by transthoracic echocardiogram (TTE). Follow-up TTE continued to demonstrate evidence of the ridge with a stable, mild, mean inflow gradient. At 13 years old, she underwent generator replacement with transvenous endocardial leads and explantation of the abdominal generator. The epicardial leads were abandoned. Imaging at that time demonstrated the posterior ridge above the mitral valve with mild left ventricular inflow obstruction (mitral inflow peak gradient of 10 mm Hg, a mean gradient of 4 mm Hg, and a heart rate of 69 beats/min) and mild left atrial enlargement (Figure 1, Videos 1, 2, 3, and 4). Chest radiographs suggested a posterior course of the abandoned lead (Supplemental Figure 1). She subsequently developed atrial tachycardia, possibly a consequence of left atrial enlargement. She underwent surgical removal of the epicardial leads through a repeat sternotomy. The atrial epicardial lead was deeply scarred and tethered at the left atrioventricular groove posteriorly. She had an uneventful postoperative course. Since the lead removal, she has done well, without mitral inflow gradient (a peak mitral inflow gradient of 3 mm Hg, a mean of 1 mm Hg, and a heart rate of 70 beats/min) or further arrhythmia episodes (Videos 5 and 6).

This is an unusual case of left atrioventricular groove strangulation by an abandoned epicardial pacing lead with mild left ventricular inflow obstruction, left atrial enlargement, and atrial tachycardia that resolved with surgical lead removal. The authors speculate that a redundant lead placed within the pericardium migrated around the left ventricular apex after placement. Although this phenomenon is uncommon, epicardial leads causing cardiac strangulation and coronary compression have been described, with a reported incidence of 0.01% to 5.5% (1,2). More commonly, these leads have been identified postmortem or in patients presenting with symptoms of myocardial ischemia; mortality has been reported to be 1.2% (1). To date, there have been no reports of left ventricular inflow strangulation. Because this situation is rare and underappreciated, its recognition can be challenging. Pacing and lead function are not usually compromised. Serial posteroanterior
(PA) and lateral chest radiographs can be used to evaluate lead position in relation to the cardiac silhouette and changes in lead position that may occur with somatic growth. In patients with epicardial pacing leads, physicians should be alert to new clinical signs and symptoms, echocardiographic findings, and electrocardiographic changes. Echocardiography can help confirm the diagnosis in cases of valvular disturbance but is unlikely to identify coronary compression. The purpose of this report is to highlight the importance of TTE as it provides aids to identifying and monitoring for dynamic compression.

**FIGURE 1 TTE Versus Color Doppler Imaging**

(A) TTE frames showing prominent posterior ridge (arrow) above the mitral valve with color Doppler (B) images with flow acceleration beginning in this area. (C) TTE following epicardial lead removal. TTE = transthoracic echocardiogram.

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**REFERENCES**

1. Mah DY, Prakash A, Porras D, Fynn-Thompson F, DeWitt ES, Banka P. Coronary artery compression from epicardial leads: more common than we think. Heart Rhythm 2018;15:1439-47.
2. Carreras EM, Duncan WJ, Djurdjev O, Campbell Al. Cardiac strangulation following epicardial pacemaker implantation: a rare pediatric complication. J Thorac Cardiovasc Surg 2015;149:522-47.

**KEY WORDS** atrial tachycardia, epicardial leads, lead strangulation, pacemaker, transthoracic echocardiogram

**ABBREVIATIONS AND ACRONYMS**

PA = posteroanterior
TTE = transthoracic echocardiogram

**APPENDIX** For supplemental videos and a figure, please see the online version of this paper.
Understanding the Analytics of Twitter in Cardiovascular Medicine

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During the past decade, the use of social media has steadily grown in the medical community. Despite the frequent claim that the use of social media, particularly Twitter, in cardiovascular medicine is widespread, the data to support such claims are not readily available. Gaining an understanding into the true global reach of discussions related to cardiovascular medicine on Twitter is complex. The purpose of this paper was to offer a better understanding of the analytics of social media, and specifically Twitter, as it relates to its use in the field of cardiovascular medicine.

