Post-valvular surgery multi-vessel coronary artery spasm — A literature review

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1. Introduction

Coronary artery spasm (CAS) refers to the spontaneous or stimuli-induced transient, often localized and intense subtotal or total constriction/occlusion of the epicardial coronary artery, usually concomitant with angina pectoris, with associated elevation of the ST segment on electrocardiogram (ECG). Postoperative, or more specifically, post-valvular surgery CAS is a multi-factorial, infrequent but lethal complication of open heart surgery, with documented implication in perioperative cases of angina pectoris, acute myocardial infarction and their associated hemodynamic instability [1,2].

With a multi-factorial mechanistic underlining, there is no universal prophylactic or definitive treatment, thus the adoption of diverse therapeutic approaches in preventing and/or alleviating post-valvular surgery CAS, including cardiorespiratory inotrope support, intracoronary or intravenous administration of nitrates, non-steroidal anti-inflammatory drugs, calcium pump blockers, phosphodiesterase inhibitors and adenosine triphosphate (ATP), as well as initiation of intra-aortic balloon pump (IABP) [2–5].

In the light of the undefined incidence of post-valvular surgery CAS, its critical role in the pathogenesis of perioperative coronary artery disease (CAD), or so called ischemic heart disease (IHD), and post-valvular surgery mortality, as well as the dearth of a documented globally-consensual therapy guideline, we herein review current literature on this subject (Table 1) and report a clinical case of multi-vessel CAS after aortic valve replacement in our facility.

2. Case report

A 77-year-old man, known tobacco smoker with a history of hypertension, aortic aneurysm of unspecified site without mention of rupture, severe aortic valve insufficiency and coronary atherosclerosis of the native coronary artery, underwent replacement of the ascending aorta, aortic valve annuloplasty with reconstruction of the sinotubular junction (Florida sleeve technique) and coronary artery vein graft on obtuse marginal branch at our facility. Preoperative coronary angiography showed no normal lesions (Fig. 1). There was intraoperative confirmation that the aortic valve and the free tricuspid edges were not thickened with fibro-calcified lesions. Aortic root remodelling plus myocardial revascularization was successfully performed. Immediate postoperative period in the critical care unit was uneventful with the patient showing regular sinus rhythm, no ischemic changes with good left ventricular contractility (Fig. 2).

Several hours later, in the night of the postoperative day 1 (1PO), the intensive care unit critical (ICU) ECG alarm was triggered. ECG findings included a recurring transient 2.5 mm ST segment elevation in the anterior leads V3, V4 with similar elevation in the inferior leads II, III, aVF (Fig. 3) which initially was non-responsive to intravenous vasodilators therapy. In addition, there was hemodynamic instability but no ventricular arrhythmia, prompting the diagnosis of postoperative vasospastic syndrome. We noted however that patient presented with no excruciating chest pain with progressive dyspnoea, as is classically
expected, nor did patient allude to previous occurrence of similar chest symptom.

Laboratory findings were deranged: elevated C-reactive protein (16.14 mg/L), and urea (30 mg/dL), with low hemoglobin (10.4 g/dL) and platelet (120 × 10^9/L).

Emergent coronary angiography to probe the cause of the hemodynamic instability confirmed the diagnosis of early post-valvular surgery multi-vessel CAS, showing over 90% spasmic occlusion of the diagonal (D1, D2) branches of the left anterior descending (LAD) artery, and marginal branches (M1, M2, M3) of the circumflex (Cx) artery (Fig. 4).

However, elevated ST segment returned to baseline (Fig. 5) and CAS progressively resolved, after infusion of intracoronary nitroglycerin infusion (Fig. 6). Recovery was uneventful thereafter, and the patient was discharged on the postoperative day 8.

3. Methods

3.1. Literature search

The PubMed database was queried for publications related to the use of the post-valvular surgery CAS. Search was limited to human subjects

