Archives of Cardiovascular Disease (2019) 112, 44—55

Available online at ScienceDirect www.sciencedirect.com

Elsevier Masson France EM|consulte www.em-consulte.com/en

REVIEW

Vasospastic angina: A literature review of current evidence

Angor vasospastique : une revue de la littérature

Fabien Picard[a,b,*], **Neila Sayah**[a], **Vincent Spagnoli**[c], **Julien Adjedj**[d], **Olivier Varenne**[a,b]

[a] *Cardiology department, hôpital Cochin, AP—HP, 75014 Paris, France*
[b] *Faculté de médecine, université Paris Descartes, 75006 Paris, France*
[c] *Cardiology department, centre hospitalier affilié universitaire régional (CHAUR) de Trois-Rivières, QC G8Z 3R9 Tois-Rivières, Canada*
[d] *Cardiology department, centre hospitalier universitaire Vaudois, 1011 Lausanne, Switzerland*

Received 31 May 2018; accepted 6 August 2018
Available online 7 September 2018

KEYWORDS
Vasospastic angina;
Vasospasm;
Prinzmetal;
Variant angina

Summary Vasospastic angina (VSA) is a variant form of angina pectoris, in which angina occurs at rest, with transient electrocardiogram modifications and preserved exercise capacity. VSA can be involved in many clinical scenarios, such as stable angina, sudden cardiac death, acute coronary syndrome, arrhythmia or syncope. Coronary vasospasm is a heterogeneous phenomenon that can occur in patients with or without coronary atherosclerosis, can be focal or diffuse, and can affect epicardial or microvasculature coronary arteries. This disease remains underdiagnosed, and provocative tests are rarely performed. VSA diagnosis involves three considerations: classical clinical manifestations of VSA; documentation of myocardial ischaemia during spontaneous episodes; and demonstration of coronary artery spasm. The gold standard diagnostic approach uses invasive coronary angiography to directly image coronary spasm using acetylcholine, ergonovine or methylergonovine as the provocative stimulus. Lifestyle changes, avoidance of vasospastic agents and pharmacotherapy, such as calcium channel blockers, nitrates, statins, aspirin, alpha1-adrenergic receptor antagonists, rho-kinase inhibitors or nicorandil, could be proposed to patients with VSA. This review discusses the pathophysiology,

Abbreviations: CCB, calcium channel blocker; ESC, European Society of Cardiology; ICD, implantable cardioverter defibrillator; MLC, myosin light chain; NO, nitric oxide; VSA, vasospastic angina; VSMC, vascular smooth muscle cell.

* Corresponding author. Département de cardiologie, hôpital Cochin, 27, rue du Faubourg Saint-Jacques, 75014 Paris, France.
E-mail address: fabien.picard@aphp.fr (F. Picard).

https://doi.org/10.1016/j.acvd.2018.08.002

clinical spectrum and management of VSA for clinicians, as well as diagnostic criteria and the provocative tests available for use by interventional cardiologists.

MOTS CLÉS
Angor vasospastique ;
Vasospasme ;
Prinzmetal ;
Angor

Résumé L'angor vasospastique (AVS) est une variante de l'angine de poitrine où l'angine se produit au repos, avec des modifications transitoires de l'électrocardiogramme et une capacité d'exercice préservée. Il peut être impliqué dans de nombreux scénarios cliniques, tels que l'angor stable, la mort subite, les syndromes coronaires aigus, les arythmies ou la syncope. Le vasospasme coronaire est un phénomène hétérogène qui peut survenir chez les patients avec ou sans athérosclérose coronaire, pouvant être focale ou diffuse, et pouvant affecter les artères coronaires épicardiques ou la microcirculation. Cette pathologie reste sous-diagnostiquée et les tests de provocation rarement pratiqués. Son diagnostic implique trois considérations: les manifestations cliniques classiques de l'AVS; la documentation de l'ischémie myocardique au cours des épisodes spontanés; et la démonstration du spasme de l'artère coronaire. L'approche diagnostique de référence utilise la coronarographie pour visualiser de manière directe le spasme coronaire en utilisant acétylcholine, ergonovine ou méthylergonovine comme stimulus provocateur. La modification du mode de vie, l'arrêt d'éventuels agents vasospastiques et la pharmacothérapie, tels que les inhibiteurs calciques, les dérivés nitrés, les statines, l'aspirine, les antagonistes des récepteurs alpha1-adrénergiques, les inhibiteurs de rho-kinase ou le nicorandil, pourraient être proposés aux patients atteints d'AVS. Cette revue traite de la physiopathologie, des aspects cliniques et de la prise en charge de l'AVS pour les cliniciens, ainsi que critères diagnostics et des tests de provocation disponibles pouvant être utilisés par les cardiologues interventionnels.

Background

Vasospastic angina (VSA) was first described by Prinzmetal et al. as a variant form of angina pectoris, in which angina occurs at rest, with transient ST-segment elevation on the electrocardiogram and preserved exercise capacity. The development of ambulatory electrocardiographic monitoring and coronary arteriography revealed it to be caused by coronary artery spasm [1]. Coronary spasm is a heterogeneous phenomenon that can occur in patients with or without coronary atherosclerosis, can be focal or diffuse, sometimes with changing patterns in the same patient [1], and can affect epicardial or microvasculature coronary arteries. Although not uncommon, and involved in many clinical scenarios, such as stable angina, sudden cardiac death, acute coronary syndrome, arrhythmia or syncope [2,3], VSA remains underdiagnosed, and provocative tests are rarely performed. Recently, the European Society of Cardiology (ESC) guidelines on ST-elevation myocardial infarction emphasized the importance of myocardial infarction with non-obstructive coronary arteries, encouraging the treating physician to investigate underlying causes, such as VSA [4]. This review will discuss the theoretical and clinical aspects of VSA for clinicians, in terms of pathophysiology, clinical spectrum and management, as well as the practical aspects, in terms of the provocative tests available for use by interventional cardiologists.