UNDERSTANDING THE USER BASE

The first question that must be addressed is “Who is on Twitter?” When an individual creates a Twitter account, there is no box to check regarding that person’s role in cardiovascular medicine. There can be limited information regarding a person’s sex, age, or geographical location. Indeed, all identifying information is optional and unverifiable unless one knows the individual or they identify their professional role.

Recent research implied significant global cardiologist participation and activity on Twitter (1,2). How accurate is this? The British Cardiovascular Society 2014 Workforce Survey estimated that in 2013, there were 1,379 active consultant cardiologists in the United Kingdom (3). However, in a study published in the British Journal of Cardiology in 2018, only 301 UK cardiologists were identified on Twitter, suggesting that in the United Kingdom, Twitter has been adopted by a relatively small percentage of cardiologists (4). Interventional cardiologists were the most represented, followed by imaging and then heart failure physicians. This information was obtained by identifying the individuals using the British Cardiovascular Society’s Twitter account and then confirming the job title, specialty, and location by the General Medical Council Register, LinkedIn, and hospital and university websites.

The number of active cardiologists in the United States is >20-fold that of the United Kingdom. In 2018, it was estimated that there were 31,890 cardiologists practicing in the United States (5). The percentage of those who are active on Twitter is more difficult to ascertain and remains uncertain despite attempts to quantify these numbers by using hashtags. In a 2019 American College of Cardiology (ACC) poster presentation, it was estimated that only 2.3% of the ACC membership are active Twitter users, divided equally among practicing physicians and trainees (6). In a recent Twitter poll structured to attempt to gain a better understanding of use of the service, the majority of respondents (84%) claimed that <25% of their colleagues were on Twitter. Thus, although this sampling may be biased, it would suggest that only a minority of cardiologists are regular users of social media platforms such as Twitter. There are few robust data available that support the concept that the adoption of Twitter in cardiovascular medicine is widespread.

USE OF HASHTAGS

A hashtag is a key word or phrase used to categorize one’s tweet. Tweets that contain at least 1 hashtag can

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be indexed, searched, and analyzed. Without any true means to measure active Twitter users, the hashtag may serve as the most accurate tool. In a study comparing Twitter use during 3 of the major cardiovascular meetings (American College of Cardiology #ACC, Transcatheter Cardiovascular Therapeutics #TCT, and Heart Rhythm Society #HRS), hashtags were used to identify the number of Twitter participants (7). Based on this analysis, in 2014, there were 3212 users participating on Twitter during these 3 conferences, which would represent <10% of the conference attendees. The number of Twitter users increased dramatically in 2016 to 10,362, representing 25% of presumed conference attendees. Although the majority of attendees at these conferences are physicians, other health care providers, pharma/industry, and media comprise a sizeable portion of the audience. Furthermore, not all those using the conference hashtags were attending in person. It is difficult to determine how many of the users were in fact registered and present on-site, although 48% of the Twitter users using these hashtags were physicians. Reliable identification of users remains elusive. One must extract various pieces of information, including that derived from the profile picture and page, to properly identify an individual.

**SOCIAL MEDIA ANALYTICS**

Social media analytics have been used occasionally to show the impact of knowledge dissemination across the world. How reliable are these numbers? Current means is through companies that measure analytics, the most popular of which is Symplur, a company dedicated to social media analytics in health care. Symplur has the ability to count the number of participants in a conference provided those participants use the official conference hashtag. Thus, if all users at a particular conference use that conference’s hashtag, an accurate count of the number of participants can be obtained for any designated time frame provided that hashtag has been registered with Symplur. It can also provide the average number of tweets per participant but cannot provide any further demographic data regarding participants. Demographic data are extracted from the Twitter profiles of the individual users. These numbers can only be accurate if the appropriate hashtag is used. Often, several hashtags may be used at any conference, confounding an accurate estimate of social media participants.

