CrossMark

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

Francesco Formica [a,d,*,1], Oluwaseun Adebayo Bamodu [b,c,d,1], Serena Mariani [a], Giovanni Paolini [a,d]

[a] Cardiac Surgery Unit, San Gerardo Hospital, Department of Medicine and Surgery, School of Medicine, University of Milano-Bicocca, Monza, Italy
[b] Graduate Institute of Clinical Medicine, College of Medicine, Taipei Medical University, Taipei City, Taiwan
[c] Department of Medical Research & Education, Taipei Medical University-Shuang Ho Hospital, New Taipei City, Taiwan
[d] The Masters Level II Program in Cardiac Surgery, Cardiac Anesthesia and Cardiology, University of Milano-Bicocca, Monza, Italy

## ARTICLE INFO

## ABSTRACT

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).
In this article, we present a literature review on post-valvular surgery CAS and report the clinical case of a 77 year-old man who experienced severe early post-aortic surgery chest pain and hemodynamic instability. Emergent coronary angiography revealed severe occlusion of multiple branches of both coronary arteries. The CAS was alleviated with intracoronary infusion of nitroglycerin.

## 1. Introduction

Coronary artery spasm (CAS) refers to the spontaneous or stimuli-induced transient, often localized and intense subtotal constriction or total occlusion of the epicardial coronary artery, often concomitant with *angina pectoris* with resultant ST segment alteration on the 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 abnormal 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 vasospasmic syndrome. We noted however that patient presented with no excruciating chest pain with progressive dyspnoea, as is classically

* Corresponding author at: Università di Milano-Bicocca, Clinica Cardiochirurgica, A.O. San Gerardo, Via Pergolesi 33, 20900 Monza, Italy.
E-mail address: francesco_formica@fastwebnet.it (F. Formica).
[1] First authorship.

**Table 1**
Review of current English language literature on post-valvular surgery coronary artery spasm.

| 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 | Tzeng 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 | 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 |

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 ($120 \times 10^9$/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
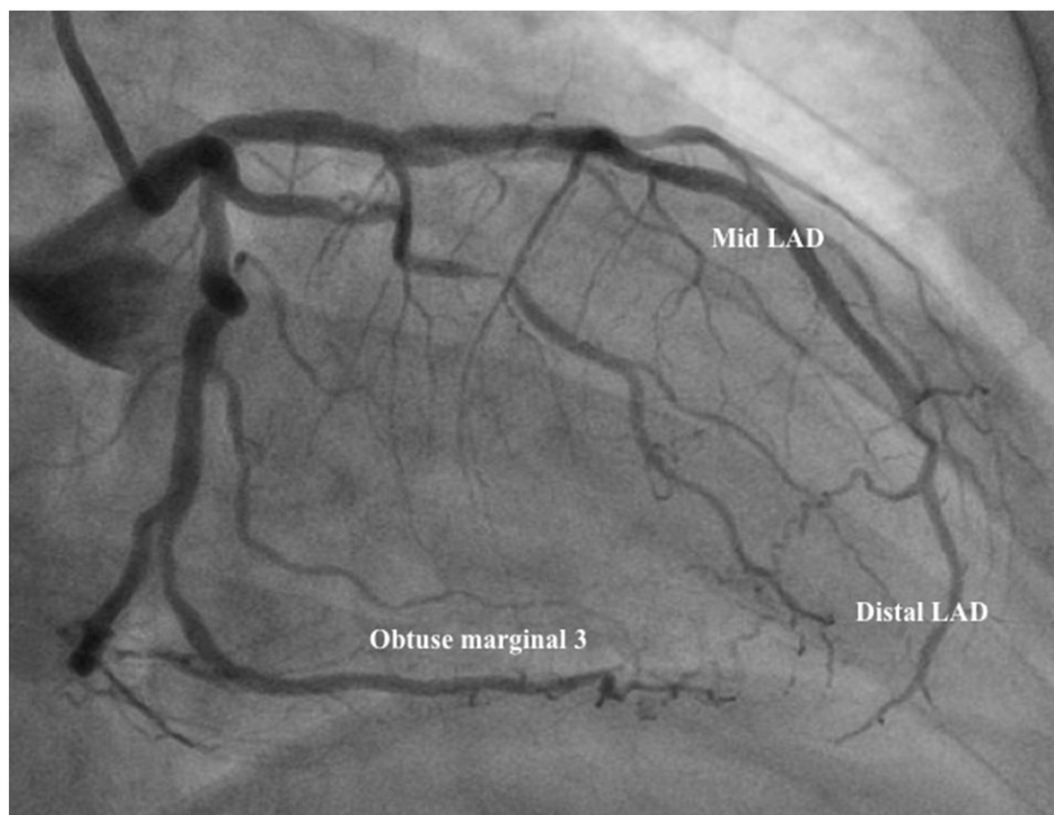