Prevalence

The incidence of VSA is unknown and highly dependent upon the population being studied, with important variations between Eastern and Western countries. Indeed, the prevalence of VSA seems to be higher in the Japanese than in the white population [5]. The prevalence rate may also vary depending on the eagerness of the practician to investigate VSA, and on the provocative tests, which may differ from one catheterization laboratory to another. Nevertheless, coronary spasm is more frequent than one might think, and may still be underdiagnosed. In a study evaluating the prevalence of epicardial and microvascular coronary spasm in patients with anginal symptoms, despite angiographically normal coronary arteries, coronary spasm was present in 62% of patients: 45% with epicardial spasm and 55% with microvascular spasm [6]. Indeed, in a recent Italian study by Montone et al. [7], which evaluated patients with a diagnosis of myocardial infarction with non-obstructive coronary arteries, excluding patients with aetiologies other than suspected coronary vasomotor abnormalities, the provocative test was positive in 46.2% of patients. Using the same design, a multicentre Japanese study evaluated coronary spasm prevalence in patients with non—ST-segment elevation acute coronary syndrome. Of 1601 patients, 72% had a culprit lesion; among the remaining patients, the acetylcholine provocation test was performed in 221 patients,

and was positive in 175 (79.2%) patients [8]. Therefore, the prevalence of VSA in different populations still needs to be better defined but such pathology should not be ignored.

Physiopathology of VSA

Coronary arteries can adapt the blood supply during different loading conditions by either vasoconstriction or vasodilation. In patients with VSA, an abnormal vasoconstrictive response can occur. Although the pathogenesis of coronary artery spasm has not been fully elucidated, different pathogenic mechanisms have been proposed, such as vascular smooth muscle cell hyperreactivity, endothelial dysfunction, magnesium deficiency, low-grade inflammation, altered autonomic nervous system response and oxidative stress — variables that could be modified by genetic factors (Fig. 1).

Coronary smooth muscle hypercontractility

Vascular smooth muscle cell (VSMC) hyperreactivity is thought to be one of the main substrates for spasm. The contraction and relaxation of VSMCs are regulated by myosin light chain (MLC) kinase and MLC phosphatase via phosphorylation and dephosphorylation of the MLC. The small guanosine triphosphatase RhoA and its downstream effector (Rho-kinase) are involved in the regulation of VSMC contractility and may play a crucial role in the pathogenesis of coronary artery spasm. Rho-kinase inhibits MLC phosphatase, leading to augmentation of MLC phosphorylation and calcium sensitization in response to vasoconstrictor stimuli [9]. Rho-kinase is upregulated at the spastic site, and plays a key role in inducing VSMC hypercontraction by inhibiting MLC phosphatase [10]. Growing evidence indicates that Rho-kinase has important roles in the pathogenesis of a large range of cardiovascular diseases. Indeed, the RhoA/Rho-kinase pathway not only mediates VSMC hypercontraction through inhibition of MLC phosphatase, but also promotes cardiovascular diseases by enhancing the production of reactive oxygen species [9]. Coronary spasm may therefore be regarded as hypercontraction of coronary smooth muscle triggered by an increase of intracellular calcium. As calcium channel blockers (CCBs) block the entry of calcium into cells, it explains their effectiveness in suppressing coronary spasm.