Impressions are probably the most misinterpreted Twitter analytic. At many conferences, it is not unusual for there to be an acclamation of millions of impressions being generated, suggestive of how far and widespread the tweets are being disseminated. An impression means that a tweet has been delivered to a Twitter account’s timeline and only gives one an idea of one’s potential reach. It does not reflect that the tweet has been read. Indeed, Twitter itself is unable to ascertain if a tweet has been read. The misconception that impressions mean the tweet was viewed is probably due to the definition given on Twitter that impressions are “times people saw a tweet on Twitter.” Impressions are really reflective of the number of active followers. The larger the number of followers, the greater the number of impressions that will be generated, which is not necessarily reflective of engagement with the author and his or her message.

For those individuals who are considered “high-volume tweeters” or who use bots to tweet at a high rate, the number of impressions they “earn” can overestimate their importance within a conversation or conference. Impressions are probably more important for accounts that are attempting to sell or promote a service or product on Twitter, which is generally not the case when used in the cardiovascular field. In business, sales of a product or service through Twitter can be ascertained reflecting the true value of impressions. This is not the case in academic medicine where Twitter is primarily used to advance medical knowledge. There is no product or service being sold that can be easily quantified. A possible exception may be in the use of a hashtag to promote a specific procedure such #RadialFirst. In 2008, 1% of coronary interventions were performed via a radial approach according to the National Cardiovascular Data Registry database. Over the following decade, this increased to 40.6% in the first quarter of 2017. In February 2017, the #RadialFirst hashtag was established, and over the following 24 months >60,000 tweets have used this hashtag across almost 7,300 users. During this timeframe, there were >120 million impressions, which seems to be a lot of impressions. How that relates to a growth of 7% in the use of radial artery access in percutaneous coronary interventions over the same timeframe is uncertain.

An example of how impressions can be misinterpreted is a recent Twitter Journal Club sponsored by *Circulation: Cardiovascular Interventions*. During a 3-h time frame surrounding a 1-h Twitter discussion, >1.6 million impressions were noted. There were a total of 219 tweets among 61 participants; almost one-half of the tweets originated from only 2 Twitter accounts. There was an average of only 4 tweets per participant. Thus, although the journal club discussion may have crossed the timeline of almost 2
million Twitter users, the interaction among users was just a fraction of that number.

In contrast to impressions, engagement rates are probably a more accurate assessment of the interaction with an individual Twitter account and are reflective of the fact that the tweet was relevant enough to interact with. Engagements include likes and retweets, and engagement rates are determined by the number of retweets per original tweet authored, number of retweets per followers, and number of followers earned per original tweet authored. All of this information is available on an individual’s Twitter account for each individual tweet.

The Twitter poll of institutional cardiologists on Twitter generated a total of 13,430 impressions but only 343 engagements, a small fraction of the impressions. Engagement included 36 profile links, 31 likes, and 29 retweets. Although the poll generated a total of 461 votes, only 129 votes came directly as a result of the primary pollster, with the majority accrued as a result of individuals retweeting the poll. This latter point emphasizes the paramount importance of the retweet.

Retweets are probably the most important means by which information is disseminated, especially for those individuals who do not have many followers. They are much better indicators of the importance of the tweet content than are the number of followers and, for that matter, impressions. For individuals with a large number of followers, there are often a proportion of inactive followers who either do not read or interact with tweets. These are often referred to as lurkers. They do not engage or retweet, making the quantification of the impact of a single tweet difficult. A message that is frequently retweeted is reflective of the importance and relevance of that information to the intended audience. Retweets are thus an important measure of the actual interaction between users, which is critical to its use in medicine.

**CONCLUSIONS**

Many claims have been made that social media, and specifically Twitter, is changing the conversation in academic medicine, yet the analytics to support these claims are lacking. The recently published article “The Kardashian Index of Cardiologists: Celebrities or Experts?” (8) and the accompanying perspectives by Califf (9) and De Maria (10) may provide the framework to address the use of social media in the cardiovascular arena. A better understanding of the analytics of Twitter will be key to the continued growth and success of this medium in our field.

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**REFERENCES**

1. Parwani P, Choi AD, Lopez-Mattei J, et al. Understanding social media opportunities for cardiovascular medicine. J Am Coll Cardiol. 2019;73:1089-93.