**Fig. 1.** Preoperative coronary angiography showed narrowing lesion on first obtuse marginal branch of circumflex artery.
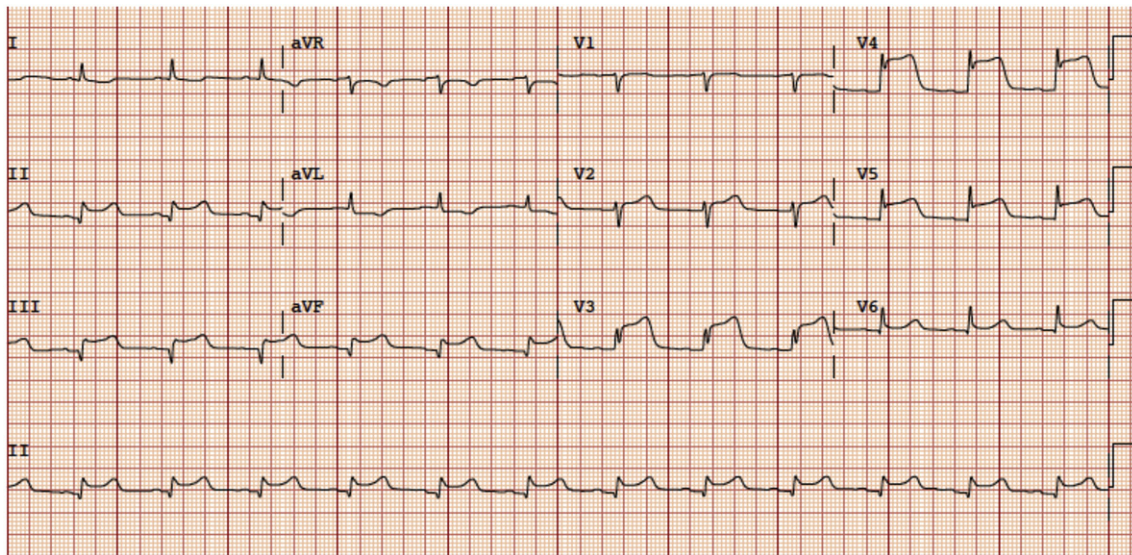
**Fig. 2.** Immediate postoperative ECG showing regular sinus rhythm, no ischemic changes with good left ventricular contractility.