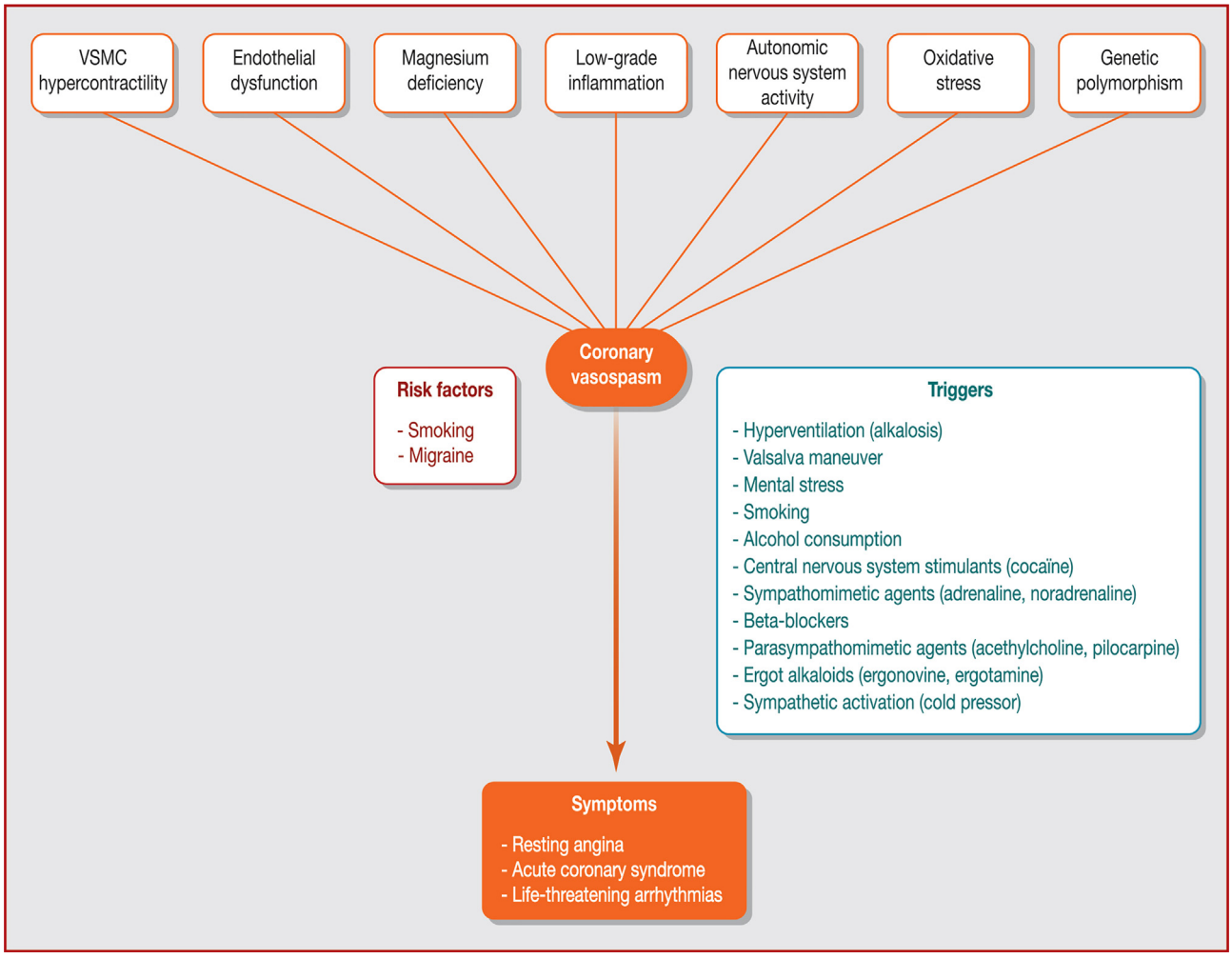

Figure 1. Coronary artery spasm pathophysiology, risk factors and precipitating factors. VSMC: vascular smooth muscle cell.

Endothelial dysfunction

The endothelium plays a key role in the regulation of coronary vascular tone, predominantly through its ability to release several vasodilator substances, named collectively as endothelium-derived relaxing factors, including vasodilator prostaglandins, nitric oxide (NO) and endothelium-derived hyperpolarizing factor. Endothelial dysfunction was thought to play an important role in coronary spasm. However, these results were challenged by a porcine model of spasm, indicating that endothelial vasodilator function was preserved at the spastic site [11]; this remains to be elucidated. Nevertheless, endothelial dysfunction with decreased NO release and reduced bioavailability combined with VSMC hyperreactivity may be an important factor in developing coronary spasm. However, endothelial dysfunction alone might not be sufficient to explain VSA.

Magnesium deficiency

Magnesium deficiency has also been considered as a possible factor contributing to coronary spasm; it has a blocking effect on calcium channels and may prevent the contraction of vascular smooth muscle. Indeed, magnesium deficiency has been reported in a large proportion of patients with variant angina [12], and magnesium infusion has been proposed to reduce spasm attacks in patients with VSA.

Low-grade inflammation

Low-grade inflammation biomarkers (C-reactive protein, monocyte chemoattractant protein-1, soluble intercellular adhesion molecule-1 and interleukin-6) are elevated in patients with VSA [13]. Moreover, smoking — an important risk factor for coronary spasm — is also associated with chronic low-grade inflammation. In addition, a recent study demonstrated that coronary spasm was associated with inflammation of coronary adventitia and perivascular adipose tissue, using 18F-fluorodeoxyglucose positron emission tomography/computed tomography. Coronary perivascular adipose tissue volume and coronary perivascular 18F-fluorodeoxyglucose uptake were increased significantly in the VSA group compared with the non-VSA group. Interestingly, during the follow-up period with medical treatment, both coronary perivascular 18F-fluorodeoxyglucose uptake and Rho-kinase activity decreased significantly in the VSA group — measures that could be useful for disease activity assessment [14]. Indeed, animal experiences demonstrated that drug-eluting stent implantation with durable polymers could enhance vasa vasorum formation and inflammation in the adventitia, combined with the pathogenesis of stent-induced coronary hyperconstriction through Rho-kinase activation [15]. Together, these findings indicate that chronic low-grade inflammation could play a role in coronary spasm.

Autonomic nervous system

Autonomic nervous system activity may play a role in the development of spasm in patients with VSA. Enhanced sympathetic nervous activity at night may be involved in the mechanism underlying multivessel coronary spasm. Yasue et al. [16] also reported that enhanced activity of the parasympathetic nervous system, which occurs at rest, could be involved in the initiation of the attacks, by stimulating the sympathetic nerve and activating alpha receptors in the large coronary arteries, which could, in turn, induce coronary spasm. Other studies reported that sympathovagal imbalance may play a role in nocturnal VSA [17].

Oxidative stress

Oxygen free radicals damage vascular endothelial cells and degrade NO, leading to vasoconstriction. Biomarkers for oxidative stress are increased [18] and antioxidants (such as vitamin E) are decreased in patients with VSA [19]. Moreover, cigarette smoking, which is highly associated with VSA, has also been shown to increase oxidative stress and to degrade NO [20].

Genetic polymorphisms

Multiple genetic polymorphisms could potentially be involved in the predisposition for coronary spasm [21,22]. Most of these mutations concern the gene encoding for NO synthase [21], but mutations in other molecules responsible for modulation of vascular tone have also been suggested [22].

Clinical spectrum and risk factors

Clinical spectrum

The typical presentation of VSA is nitrate-responsive rest angina, especially at night or in the early morning. Chest pain is similar to effort angina, but is often more severe and prolonged, accompanied by cold sweat, nausea and sometimes syncope. The other characteristics of VSA may include precipitation by hyperventilation (but not usually exertion), a circadian pattern, preserved exercise tolerance and typically suppression by CCBs (and fast-acting nitrates). Nevertheless, there is a great variability of symptoms. When the vasospasm lasts long enough, it can result in angina or even myocardial infarction, life-threatening arrhythmia, atrioventricular block and sometimes sudden death [2,3].