2. Kuehn BM. Social media becomes a growing force in cardiology. Circulation 2019;140:790-2.

3. Fox K, Wragg A, Cooper G. The British Cardiovascular Society 2014 Work Force Survey. A Report to the BCS October 2014. Available at: http://www.bcs.com/documents/139_BCS_survey_Report_to_the_BCS_October_2014.pdf. Accessed October 28, 2019.

4. Hudson S, French A. CardioTweeters: an analysis of Twitter use by UK cardiologists. Br J Cardiol 2018;25:102–6.

5. Effiein J. Number of active physicians in the U.S. in 2019, by specialty area. Available at: https://www.statista.com/statistics/209424/us-number-of-active-physicians-by-specialty-area/. Accessed October 28, 2019.

6. Douglas A, Suero-Abreu G, Barajas-Ochoa A. Cardiology in 280 characters: cardiologists use of Twitter in the United States. J Am Coll Cardiol 2019;73 Suppl 1:3034.

7. Tanoue MT, Chatterjee D, Nguyen HL, et al. Tweeting the meeting: rapid growth in the use of social media at major cardiovascular scientific sessions from 2014 to 2016. Circ Cardiovasc Qual Outcomes 2018;11:e005018.

8. Khan MS, Shahadat A, Khan SU, et al. The Kardashian index of cardiologists: celebrities or experts? J Am Coll Cardiol Case Rep 2020;2:330–2.

9. Califf RM. A perspective on the K-Index. J Am Coll Cardiol Case Rep 2020;2:335–6.

10. DeMaria A. Social media and assessing the “impact” of medical publications. J Am Coll Cardiol Case Rep 2020;2:333–4.

**KEY WORDS** analytics, impressions, social media, Twitter
If You Can’t See It, You Can’t Be It
Mentorship for Female Internal Medicine Residents

Neha V. Chandra, MD,a Karol E. Watson, MD, PhD,b Janet K. Han, MDb,c

The under-representation of women in cardiology is widely recognized. In 2017, women represented 42% of internal medicine residents and only 23% of cardiology fellows (1). These disproportionate numbers have been attributed to workplace barriers faced by women, including gender and parenting discrimination, challenges in balancing family responsibilities, radiation exposure during pregnancy, and lack of professional advancement (2). As of a 2018 survey of internal medicine residents, female residents were more likely to have a negative perception of cardiology due to concerns about adverse job conditions, interference with work-life balance, and lack of diversity within the specialty (3).

However, this survey also revealed that women highly valued the presence of a positive role model as a part of their professional development (3). The positive influence of a mentor in a trainee’s career decision-making process has been supported extensively in the surgical literature where women are also underrepresented. Female medical students were more likely to choose a surgical career at institutions with a higher proportion of female faculty surgeons (4); both men and women who identified a positive surgical role model were more likely to choose a surgical career (5); and female physicians and trainees in surgical specialties placed more importance on mentorship in their careers compared with men (6).

This was recently echoed in a survey of cardiology fellows, which revealed that a lack of female role models had a negative effect on a female fellow’s decision to pursue a career in interventional cardiology (7).

These survey data are initially discouraging, but on closer look, offer an impactful conclusion: female residents are significantly influenced by the presence of positive female role models when making career decisions. How can this knowledge be used to bridge the gender gap in cardiology? Increasing mentorship for women trainees, especially at the level of residency, has the potential to promote the recruitment of women into cardiology. Mentorship allows for professional guidance and sponsorship but also provides visibility into the specialty. Although female cardiologists are more likely to have same-sex mentors (2), the responsibility of mentorship does not fall solely on women in cardiology. Women in cardiology have the unique ability to serve as role models for female trainees; however, diversity in mentorship is key. A mentor can be found in a man or woman, faculty or fellow.