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
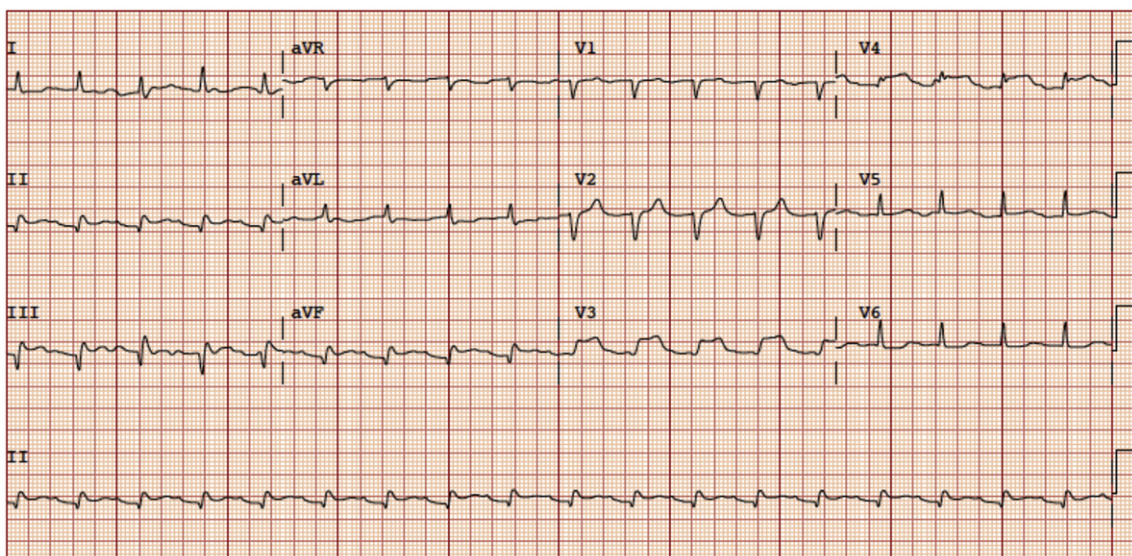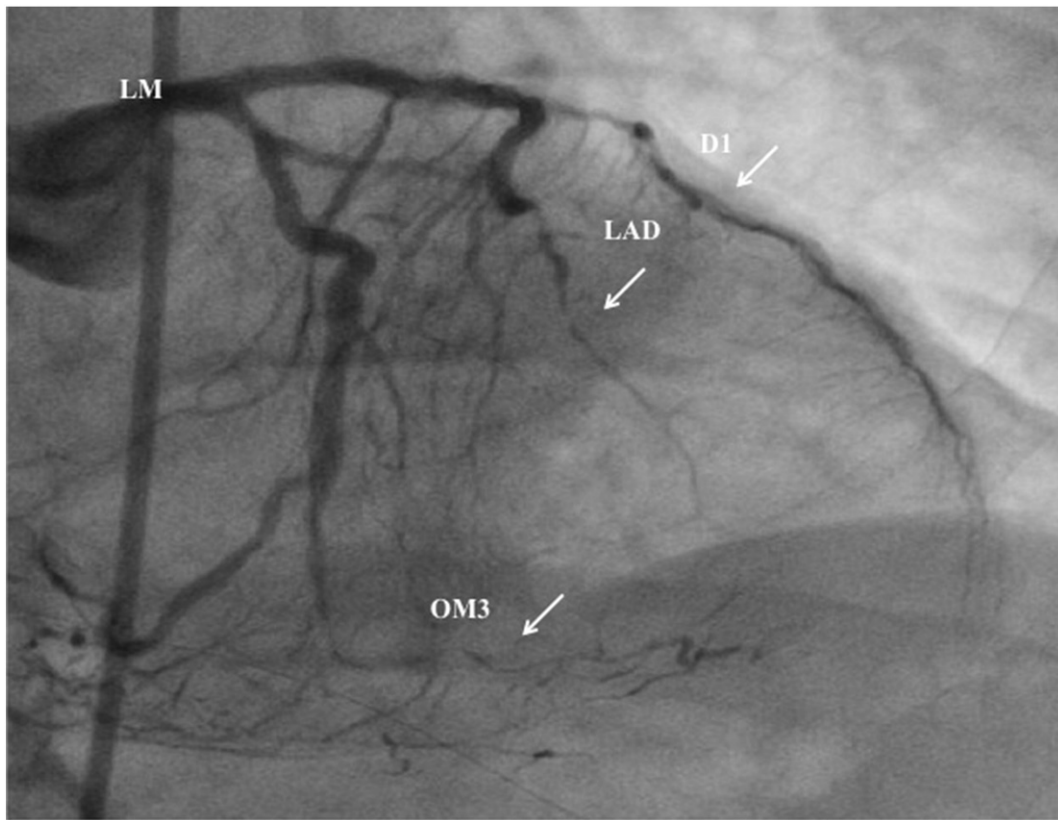