Risk factors

Smoking has been reported as the most important predisposing risk factor for VSA [23]. Previous reports have suggested that VSA could also be associated with Raynaud's phenomenon and migraine, as part of a generalized vasomotor disorder [24]. However, while VSA seems to have a strong association with migraine, its association with Raynaud's phenomenon is less clear [25]. Ethnic differences also exist as a predisposing factor, with increased prevalence in Asian populations [26].

Precipitating factors

In addition to risk factors, some elements may contribute to the onset of coronary spasm, such as hyperventilation,

Valsalva manoeuvre, mental stress [27], magnesium deficiency [12], alcohol consumption [28], cocaine [29], or the use of pharmacological molecules such as sympathomimetic agents (adrenaline, noradrenaline), beta-blockers, parasympathomimetic agents and ergot alkaloids (ergonovine, ergotamine, etc.).

Spasm diagnosis

International standardization

Recently, the Coronary Vasomotion Disorders International Study Group (COVADIS) published standardized diagnostic criteria for VSA [30]. VSA diagnosis involves three considerations: (1) classical clinical manifestations of VSA; (2) documentation of myocardial ischaemia during spontaneous episodes; and (3) demonstration of coronary artery spasm. The extent of evidence subclassifies VSA into either ''definitive'' or ''suspected'' VSA. These criteria are summarized in Table 1. Moreover, VSA diagnosis, as defined before, combined with chest pain, preserved effort capacity and electrocardiogram modifications resolved with administration of nitrates, is seen rarely.

Electrocardiogram changes

An electrocardiogram may appear normal at the beginning of VSA or when the spasm is mild. Total or subtotal spasm of a major coronary artery may result in a change in the electrocardiogram leads, corresponding to the distribution of the vasospastic coronary artery. The most frequent electrocardiogram change during a focal proximal coronary spasm is the appearance of a peaked and symmetrical T wave in around 50% of cases. Nevertheless, various changes can occur, including ST-segment elevation and/or depression (Fig. 2), T wave negativation, an increase in the height and width of the R wave, a coincident decrease in the magnitude or disappearance of the S wave and the appearance of a negative U wave. Various forms of arrhythmia can also appear during VSA, including ventricular premature complex, ventricular tachycardia and/or fibrillation (mostly in case of anterior ischaemia), atrioventricular block (mostly in case of inferior ischaemia), asystole and supraventricular tachyarrhythmias [2,3]. The prevalence and importance of ventricular arrhythmias have been related to the duration of episodes, the degree of ST-segment elevation, the presence of ST − T wave alternans and an increase in the R wave of > 25% [31].

Provocative methods and indications

The gold-standard approach uses invasive coronary angiography to image coronary spasm directly (Fig. 2), using acetylcholine, ergonovine or methylergonovine as the provocative stimulus. Different indication recommendations by specialist groups [32,33] are summarized in Table 2. Provocative spasm testing involves the use of a provocative stimulus, either pharmacological (acetylcholine, ergonovine or methylergonovine) or non-pharmacological (hyperventilation or cold pressor testing), and an assessment modality to evaluate the vasomotor response, which may include angina symptoms, ischaemic electrocardiogram changes and angiography. A positive provocative test for coronary artery spasm must induce all of the following in response to the provocative stimulus: (1) reproduction of the usual chest pain; (2) ischaemic electrocardiogram changes; and (3) ≥ 90% vasoconstriction on angiography. The test result is considered equivocal if the provocative stimulus does not induce all three components [32]. Potential provocative methods are summarized in Table 3.

Intracoronary imaging

The diagnosis of focal coronary vasospasm can be challenging, especially when this condition is spontaneous (e.g. after an acute coronary syndrome) and not induced by acetylcholine or ergonovine. Then, intracoronary nitroglycerine

Table 1 Coronary Artery Vasospastic Disorders Summit diagnostic criteria for vasospastic angina; adapted from Beltrame et al. [30].

1. Nitrate-responsive angina during spontaneous episode, with at least one of the following
Rest angina, especially between night and early morning
Marked diurnal variation in exercise tolerance (reduced in morning)
Hyperventilation can precipitate an episode
CCBs (but not beta-blockers) suppress episodes
2. Transient ischaemic electrocardiogram changes during spontaneous episode, including any of the following in at least two contiguous leads
ST-segment elevation ≥ 0.1 mV
ST-segment depression ≥ 0.1 mV
New negative U waves
3. Coronary artery spasm, defined as transient total or subtotal coronary artery occlusion (> 90% constriction) with angina and ischaemic electrocardiogram changes, either spontaneously or in response to a provocative stimulus (typically acetylcholine, ergot or hyperventilation)

CBB: calcium channel blocker. ''Definitive vasospastic angina'' is diagnosed if nitrate-responsive angina is evident during spontaneous episodes and either the transient ischaemic electrocardiogram changes during the spontaneous episodes or coronary artery spasm criteria are fulfilled. ''Suspected vasospastic angina'' is diagnosed if nitrate-responsive angina is evident during spontaneous episodes, but transient ischaemic electrocardiogram changes are equivocal or unavailable and coronary artery spasm criteria are equivocal.