As a female internal medicine resident, one of us (N.V.C.) can attest to the invaluable impact of mentorship during residency. The actions of a female faculty cardiologist (J.K.H.) put me on a path to pursue a career I had not previously imagined—a career in cardiology. I feared the same conditions cited by the recent survey data: work-life imbalance, adverse work conditions, and lack of diversity in a male-predominant specialty. But, through the guidance of my mentor, I had the opportunity to debunk these misconceptions. Mentorship additionally provided me with a role model who can relate to and guide me through challenges, access to a professional network that includes faculty members and fellows-in-training, exposure to clinical and academic opportunities, and, most importantly, sponsorship.

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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.
mentorship from both faculty and fellows, I have had the opportunity to imagine a career in cardiology and engage in steps toward professional advancement.

In light of the 2018 survey data, it seems that the field of cardiology is susceptible to losing talent and diversity in the transition from residency to fellowship. Strengthening the presence of mentorship at this juncture is a potential area of intervention. Figure 1 describes a framework for mentorship interventions at the residency level, ranging from individual to systems-based approaches. Fellows and faculty can engage in mentorship by identifying residents interested in cardiology and providing them with introductions to faculty and program leadership, opportunities in academic projects, and exposure to cardiology as a career. One particularly well-received program-level intervention at our institution is the Women In Cardiology initiative pioneered by 2 fellows-in-training. This initiative involves quarterly discussion panels with female cardiology faculty to promote mentorship and sponsorship between faculty and trainees. The first 2 meetings sparked discussion about career advancement, family planning, and mentorship, and were attended by male and female residents, fellows, and cardiology program leadership. An example of an innovative program created by a specialty society is the Association of Women Surgeons and their recent development of the AWS Coaching Project (8). This program provides faculty members with training on how to coach residents in personal and professional development to improve trainees’ career fulfillment and minimize burnout. Social media can additionally be a powerful tool in establishing mentorship. Social media, such as Twitter, allows for communication and networking beyond barriers, including geography, specialty, or practice setting (9). This format is particularly useful in medical specialties with female underrepresentation. Women with limited access to mentors at their home institutions can harness the strength of social media to build mentorship networks that would otherwise be inaccessible (6,9).

Early mentorship is essential to the successful recruitment of women trainees into cardiology. Mentorship paves the way for professional development, personal coaching, and, most importantly,
visibility. It enables trainees to appreciate that women in cardiology have high rates of career satisfaction (2) despite balancing personal and professional responsibilities and addressing workplace barriers for their community. Faculty and fellows have the power to step forward as mentors and show trainees what it means to be a cardiologist.

After all, if you can’t see it, you can’t be it.

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REFERENCES

1. Association of American Medical Colleges. Physician Specialty Data Report: ACGME Residents and Fellows by Sex and Specialty, 2017. September 2018. Available at: https://www.aamc.org/data/workforce/reports/492576/2-2-chart.html. Accessed January 19, 2020.
2. Lewis SJ, Mehta LS, Douglas PS, et al. Changes in the professional lives of cardiologists over 2 decades. J Am Coll Cardiol 2017;69:452–62.
3. 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;3:682–89.
4. Neumayer L, Kaiser S, Anderson K, et al. Perceptions of women medical students and their influence on career choice. Am J Surg 2002;183:146–50.
5. Ravindra P, Fitzgerald JE. Defining surgical role models and their influence on career choice. World J Surg 2011;35:704–9.
6. Luc JS, Stamp NL, Antonoff MB. Social media in the mentorship and networking of physicians: important role for women in surgical specialties. Am J Surg 2018;215:752–60.
7. Yong CM, Abnousi F, Rzeszut AK, et al. Sex differences in the pursuit of interventional cardiology as a subspecialty among cardiovascular fellows-in-training. J Am Coll Cardiol Intv 2019;12:219–28.
8. Association of Women Surgeons. The AWS Coaching Project. Available at: https://www.womensurgeons.org/page/CoachingProject. Accessed January 19, 2020.
9. Shillcutt SK, Silver JK. Social media and advancement of women physicians. N Engl J Med 2018;378:2342–5.
Presently, I find myself on the path with a few more steps in front of me. I am a second-year general cardiology fellow at Creighton University with aspirations for an electrophysiology fellowship in the upcoming year. The path to this place has not been conventional; however, this path is what fuels my passion and desire.