**Fig. 3.** ECG strip showing transient a 2 mm ST segment elevation in the anterior leads V3, V4 with similar elevation in the inferior leads II, III, aVF.
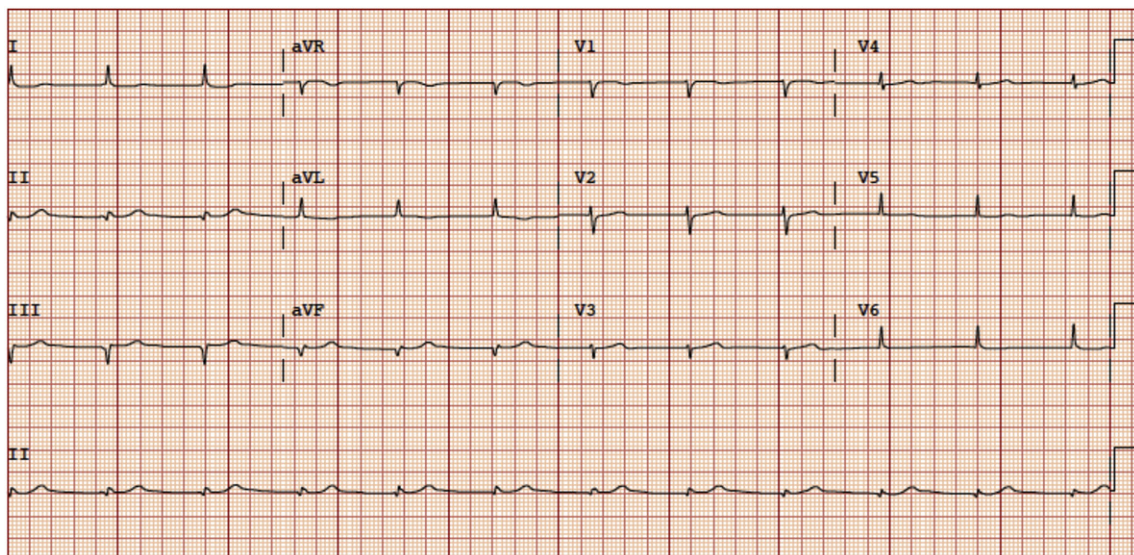
**Fig. 4.** Emergent coronary angiogram showing spasmic occlusion of the diagonal branches (D1) of the left anterior descending (LAD) artery and marginal branches (OM3) of the circumflex artery (Cx).

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 electro-cardiographic 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]. Electro-cardiographic 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 a*ngina* 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 ischeamic episodes [16]. These syncopes have been associated with severe



**Fig. 5.** ECG strip showing ST segment returned to baseline.
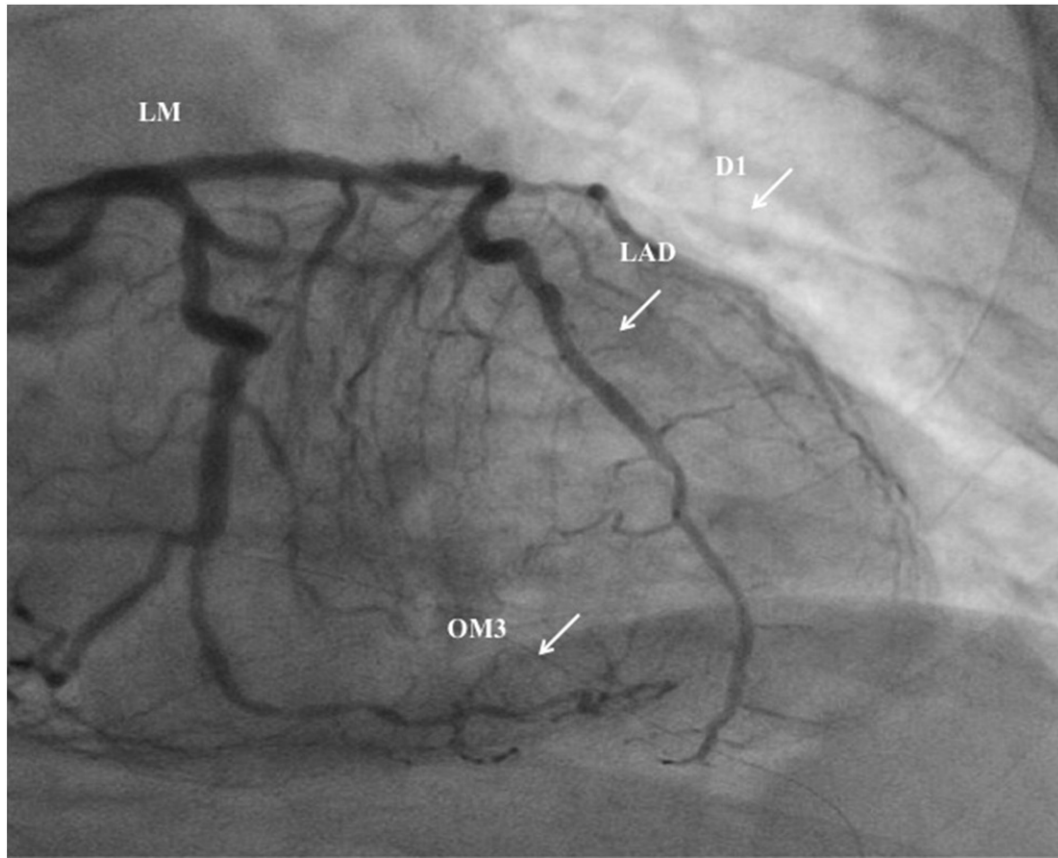
**Fig. 6.** Coronary spasm resolution after nitroglycerin coronary infusion. Diagonal branches (D1) of the left anterior descending (LAD) artery and marginal branches (OM3) of the circumflex artery (Cx).