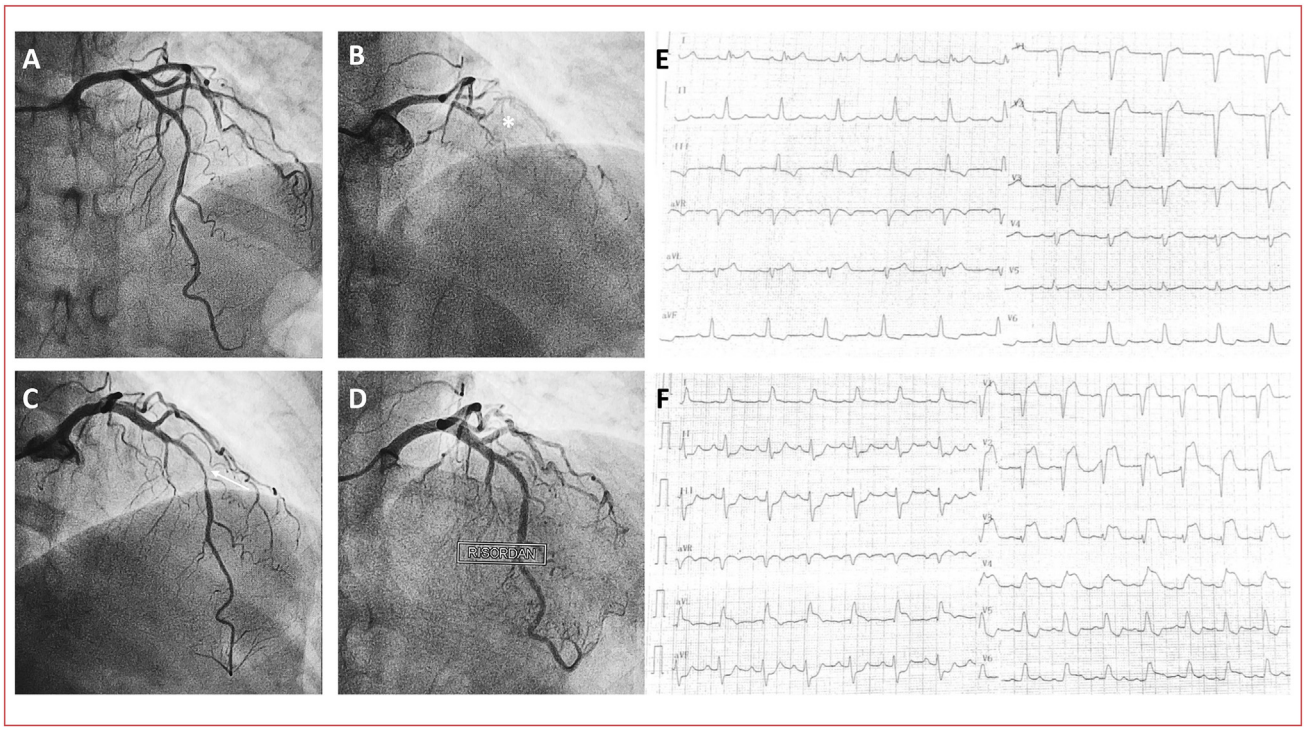

Figure 2. Coronary artery spasm on left anterior descending coronary artery: electrocardiogram changes and coronary angiography methylergonovine provocative test. A. Basal left anterior descending artery. B. Occlusive left anterior descending coronary artery vasospasm after methylergonovine administration (*). C. Slow vasospasm reduction with persistent focal spasm after intracoronary administration of 2 mg of isosorbide dinitrate (arrow). D. Complete vasospasm reversion after intracoronary administration of 4 mg of isosorbide dinitrate. E. Surface electrocardiogram of the patient in a stable setting, showing left bundle block with aspecific repolarization changes. F. Surface electrocardiogram of the same patient during Prinzmetal anginal episode; ST-segment elevation in the anterior leads associated with inferior ST-segment depression.

administration can be useful to discriminate the nature of the stenosis. Intracoronary imaging, such as optical coherence tomography, can address the conformational changes of intima and media during vasospasm. In addition, optical coherence tomography can provide information regarding the association of vasospasm with underlying atherosclerotic plaque, fibrous cap disruption, erosion or thrombus formation. Analysis during coronary spasm reveals a typical aspect of intimal bumps deforming the lumen, combined with intimal gathering (kinks), without alteration of the intimal area. Medial contraction is reflected in an increment in medial thickness [34].

VSA management

Conventional management of VSA involves lifestyle changes, use of established pharmacological therapies, avoidance of aggravating factors and possibly the use of percutaneous coronary intervention for associated obstructive coronary artery disease.

Lifestyle changes and avoidance of vasospastic agents

As VSA is related to endothelial dysfunction, the control of factors that could influence oxidative stress or endothelial function is crucial; therefore, smoking cessation is imperative in patients with VSA [23]. Avoiding VSA risk factors, such as mental stress [27], magnesium deficiency [12], alcohol consumption [28] and the use of pharmacological molecules, such as cocaine [29], sympathomimetic agents (adrenaline, noradrenaline), beta-blockers, parasympathomimetic agents and ergot alkaloids (ergonovine, ergotamine, etc.), is also crucial in patients with VSA.

Pharmacotherapy

Calcium channel blockers

CCBs inhibit the voltage-dependent L-type calcium channel, and thus are smooth muscle dilators and negative inotropic and chronotropic agents. Several studies have reported the effectiveness of CCBs (both dihydropyridine and non-dihydropyridine) in reducing angina frequency [35,36]. CCBs are actually recommended as a first-line treatment in newly diagnosed VSA [37]. Either dihydropyridine or non-dihydropyridine CCBs (verapamil and nifedipine) can be proposed, depending on patient characteristics and predictable adverse effects. Non-dihydropyridine CCBs can more frequently induce side-effects (orthostatic hypotension, nausea, dizziness), especially in elderly patients. In some cases of refractory VSA, the combination of

Table 2 Provocative coronary spasm testing indications by group recommendations.