I was born in Tucson, Arizona, in the early 1980s. At my 6-month checkup, the physician noticed that my heart rate was slower than it should be. An electrocardiogram was performed that immediately diagnosed a congenital third-degree heart block with a junctional escape rhythm. From that day, I took my first step on the path; I became the patient.

I spent the next 9 years of my life making frequent visits to the pediatric cardiologist. I spent a significant amount of time as an infant, toddler, and young child having noninvasive tests performed on me. At that age, I never truly understood what made me so different from the rest of my peers, but it never bothered me. Shortly after my ninth birthday, I was admitted to Phoenix Children’s Hospital for implantation of a permanent pacemaker. I did not understand what a pacemaker was or the fact that I would be living with a device connected to my heart for the rest of my life. Living with a pacemaker as a child and teenager was not all that different though. Other than 6-month telephonic pacemaker checks and the yearly office visit, I went about my adolescent years like normal. When I was 16 years of age, I started to think about what my future career might look like. I was set on joining the military to become a pilot, as this had been my childhood passion. A short time later, I got the shocking news that my pacemaker would indeed prohibit me from going down that path. As I pondered what my new path might look like, I recall looking at myself in the mirror, focusing on the scar located on my upper left chest. I realized that I wanted to work with the pacemaker.

The older I became, the more interested I became in the relationship between the pacemaker and my heart. I was fascinated that this device was smart enough to restore normal rhythm to my heart through a series of timers and algorithms. This led me to my undergraduate biomedical engineering degree, MBA, and my first career with one of the largest pacemaker manufacturers. I was hired as a technical service representative and was involved in troubleshooting and implanting cardiac rhythm devices. I was taking care of patients with very similar cardiac rhythm disorders as myself. I had envisioned this as being the career I was meant for. I was on the second part of my path; the device engineer. However, this path was also about to make a turn.

The patient encounter began like most others. I sat across from the patient to interrogate her newly implanted pacemaker. The dual-chamber pacemaker was implanted 7 days prior for symptomatic third-degree heart block, and this was her first office visit post-implant. I gently wrapped the interrogation wand around her neck but could not help but notice the tears rolling down her face. She was noticeably anxious and frightened by the very process. I removed the wand from her neck and placed it back on the programmer. Not only was I experienced in interrogating cardiac devices, but I was also experienced in the vast array of emotions that patients exhibit with the first interrogation of a newly implanted pacemaker. I gently held her hand and said, “I know how you feel.” The patient looked back at me with a face of confusion and replied, “How do you know what it feels like?” I unbuttoned the top of my dress shirt and revealed a very similar scar in the
exact position as hers. She immediately got up from the chair, still with tears streaming down her face, and gave me a hug saying, “Thank you for taking care of me.” She was relieved of her initial anxiety and fright. She took comfort in knowing that someone who was taking care of her had actually experienced the same disease process and had the same cardiac device implanted. I spoke to the patient not only from the perspective of the pacemaker manufacturer, but from a point of empathy, something she had lacked prior to and post-implantation. She expressed that much of her anxiety stemmed from not receiving adequate information pre-operatively on how the pacemaker would interact with her native heart and what life would be like living with a pacemaker. Fortunately, I could answer the technical questions about the pacemaker and its interaction with the heart as well as the questions about how to live life with a pacemaker.

At this point in time, I had been pacemaker-dependent for 17 years and was on my second pacemaker. I had already lived more than one-half of my life with a pacemaker inside of me. There were not many aspects of life that I had not already experienced with the pacemaker: everything from traveling in airports to learning how to ride roller-coasters with it.

The patient had spent the prior 7 days searching the internet about how to live life with a pacemaker. The information that she obtained during this time came from a variety of sources, and as I can only imagine, were not all from trusted sources. By the time of her first office visit, she was so confused about the new pacemaker and even had doubts about wanting to continue living with it. She had thought that her native heart was no longer even functional, as the pacemaker had taken over all of her heart’s functions. It was the combination of knowledge and empathy that I conferred that made all the difference to her. At the end of the office visit, as she was leaving the room, she gave me one last hug and said, “You should become a doctor and take care of all us pacemaker patients.” That patient encounter set me on my next part of my path: to become an electrophysiologist.