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 notedly 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]].

**Table 2**
Electrocardiographic alterations during CAS.

| ↑ | P wave | Q wave | QRS complex | R wave | S wave | T wave | ST segment | U wave |
|---|---|---|---|---|---|---|---|---|
| | | | | + | | + | ± | |
| ↓ | | | | − | | − | ± | + |
| 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 sign 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 spasmic 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 total or subtotal coronary artery occlusion (> 90% 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 amlodipine, 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 excitement 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 minute 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 pathophysiologic 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.

## Acknowledgements

## References

[1] L.R. Guo, M.L. Myers, E.L. Kuntz, Coronary artery spasm: a rare but important cause of postoperative myocardial infarction, Ann. Thorac. Surg. 86 (3) (2008) 994–995, http://dx.doi.org/10.1016/j.athoracsur.2008.02.094.

[2] C. Pragliola, M. Gaudino, P. Farina, M. Massetti, Postoperative coronary artery spasm after mitral valve replacement, Int. J. Surg. Case Rep. 8 (2015) 185–188, http://dx.doi.org/10.1016/j.ijscr.2015.01.049.

[3] A. Anselmi, H. Corbineau, D. Boulmier, V.G. Ruggieri, Early diffuse coronary artery spasm after heart valve surgery in the carcinoid syndrome, J. Card. Surg. 28 (4) (2013) 402–403, http://dx.doi.org/10.1111/jocs.12138.

[4] S.S. Tzeng, J.T. Liou, Bead-like coronary spasm, Intern. Med. J. 42 (3) (2012) 340–341, http://dx.doi.org/10.1111/j.1445-5994.2012.02715.x.

[5] M.H. Song, K. Sakurai, T. Nakayama, M. Shirakawa, H. Hagiwara, H. Kamiya, Intracoronary adenosine triphosphate for refractory coronary artery spasm, Asian Cardiovasc. Thorac. Ann. 14 (2) (April 2006) e21–e23, http://dx.doi.org/10.1177/021849230601400226.

[6] A. Prasad, Cardiology, in: R.D. Ficalora (Ed.), Mayo Clinic Internal Medicine Board Review, 10th editionOxford University Press, New York, NY 2013, pp. 80–97.

[7] H. Yasue, K. Kugiyama, Coronary spasm: clinical features and pathogenesis, Intern. Med. 36 (1997) 760–765.

[8] H. Onaka, Y. Hirota, S. Shimada, et al., Clinical observation of spontaneous anginal attacks and multivessel spasm in variant angina pectoris with normal coronary arteries: evaluation by 24-hour 12-lead electrocardiography with computer analysis, J. Am. Coll. Cardiol. 27 (1996) 38e44.