COVADIS group	
Class I (strong indications)	History suspicious of VSA without documented episode, especially if: nitrate-responsive rest angina and/or; marked diurnal variation in symptom onset/exercise tolerance and/or; rest angina without obstructive CAD; unresponsive to empiric therapy ACS presentation in the absence of a culprit lesion Unexplained resuscitated cardiac arrest Unexplained syncope with antecedent chest pain Recurrent rest angina following angiographically-successful PCI
Class IIa (good indications)	Invasive testing for non-invasively diagnosed patients unresponsive to drug therapy Documented spontaneous episode of VSA to determine the ''site and mode'' of spasm
Class IIb (controversial indications)	Invasive testing for non-invasively diagnosed patients responsive to drug therapy
Class III (contraindications)	Emergent ACS Severe fixed multivessel CAD, including left main stenosis Severe myocardial dysfunction (Class IIb if symptoms suggestive of vasospasm) Patients without any symptoms suggestive of VSA
2013 Japanese Circulation Society Guidelines	
Class I (strong indications)	Patients in whom VSA is suspected based on symptoms, but who have not been diagnosed with coronary spasm by non-invasive evaluation
Class IIa (good indications)	Patients who have been diagnosed with coronary spasm by non-invasive evaluation, and in whom medical treatment is ineffective or insufficiently effective
Class IIb (controversial indications)	Acetylcholine provocation test during coronary angiography performed in patients who have been diagnosed with coronary spasm by non-invasive evaluation, and in whom medical treatment has been proven to be effective
Class III (contraindications)	Patients without symptoms suggestive of VSA Patients who are considered at high risk of a life-threatening complication of induced coronary spasm (e.g. patients with left main coronary trunk lesions, those with multivessel coronary lesions, including obstructive lesions, those with severe cardiac dysfunction and those with untreated congestive heart failure); however, in cases in which the onset of severe cardiac dysfunction or congestive heart failure may be a consequence of coronary spasm, the criteria for Class IIb apply Patients with ACS
2013 ESC guidelines on the management of stable CAD	
Class IIa, Level of Evidence C	Intracoronary provocative testing should be considered to identify coronary spasm in lesions on coronary arteriography and the clinical picture of coronary spasm

ACS: acute coronary syndrome; CAD: coronary artery disease; COVADIS: Coronary Vasomotion Disorders International Study Group; ESC: European Society of Cardiology; PCI: percutaneous coronary intervention; VSA: vasospastic angina.

two CCBs may be required, but few data exist for this approach.

Nitrates

Nitrates can help to reduce symptoms of VSA by dilating the coronary vasculature and also by reducing ventricular filling pressures, which decreases myocardial oxygen demand and thus decreases myocardial ischaemia. Several prospective randomized trials comparing the effect of long-acting nitrates alone or in combination with CCBs demonstrated that nitrates are an effective treatment for reducing the frequency of angina in patients with VSA [38]. Long-acting nitrates can be proposed in addition to CCBs to improve the efficacy of the treatment; their administration should be adapted to cover the periods when vasospasms are more likely to occur. Currently, ESC guidelines recommend the use of long-acting nitrate agents in combination with CCBs in patients who remain symptomatic despite treatment with CCBs [37].

Aspirin

The use of aspirin in VSA without concomitant obstructive coronary disease is currently being debated. Administration of high doses of aspirin (> 325 mg daily) is known to block the production of prostacyclin, which is a potent endogenous vasodilator, and thus can aggravate coronary artery vasospasm [39]. Administration of low doses of aspirin (< 100 mg) remains controversial; low doses of aspirin are known to block thromboxane A2, which is implicated in coronary artery spasm, but results from clinical studies are

Table 3 Provocative tests dosing protocols reported in the literature.

Provocative molecule	Dosage	Protocol
Ergonovine maleate	IV: 100 μg (up to 400 μg)	1. Simultaneous electrocardiogram monitoring 2. Angiography of LCA and RCA 3. 100 μg IV bolus of ergonovine maleate (up to 400 μg) at 5-minute intervals 4. Control angiography of LCA and RCA immediately after chest pain with ST-segment elevation or depression is observed or 5 minutes after the last dose of ergonovine maleate 5. LCA and RCA angiography after IC/IV/sublingual nitrate administration
	IC: LCA 20—60 μg; RCA 20—60 μg	1. Simultaneous electrocardiogram monitoring 2. Angiography of LCA and RCA 3. Injection of 20—60 μg of ergonovine maleate into the LCA over a period of several (about 2—5) minutes 4. Perform LCA angiography 1—2 minutes after completion of the injection; in the event of an ischaemic change on the electrocardiogram or chest symptom, perform angiography at the time of its onset; in case of a negative result in the provocation test, proceed to the RCA provocation test 5 minutes later 5. Injection of 20—60 μg of ergonovine maleate into the RCA over a period of several (about 2—5) minutes; the timing of angiography is the same as for the LCA 6. LCA and RCA angiography after IC nitrate administration
Methylergonovine	IV: 400 μg	1. Simultaneous electrocardiogram monitoring 2. Angiography of LCA and RCA 3. 400 μg IV bolus of methylergonovine 4. Control angiography of LCA and RCA immediately after chest pain with ST-segment elevation or depression is observed or 5 minutes after the last dose of methylergonovine 5. LCA and RCA angiography after IC/IV/sublingual nitrate administration
Acetylcholine	IC: LCA 20—100 μg; RCA: 20—50 μg	1. Simultaneous electrocardiogram monitoring 2. Insertion of a temporary pacing electrode; administration of acetylcholine, especially in the RCA, may cause transient episodes of severe bradycardia 3. Angiography of LCA and RCA 4. Injection of 20, 50 or 100 μg of acetylcholine (concentration adjusted to obtain 5 mL solution volume for each quantity of acetylcholine) into the LCA over a period of 20 seconds; perform angiography 1 minute after the start of each injection; in the event of an ischaemic change on the electrocardiogram or chest pain, perform angiography at that time; doses of acetylcholine should be given at 5-minute intervals 5. Injection of 20 or 50 μg of acetylcholine (each in 5 mL solution) into the RCA over a period of 20 seconds; the timing of angiography is the same as for the LCA 6. LCA and RCA angiography after IC nitrate administration

IC: intracoronary; IV: intravenous; LCA: left coronary artery; RCA: right coronary artery.

conflicting. Indeed, Kim et al. found that administration of low-dose aspirin was associated with frequent coronary artery spasm in patients with VSA [40]. Thus, no beneficial effect of low-dose aspirin has been yet proven in patients with VSA.