| No. | Author(s) Year | Diagnosis | Study type | Note |
|-----|----------------|-----------|------------|------|
| 1   | Alizadeh-Ghavidel A, et al. 2015 | CAS following aortic valve replacement | Case report | Focal RCA lesion, relieved by intracoronary nitrates infusion |
| 2   | Pragliola C, et al. 2015 | CAS after mitral valve replacement | Case report | Focal RCA lesion, intracoronary injection of nitrates |
| 3   | Anselmi A, et al. 2013 | CAS after tricuspid valve surgery | Case report | Diffuse CAS, intracoronary injection of nitrates |
| 4   | Tseng SS, et al. 2012 | Bead-like CAS | Imaging | Diffuse CAS, treated with nitrates and aspirin |
| 5   | Casquero E, et al. 2009 | CAS after mitral and tricuspid annuloplasty | Imaging | Diffuse CAS, stabilized with intracoronary nitroglycerine and IABP |
| 6   | Pinho T, et al. 2007 | CAS following aortic valve replacement | Case report | Focal RCA lesion, relieved with intracoronary administration of isosorbide dinitrate, removal of pericardial drainage tube, and IABP |
| 7   | Pragliola C, et al. 2007 | CAS after aortic valve replacement | Case report | Diffuse CAS, resolved with intracoronary infusion of nitrates and verapamil |
| 8   | Song MH, et al. 2006 | Refractory CAS after aortic valve replacement | Case report | Multifocal RCA lesion, refractory to intracoronary infusion of nitrates and calcium antagonists, resolved fully after ATP injection. |
| 9   | Minato N, et al. 1995 | Perioperative CAS in modified Bentall's operation for annulo-aortic ectasia in Marfan's syndrome | Case report | Diffuse CAS, refractory to nitrates infusion, resolved by nicardipine (a calcium antagonist) |
| 10  | Tsuchida K, et al. 1993 | CAS after aortic valve replacement | Case report | Diffuse CAS, refractory to intracoronary administration of isosorbide dinitrate, nitroglycerin, diltiazem methylprednisolone, papaverine, lidocaine, and nifedipine through the nasogastric tube. Treated with inotropic agents, coronary vasodilators, IABP, and deep sedation with pentobarbital. |
| 11  | Kinoshita K, et al. 1991 | Perioperative CAS | Retrospective cohort study | Diverse. 1 died, 4 others responded to intravenous administration of nitroglycerin and diltiazem ± IABP |

Fig. 1. Preoperative coronary angiography showed narrowing lesion on first obtuse marginal branch of circumflex artery.
and with an open time-frame. The initial search was conducted by entering the keywords: “coronary artery spasm,” “postoperative,” and “valve” using the Boolean operator “or” and ‘and’, then the final output was reviewed for relevant English language publications. (Table 1).

Summarily the search detail was — (“coronary vasospasm”[MeSH Terms] OR (“coronary”[All Fields] AND “vasospasm”[All Fields]) OR “coronary vasospasm”[All Fields] OR (“coronary”[All Fields] AND “artery”[All Fields] AND “spasm”[All Fields]) OR “coronary artery spasm”[All Fields]) AND (“postoperative period”[MeSH Terms] OR (“postoperative”[All Fields] AND “period”[All Fields]) OR “postoperative period”[All Fields] OR “postoperative”[All Fields]) AND valve[All Fields].

4. Review of literature and comment

As alluded above, Post-valvular surgery CAS refers to the stimuli-induced transient, subtotal constriction or total occlusion of some branches of, or the entire coronary artery tree, often concomitant with angina pectoris, with associated alteration of the ST segment on electrocardiogram (ECG) and resulting in fetal clinical outcomes, if not adequately managed.

In this present report, through meticulous medical history review, laboratory tests, physical examination, ECG and coronary angiography, we promptly diagnosed and treated the patient’s condition. In the context of the reported clinical case, we herein review the current literature for the clinical presentation, etiology, pathophysiology, epidemiology, diagnosis, therapy and prognosis of post-valvular surgery CAS.

4.1. Clinical presentation

Connate to the generic vasospasmic crisis, a characteristic feature of post-valvular surgery CAS is episodes of sudden severe rest angina pectoris associated with ST-segment variation and usually responsive to nitrate infusion. We deliberately use the term ST-segment variation — elevation or depression, and not elevation as noted in our case report and is commonly used in classical teachings or texts [6].

ST-segment variation depends on two principal factors, amongst others, namely, the extent of occlusion and the resultant impact of

Fig. 2. Immediate postoperative ECG showing regular sinus rhythm, no ischemic changes with good left ventricular contractility.

Fig. 3. ECG strip showing transient a 2 mm ST segment elevation in the anterior leads V3, V4 with similar elevation in the inferior leads II, III, aVF.
restricted or severed blood flow to the myocardial layers. Where induced occlusion is total or near-total and sustained, there is transmural ischemia, then occurrence of angina pectoris is accompanied by electrocardiographic elevation of the ST-segment. However, for partial/subtotal occlusion or patent collateral supply, as is the case with many CAS, ischemia is subendocardial or non-transmural and angina is associated with ST-segment depression. This dynamic ST-segment — associated angina is often with diaphoresis, syncope, nausea and/or vomiting [7]. Electrocardiographic alterations during CAS [8,9] are summarized below in Table 2.