[9] A. Bayes de Luna, M. Fiol-Sala, in: G. Almond (Ed.), Electrocardiography in Ischemic Heart Disease: Clinical and Imaging Correlations and Prognostic Implications, Blackwell Publishing, Inc., Massachusetts 2008, pp. 80–97 (Chapter 8).

[10] M. Prinzmetal, R. Kennamer, R. Merlis, T. Wada, N. Bor, Angina pectoris. 1. A variant form of angina pectoris, Am. J. Med. 27 (1959) 375–388.

[11] P.B. Oliva, D.E. Pottsm, Pluss RG coronary arterial spasm in Prinzmetal angina: documentation by coronary arteriography, N. Engl. J. Med. 288 (1973) 745–750.

[12] G.G. Gensini, S. Di Giorgi, S. Murad-Netto, Black A arteriographic demonstration of coronary artery spasm and its release after the use of a vasodilator in a case of angina pectoris and in the experimental animal, Angiology 13 (1962) 550–553.

[13] A. Maseri, A. L'Abbate, G. Baroldi, S. Chierchia, M. Marzilli, A.M. Ballestra, et al., Coronary vasospasm as a possible cause of myocardial infarction. A conclusion derived from the study of "preinfarction" angina, N. Engl. J. Med. 299 (1978) 1271–1277.

[14] A. Maseri, S. Severi, M.D. Nes, A. L'Abbate, S. Chierchia, M. Marzilli, et al., "Variant" angina: one aspect of a continuous spectrum of vasospastic myocardial ischemia. Pathogenetic mechanisms, estimated incidence and clinical and coronary arteriographic findings in 138 patients, Am. J. Cardiol. 42 (1978) 1019–1035.

[15] H. Yasue, S. Omote, A. Takizawa, A. Takizawa, M. Nagao, K. Miwa, et al., Circadian variation of exercise capacity in patients with Prinzmetal's variant angina: role of exercise-induced coronary arterial spasm, Circulation 59 (1979) 938–948.

[16] N. Parchure, V. Batchvarov, M. Malik, et al., Increased QT dispersion in patients with Prinzmetal's variant angina and cardiac arrest, Cardiovasc. Res. 50 (2001) 379e85.

[17] H. Kishida, Y. Tada, N. Fukuma, et al., Significant characteristics of variant angina patients with associated syncope, Jpn. Heart J. 37 (1996) 317–326.

[18] A. Ledakowicz-Polak, P. Ptaszynski, L. Polak, et al., Prinzmetal's variant angina associated with severe heart rhythm disturbances and syncope: a therapeutic dilemma, Cardiol. J. 16 (2009) 269e72.

[19] N. Chalfoun, F. Morady, A. Chugh, et al., Painless coronary spasm causing recurrent ventricular tachycardia, Heart Rhythm. 4 (2007) 1471e2.

[20] I. Crozier, D. Stewart, H. Ikram, Sudden death due to painless spasm in near normal coronary arteries, Aust. NZ J. Med. 16 (1986) 64e5.

[21] R.J. Myerburg, K.M. Kessler, S.M. Mallon, et al., Life-threatening ventricular arrhythmias in patients with silent myocardial ischemia due to coronary artery spasm, N. Engl. J. Med. 326 (1992) 1451e5.

[22] G.A. Lanza, G. Careri, F. Crea, Contemporary reviews in cardiovascular medicine: mechanisms of coronary artery spasm, Circulation 124 (2011) 1774–1782, http://dx.doi.org/10.1161/CIRCULATIONAHA.111.037283.

[23] P.J. Scanlon, D.P. Faxon, A.M. Audet, B. Carabello, G.J. Dehmer, K.A. Eagle, et al., ACC/AHA guidelines for coronary angiography. A report of the American College of Cardiology/American Heart Association Task Force on practice guidelines (Committee on Coronary Angiography). Developed in collaboration with the Society for Cardiac Angiography and Interventions, J. Am. Coll. Cardiol. 33 (6) (1999) 1756–1824.