Statins

Several studies have shown that statins are effective at preventing coronary artery vasospasm. A prospective randomized study found that the addition of fluvastatin to conventional medical therapy with CCBs for 6 months significantly reduced acetylcholine-provoked spasm in patients with VSA without obstructive coronary artery disease [41]. A more recent retrospective study found a correlation between statin administration and the reduction of long-term cardiovascular events in patients with VSA without obstructive coronary artery disease [42]. Thus, statin therapy should be considered as an effective and safe treatment in addition to conventional therapy in patients with VSA.

Alpha 1-adrenergic receptor antagonists

Little evidence is available to support the systematic use of alpha 1-adrenergic receptor antagonists in the treatment of patients with VSA. Indeed, studies that have tested this treatment produced conflicting results, and enrolled small numbers of patients among those who had concomitant obstructive coronary artery disease [43,44]. Current guidelines do not provide a specific class recommendation for the use of an alpha1-adrenergic receptor antagonist. Nevertheless, it could be considered as an additional therapy in patients with refractory VSA, if well tolerated.

Rho-kinase inhibitors

The inhibition of Rho kinase activity, which is known to reduce the contraction of VSMCs, could be of potential interest. Masumoto et al. [45] conducted a study including 20 patients in whom coronary artery spasm was provoked by acetylcholine, who were treated with intracoronary fasudil ($n = 15$) or intracoronary saline ($n = 5$). The authors found that fasudil significantly reduced the constriction induced by acetylcholine and prevented the occurrence of chest pain and ischaemic electrocardiogram changes in all patients [45]. Nevertheless, to date, no Rho-kinase inhibitor has been approved for the treatment of VSA, and there is still a need for more clinical evidence.

Nicorandil

Nicorandil has a nitrate-like effect by opening adenosine triphosphate-sensitive potassium channels. The efficacity of nicorandil, either as monotherapy or in conjunction with other agents, has been evaluated [46]; the results demonstrated the effectiveness of nicorandil in the treatment of VSA. Nevertheless, current guidelines do not recommend the use of nicorandil as a first-line treatment [37]; it can be proposed in patients with refractory VSA.

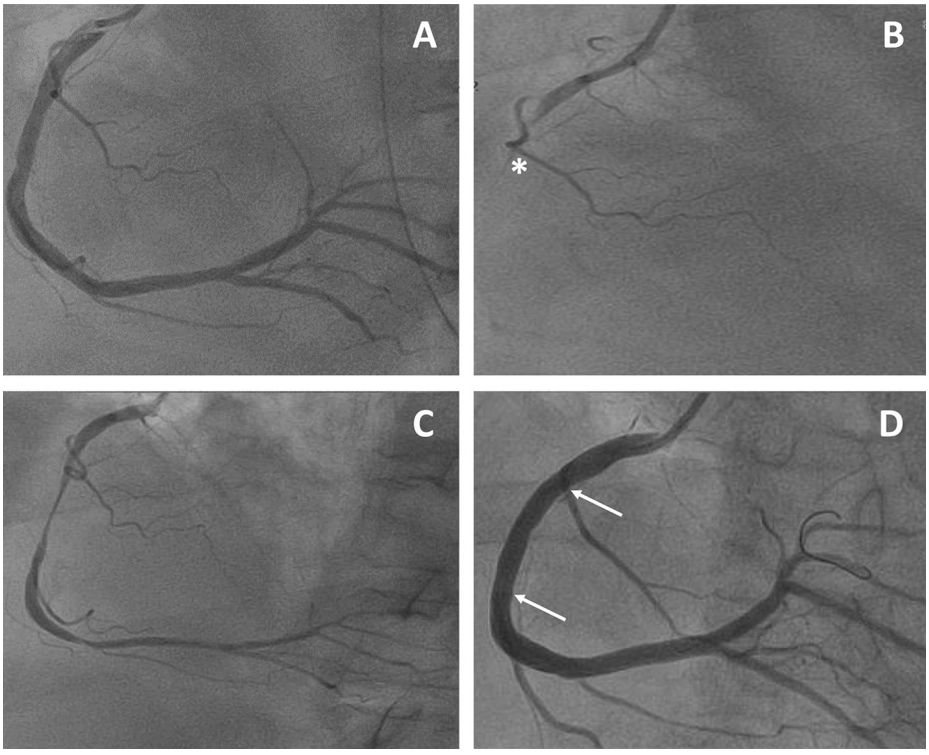

Figure 3. Right coronary artery occlusive vasospasm refractory to medical treatment treated by drug- eluting stent implantation. A. Basal right coronary artery. B. Right coronary artery vasospasm after methylergonovine administration (*). C. Refractory vasospasm under two calcium channel blockers (verapamil and amlodipine) and nitrates. D. Stent implantation to treat refractory vasospasm (arrows indicate the drug-eluting stent margins).

Refractory spasm management

Refractory VSA and percutaneous coronary intervention

When spontaneous, focal, severe or occlusive and resistant to medical therapy, a mechanical approach of the spasm at the site of spasm, with percutaneous coronary intervention and stent implantation (Fig. 3), could be of interest, and has been evaluated in small series [47]. Nevertheless, maintenance of CCB and nitrate therapy should be continued after the procedure, as vasospasm might occur at other sites.

Implantable cardioverter defibrillator

Coronary spasm can lead to sudden cardiac death as a result of ventricular arrhythmias. In these patients, the implantation of an implantable cardioverter defibrillator (ICD) for secondary prevention of resuscitated sudden cardiac death can be considered. Although evidence in patients with VSA remains insufficient, Meisel et al. demonstrated a high ICD therapy rate in patients with VSA who received an ICD for secondary prevention [48]. At the current time, there are no consensual guidelines for patients with VSA, and the decision should be adapted to each patient, considering the existence of refractory VSA despite optimal medical treatment or the persistence of non-modifiable risk factors. However, in patients with life-threatening ventricular arrhythmias as a result of VSA, an ICD should be considered because of the risk of recurrence despite optimal medical management [49].