Post-valvular surgery CAS, similar to CAS of other etiologies, has been implicated as a common cause of variant angina [2–4,10–14]. This CAS-related angina or chest pain occurs usually at rest, free from exertion and most often late in the night [7,9,10]. This biopattern is commonly referred to as the circadian variation and may not be unrelated to the cyclic day-night variation in the tone of the epicardial coronary artery — increased tone in the night/dawn, and decrease in the day [15].

The occurrence of syncopes is not rare during CAS ischaemic episodes [16]. These syncopes have been associated with severe

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Fig. 4. Emergent coronary angiogram showing spasmic occlusion of the diagonal branches (D1) of the left anterior descending (LAD) artery and marginal branches (OM3) of the circumflex artery (Cx).

Fig. 5. ECG strip showing ST segment returned to baseline.
cardiac arrhythmias such as ventricular tachycardia or fibrillation, bradyarrhythmias, as well as atrioventricular block [17].

It is opined that a functional association exist between spasmic vessel and type of arrhythmia. While left CAS is associated with ventricular arrhythmias and elevation of the ST segment in the anterior leads V3 and V4, right CAS is notably associated with bradyarrhythmic cases with acute ST-segment elevation in the inferior leads II, III, and aVF [18].

Though the predispository mechanistic underlying still remains unclear, there is documented association of cardiac arrhythmias with CAS [8,19–21]. Amongst others, ventricular arrhythmia is the most common CAS complication with sudden cardiac arrest and resultant death [20–21]. Mechanistically, prolongation of the QT duration with is common in syncope- or cardiac arrest-complicated variant angina [16] may be suggestive of impaired ventricular repolarization and invariably, an increased predisposition to malignant cardiac arrhythmias.

4.2. Etiology & pathophysiology

As alluded to earlier, unravelling the underlying mechanism in the causation of post-valvular surgery CAS is an ongoing process, especially with the accumulating documentation of identified triggering factors, including endothelial dysfunction, increased oxidative stress and autonomic tone, coronary smooth muscle calcium hypersensitivity, magnesium insufficiency, chronic low-grade inflammation, respiratory alkalosis and genetic susceptibility [reviewed in [7,22]].

Fig. 6. Coronary spasm resolution after nitroglycerin coronary infusion. Diagonal branches (D1) of the left anterior descending (LAD) artery and marginal branches (OM3) of the circumflex artery (Cx).

Table 2

| Electrocardiographic alterations during CAS. |
|--------------------------------------------|
| Q wave | R wave | S wave | T wave | ST segment | U wave |
|------|--------|--------|--------|------------|--------|
| ↑P    | +      | +      | ±      | ±          | ±      |
| ↓P    | −      | −      | −      | −          | −      |

Notes: A transient Q wave may appear during vasospasmic attack. A time-lag in the peaking of R results in R-T fusion and S wave loss/decrease. Tall and peaked T wave is indicative of a subendocardial ischemia. Direction depends on extent of occlusion. Accompanied by reciprocal dynamic in opposite leads. Noted at the commencement or weaning of the vasospasmic attack. Often the only electrocardiographic signs in mild subtotal occlusion.

Abbreviations: ↑ = elevation, peaking; ↓ = depression; + = present; − = absent.
4.3. Diagnosis

Until recently, the diagnostic holy grail for CAS, including post-valvular surgery CAS, is demonstrated constriction (≥50%) at the site of vessel spasm, responsive to and reversed by intracoronary infusion of nitroglycerin [23].

In most cases, clinical diagnosis is reached based on the classical triad of recurrent episodes of rest pain with associated ST-segment alteration and symptomatic response to nitrates and/or calcium channel blockers [6].

The occurrence of postoperative coronary artery embolism (CAE) is not a complete rarity after valvular surgery [24]. This is often secondary to aortic cross-clamp removal, mechanical thrombectomy or decalcification of fibro-calcified valves; while the first may resolve spontaneously with or without specific treatment; the latter two may myocardial revascularisation for reperfusion of affected sites. CAE should be ruled out when the diagnosis of post-valvular surgery CAS is in consideration.

Though controversial in clinical practice [25,26], in some patients, a ‘spasm provocation test’ using stimuli like histamine, serotonin, acetylcholine, and ergonovine, or even hyperventilation are used to elicit spasm [27–29] and confirm the clinical diagnosis of CAS.

Induced constriction less than 30% is considered normal vascular response, however, vasoconstriction of at least 50% at the spasmonic site that is reversible with intracoronary nitroglycerin is considered a positive result [23].