[24] O.H. Kwok, C. Rogers, Coronary artery embolism complicating heart valve surgery: role of mechanical thrombectomy, Heart 86 (2001) 288.

[25] K.K. Hamilton, C.J. Pepine, A renaissance of provocative testing for coronary spasm? J. Am. Coll. Cardiol. 35 (7) (2000) 1857–1859.

[26] D. Adlam, T. Azeem, T. Ali, A. Gershlick, Is there a role for provocation testing to diagnose coronary artery spasm? Int. J. Cardiol. 102 (1) (2005) 1–7 (52).

[27] J.C. Kaski, F. Crea, D. Meran, L. Rodriguez, L. Araujo, S. Chierchia, et al., Local coronary supersensitivity to diverse vasoconstrictive stimuli in patients with variant angina, Circulation 74 (6) (1986) 1255–1265.

[28] S. Sueda, H. Kohno, H. Fukuda, N. Ochi, H. Kawada, Y. Hayashi, et al., Clinical impact of selective spasm provocation tests: comparisons between acetylcholine and ergonovine in 1508 examinations, Coron. Artery Dis. 15 (8) (2004) 491–497.

[29] K. Nakao, M. Ohgushi, M. Yoshimura, K. Morooka, H. Okumura, H. Ogawa, et al., Hyperventilation as a specific test for diagnosis of coronary artery spasm, Am. J. Cardiol. 80 (5) (1997) 545–549.

[30] Beltrame JF, Crea F, Kaski JC, Ogawa H, Ong P, Sechtem U, et al., On Behalf of the Coronary Vasomotion Disorders International Study Group (COVADIS): International Standardization of diagnostic criteria for vasospastic angina. Eur. Heart J. http://dx.doi.org/10.1093/eurheartj/ehv351.

[31] M.B. Harding, M.E. Leithe, D.B. Mark, C.L. Nelson, J.K. Harrison, J.B. Hermiller, et al., Ergonovine maleate testing during cardiac catheterization: a 10-year perspective in 3,447 patients without significant coronary artery disease or Prinzmetal's variant angina, J. Am. Coll. Cardiol. 20 (1) (Jul. 1992) 107–111.

[32] M.E. Bertrand, J.M. LaBlanche, P.Y. Tilmant, F.A. Thieuleux, M.R. Delforge, A.G. Carre, et al., Frequency of provoked coronary arterial spasm in 1089 consecutive patients undergoing coronary arteriography, Circulation 65 (7) (Jun. 1982) 1299–1306.

[33] J.F. Beltrame, S. Sasayama, A. Maseri, Racial heterogeneity in coronary artery vasomotor reactivity: differences between Japanese and Caucasian patients, J. Am. Coll. Cardiol. 33 (6) (1999) 1442–1452.

[34] S. Sueda, H. Kohno, H. Fukuda, N. Ochi, H. Kawada, Y. Hayashi, et al., Frequency of provoked coronary spasms in patients undergoing coronary arteriography using a spasm provocation test via intracoronary administration of ergonovine, Angiology 55 (4) (Jul.-Aug. 2004) 403–411.

[35] S. Sueda, H. Kohno, A. Oshita, H. Fukuda, T. Kondou, K. Yano, et al., Coronary abnormal response has increased in Japanese patients: analysis of 17 years' spasm provocation tests in 2093 cases, J. Cardiol. 55 (3) (May 2010) 354–361.

[36] C. Pristipino, J.F. Beltrame, M.L. Finocchiaro, R. Hattori, M. Fujita, R. Mongiardo, et al., Major racial differences in coronary constrictor response between Japanese and Caucasians with recent myocardial infarction, Circulation 101 (10) (2000) 1102–1108.

[37] M.Y. Hung, K.H. Hsu, M.J. Hung, C.W. Cheng, W.J. Cherng, Interactions among gender, age, hypertension and C-reactive protein in coronary vasospasm, Eur. J. Clin. Investig. 40 (2010) 1094–1103.