A few months after that patient encounter, I left the world of pacemakers and embarked on the 12-year journey to become an electrophysiologist (which I am still on). Since joining the world of medicine, I have had countless interactions with patients who were receiving newly implanted cardiac devices and those who have had them for years. Each encounter is different, yet very similar in that patients appreciate knowing that someone else also knows what it feels like. I initially thought my career path was to work with just the pacemaker. I was wrong. My path is to work with the patient.

My goal is to use my 3 different perspectives in life, as the patient, the device engineer, and the electrophysiologist, to establish and maintain patient connections. I am the physician who also knows what it feels like to be the patient, because ultimately, my path began as the patient. I know what it feels like to be on both sides of the scalpel.
Responding is one of the vital aspects of public health, as is anticipating. A large-scale public health emergency can easily overwhelm the existing venues and mechanisms that provide medical care, a situation that is currently unfolding with the coronavirus disease-2019 (COVID-19) pandemic in many countries, including the United States. The current dire state of affairs is at least partially reflective of the lack of preparedness and proper anticipation as it related to the outbreak of COVID-19 in Wuhan, China. The anticipation failure for the “first wave” will be analyzed in years to come, so that similar mistakes do not happen in the future. The current response in hardly hit, mostly metropolitan areas of the country includes mobilization and augmentation of the existing health care resources; both strategies are aimed at optimizing medical care capacity. In addition, health care facilities have reorganized their care models by canceling nonurgent visits, elective procedures, and surgeries, and have encouraged patients to come to the hospital or emergency room only if it is absolutely necessary. Some areas report a decrease in non-COVID-19 related urgent visits during the pandemic. These strategies certainly help dealing with the “first wave,” but do not eliminate the need of anticipation for the potential “second wave” of health care strain once the COVID-19 case load flattens or starts to decrease. “Second wave” here does not refer to the possible cyclic or seasonal nature of COVID-19 infection itself, but rather to the byproducts of the initial wave. One should anticipate 3 important components of the “second wave” in the weeks and months to come: a rebound in medical needs, intermediate-term COVID-19 infection consequences, and health care provider burnout.

Health care facilities in densely populated metropolitan areas normally handle a high volume of nonurgent and elective visits and commonly serve populations with high burden of comorbidities. Postponement of these visits as well as elective procedures and surgeries will likely result in a rebound effect: patients with ignored medical needs presenting to hospitals and offices with exacerbated conditions and decompensated states. Telemedicine has been promoted as a possible solution for this problem, but unfortunately, it has significant shortcomings. First, it does not replace effective patient–physician interaction, including proper physical examination. Second, it may provide false reassurance without proper testing or laboratory assessment. Finally, many patients, unfortunately mostly in underserved communities, may not be able to use telemedicine due to unfamiliarity with the technology or other barriers.

The emerging clinical data suggests that a percentage of COVID-19 patients experience respiratory failure and some may have cardiac involvement. Patients that require endotracheal intubation have unfavorable prognosis, and the survivors among those typically experience prolonged mechanical ventilation time. Importantly, the intermediate and long-term consequences of COVID-19 infection, especially in patients with moderate to severe disease, are largely unknown. One could speculate that the recovered patients will need close clinical follow-up
to detect and manage adverse respiratory and cardiac consequences of the infection.

Health care workers face enormous challenges during the pandemic. They work in a stressful environment in a situation when the increased need for acute care is exacerbated by an unacceptable lack of protective equipment, unreliable guidance on infection prevention strategies, and widespread lack of testing. In addition, emerging reports indicate providers contracting the virus and even dying from COVID-19 infection. In a country where providers experienced high rates of burnout even in the pre-COVID era, the intermediate-term consequences can become devastating.

Anticipation creates a window of opportunity to respond to health care challenges. Public health officials are busy dealing with the immediate consequences of COVID-19 infection, but they should be aware: the “second wave” that can put another significant strain on the health care system is coming!

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