It should however be mentioned that the Coronary Vasomotion Disorders International Study Group (COVADIS) after their first symposium held in September, 2013 to create a standardized international diagnostic criteria for vasospastic angina, recommended that CAS be ‘defined as transient or subtotal coronary artery occlusion (>50% constriction) with angina and ischemic ECG changes either spontaneously or in response to a provocative stimulus (typically acetylcholine, ergot, or hyperventilation)’ [30]. According to COVADIS, a spasm provocation test for CAS should be considered equivocal if it does not reproduce the usual chest pain, elicit ischemic ECG changes, and induce at least 90% vasoconstriction on angiography. The emphasis being laid on 90% vasoconstriction, compared to the classical 50% vasoconstriction. The consensus was that 90% vasoconstriction is the angiographic threshold to diagnose inducible spasm. This consensus was based on validation studies demonstrating significantly high sensitivity and specificity (≥90%) for both ergonovine and acetylcholine in the diagnosis of spontaneous vasospasmic angina.

4.4. Epidemiology

There is a dearth of a standardized evidence-based global CAS incidence and prevalence statistics, thus most reports are population-specific, and highly dependent on the diagnostic criteria.

Compared to the CAS prevalence in the United States, France and Taiwan of about 4%, 12%, and 19% respectively [31–33], the prevalence of CAS is significantly high (approximately 30%) in Japan [34,35], with a large proportion being diffuse or multivessel spasm [36]. In addition, there is divergent gender and age preponderance [37–39].

4.5. Therapy

Optimal therapeutic strategy for postoperative CAS continues to evolve. Currently, the therapeutic agents of choice with demonstrated efficacy for CAS are long-acting nitrates and calcium channel blockers [2–4,40–42]. Of the 11 post-valvular surgery CAS reports reviewed, only in 2 reports were nitrates and/or calcium pump blockers found to be ineffective (Table 1). Calcium channel blockers such as diltiazem, nifedipine, verapamil, and amiodipine, either alone or in combination with nitrates, effectively ameliorate coronary vasospasmic and angina attack. Most spontaneous acute CAS crisis are usually responsive to sublingual or intravenous administration of isosorbide dinitrate or nitroglycerin, however in cases as presented in our case report, where CAS is refractory to sublingual or intravenous injection of either drugs, intracoronary infusion proves effective. The general therapeutic trend as noted in all 11 post-valvular surgery reports reviewed is avoidance of non-selective β-blockers because of their ambivalent, or better put, case-dependent effect; being beneficial in atherosclerosis-associated CAS, but detrimental in other cases, wherein via blockage of β-adrenergic receptors, they initially mediate vasodilation, then enhance unrestricted intravascular calcium influx, and consequently result in increased vasoconstriction via activation of the α-adrenergic receptors, thus, exacerbating the CAS crisis [43,44].

There is accumulating evidence of the beneficial effect of magnesium, an endogenous inhibitor of calcium-entry [45], antioxidants such as vitamin C and E [46,47], fasudil, a selective rho-kinase inhibitor [48,49], and fluvastatin, a 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor [50] on the resolution of CAS.

4.6. Prognosis

Post-therapy immediate or early clinical outcome and long-term prognosis is generally good [51,52], with a relatively low incidence of CAS-related cardiac mortality and disease recurrence rate [53,39]. In the context of post-valvular surgery CAS, of the total number of patients (n = 16) reported in the 12 reviewed case reports, only a relatively minority 6% (n = 1) mortality due to left ventricular free wall rupture sequel to direct cardiac massage was recorded (Table 1). Despite reported higher CAS prevalence, the clinical outcome amongst Japanese patients is better compared to that of their western counterparts, and this may not be unconnected to the initiation of at least one calcium antagonist as first line therapy in a higher percentage of the Japanese cohort than in the western cohort [51,52]. Cardiac events such as coronary artery disease and acute myocardial infarction, as well as multiplicity of vessel lesion play critical role in patient survival [51]. In addition, diminished left ventricular ejection fraction (LVEF) has been implicated in poorer clinical outcome and is a predictor of coronary events and all-cause mortality [53].

In conclusion, this study while showcasing the progress made in our generic understanding of CAS, however highlights the need for internationally standardized diagnostic guideline and therapeutic protocol, as well as continued research of the mechanistic basis of CAS as a pathophysiological event.

Consent

Written informed consent was obtained from the patient for publication of this case report. A copy of the written consent is available for review by the Editor of this journal. The procedures followed were in accordance with the ethical standards of the Helsinki Declaration (1964, amended most recently in 2008) of the World Medical Association.

Authors’ contributions

FF – conception of study, as well as participated in manuscript drafting.
OAB – conceived the study, literature review, interpretation of clinical data and draft the manuscript.
SM – acquisition of clinical data.
FF, GP – final approval of the study and manuscript was done. All authors read and approved the final manuscript.

Conflicts of interest

The authors declare no conflict of interest.
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