[38] R. Seung-Woon, Y.P. Ji, K.R. Sung, et al., TCT-437 the impact of gender difference on angiographic characteristics during intracoronary acetylcholine provocation test in Korean patients, J. Am. Coll. Cardiol. 60 (12_S) (2012)http://dx.doi.org/10.1016/j.jacc.2012.08.467.

[39] M. Bory, F. Pierron, D. Panagides, J.L. Bonnet, S. Yvorra, L. Desfossez, Coronary artery spasm in patients with normal or near normal coronary arteries. Long-term follow-up of 277 patients, Eur. Heart J. 17 (7) (1996) 1015–1021.

[40] S.B. Freedman, D.R. Richmond, D.T. Kelly, Long-term follow-up of verapamil and nitrate treatment for coronary artery spasm, Am. J. Cardiol. 50 (4) (1982) 711–715.

[41] S.H. Taylor, Usefulness of amlodipine for angina pectoris, Am. J. Cardiol. 73 (3) (Jan 27 1994) 28A–33A.

[42] E. Kimura, H. Kishida, Treatment of variant angina with drugs: a survey of 11 cardiology institutes in Japan, Circulation 3 (1981) 844e8.

[43] P.D. Turlapaty, B.M. Altura, Propranolol induces contractions of canine small and large coronary arteries, Basic Res. Cardiol. 77 (1) (1982) 68–81.

[44] T.L. Svendsen, Central hemodynamics of beta-adrenoceptor blocking drugs: beta 1 selectivity versus intrinsic sympathomimetic activity, J. Cardiovasc. Pharmacol. 5 (Suppl. 1) (1983) S21–S25.

[45] H. Teragawa, M. Kato, T. Yamagata, H. Matsuura, G. Kajiyama, The preventive effect of magnesium on coronary spasm in patients with vasospastic angina, Chest 118 (2000) 1690–1695.

[46] O. Hirashima, H. Kawano, T. Motoyama, N. Hirai, M. Ohgushi, K. Kugiyama, et al., Improvement of endothelial function and insulin sensitivity with vitamin C in patients with coronary spastic angina: possible role of reactive oxygen species, J. Am. Coll. Cardiol. 35 (7) (2000) 1860–1866.

[47] T. Motoyama, H. Kawano, K. Kugiyama, et al., Vitamin E administration improves impairment of endothelium-dependent vasodilation in patients with coronary spastic angina, J. Am. Coll. Cardiol. 32 (1998) 1672–1679.

[48] A. Masumoto, M. Mohri, H. Shimokawa, L. Urakami, M. Usui, A. Takeshita, Suppression of coronary artery spasm by a Rho-kinase inhibitor fasudil in patients with vasospastic angina, Circulation 105 (2002) 1545–1547.

[49] T. Otsuka, C. Ibuki, T. Suzuki, et al., Administration of the Rho-kinase inhibitor, fasudil, following nitroglycerin additionally dilates the site of coronary spasm in patients with vasospastic angina, Coron. Artery Dis. 19 (2008) 105–110.

[50] H. Yasue, Y. Mizuno, E. Harada, et al., SCAST (Statin and Coronary Artery Spasm Trial) investigators: effects of a 3-hydroxy-3-methylglutaryl coenzyme reductase inhibitor, fluvastatin, on coronary spasm after withdrawal of calcium-channel blockers, J. Am. Coll. Cardiol. 51 (2008) 1742–1748.

[51] A. Walling, D.D. Waters, D.D. Miller, D. Roy, G.B. Pelletier, P. Theroux, Long-term prognosis of patients with variant angina, Circulation 76 (5) (1987) 990–997.

[52] H. Yasue, A. Takizawa, M. Nagao, S. Nishida, M. Horie, J. Kubota, et al., Long-term prognosis for patients with variant angina and influential factors, Circulation 78 (1) (1988) 1–9.

[53] P. Ong, A. Athanasiadis, G. Borgulya, M. Voehringer, Sechtem U.3-year follow-up of patients with coronary artery spasm as cause of acute coronary syndrome. The CASPAR (coronary artery spasm in patients with acute coronary syndrome) study follow-up, J. Am. Coll. Cardiol. 57 (2011) 147–152.