Spasm provocation tests performed under medical therapy

There are no recommended methods for evaluating the severity of vasospasms in patients with refractory VSA under adequate medical therapy. Nevertheless, provocation tests performed under medical therapy can be useful to assess the disappearance of pharmacologically induced coronary spasm under treatment and determine the subsequent treatment strategy [50]. Indeed, in case of spasm disappearance under treatment, the same medication should be continued. Meanwhile, when chest pain continues despite the provocative test being negative under treatment, a psychosomatic medicine consultation could be advised. In contrast, in patients who still exhibit vasospasticity, irrespective of the administration of aggressive medical therapy, doses of vasoactive drugs should be increased to suppress coronary artery spasm.

Prognosis

The long-term prognosis of patients with VSA without coronary artery disease is reasonably good. In a Japanese study of 245 patients with VSA, the survival rates at 1, 3, 5 and 10 years were 98%, 97%, 97% and 93%, respectively. Survival rates without myocardial infarction at 1, 3, 5 and 10 years were 86%, 85%, 83% and 81%, respectively [51]. In this study, the use of CCBs and the extent and severity of coronary artery disease were independent predictors of survival without myocardial infarction. Nevertheless, recent studies have demonstrated that patients with VSA can experience fatal events, and that patients experiencing acute coronary syndrome or myocardial infarction had a worse prognosis [52].

Conclusion and perspectives

VSA, although well described, remains poorly understood, and is likely to be multifactorial. Even if its frequency seems to decrease, VSA remains underdiagnosed, and provocative tests are rarely performed, despite their proven safety and effectiveness; this leads to undertreatment of an easily controlled pathology. The long-term prognosis of such patients is usually good, but with an increased rate of major cardiac events, including acute myocardial infarction and sudden cardiac death. Therefore, substantial work must be done by clinicians to improve the understanding of this pathology and the diagnosis rate, and to develop new effective therapies.

Sources of funding

None.

Disclosure of interest

The authors declare that they have no competing interest.

References

[1] Oliva PB, Potts DE, Pluss RG. Coronary arterial spasm in Prinzmetal angina. Documentation by coronary arteriography. N Engl J Med 1973;288:745—51.
[2] Nakamura M, Takeshita A, Nose Y. Clinical characteristics associated with myocardial infarction, arrhythmias, and sudden death in patients with vasospastic angina. Circulation 1987;75:1110—6.
[3] Rodriguez-Manero M, Oloriz T, le Polain de Waroux JB, et al. Long-term prognosis of patients with life-threatening ventricular arrhythmias induced by coronary artery spasm. Europace 2018;20:851—8.
[4] Ibanez B, James S, Agewall S, et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J 2018;39:119—77.
[5] Beltrame JF, Sasayama S, Maseri A. Racial heterogeneity in coronary artery vasomotor reactivity: differences between Japanese and Caucasian patients. J Am Coll Cardiol 1999;33:1442—52.
[6] Ong P, Athanasiadis A, Borgulya G, Mahrholdt H, Kaski JC, Sechtem U. High prevalence of a pathological response to acetylcholine testing in patients with stable angina pectoris and unobstructed coronary arteries. The ACOVA Study (Abnormal COronary VAsomotion in patients with stable angina and unobstructed coronary arteries). J Am Coll Cardiol 2012;59:655—62.
[7] Montone RA, Niccoli G, Fracassi F, et al. Patients with acute myocardial infarction and non-obstructive coronary arteries: safety and prognostic relevance of invasive coronary provocative tests. Eur Heart J 2018;39:91—8.

[8] Nakayama N, Kaikita K, Fukunaga T, et al. Clinical features and prognosis of patients with coronary spasm-induced non-ST-segment elevation acute coronary syndrome. J Am Heart Assoc 2014;3:e000795.
[9] Shimokawa H, Sunamura S, Satoh K. RhoA/Rho-Kinase in the Cardiovascular System. Circ Res 2016;118:352—66.
[10] Kandabashi T, Shimokawa H, Miyata K, et al. Inhibition of myosin phosphatase by upregulated rho-kinase plays a key role for coronary artery spasm in a porcine model with interleukin-1beta. Circulation 2000;101:1319—23.
[11] Miyata K, Shimokawa H, Yamawaki T, et al. Endothelial vasodilator function is preserved at the spastic/inflammatory coronary lesions in pigs. Circulation 1999;100:1432—7.
[12] Satake K, Lee JD, Shimizu H, Ueda T, Nakamura T. Relation between severity of magnesium deficiency and frequency of anginal attacks in men with variant angina. J Am Coll Cardiol 1996;28:897—902.
[13] Hung MJ, Cherng WJ, Cheng CW, Li LF. Comparison of serum levels of inflammatory markers in patients with coronary vasospasm without significant fixed coronary artery disease versus patients with stable angina pectoris and acute coronary syndromes with significant fixed coronary artery disease. Am J Cardiol 2006;97:1429—34.
[14] Ohyama K, Matsumoto Y, Takanami K, et al. Coronary adventitial and perivascular adipose tissue inflammation in patients with vasospastic angina. J Am Coll Cardiol 2018;71:414—25.
[15] Nishimiya K, Matsumoto Y, Shindo T, et al. Association of adventitial vasa vasorum and inflammation with coronary hyperconstriction after drug-eluting stent implantation in pigs in vivo. Circ J 2015;79:1787—98.
[16] Yasue H, Touyama M, Shimamoto M, Kato H, Tanaka S. Role of autonomic nervous system in the pathogenesis of Prinzmetal's variant form of angina. Circulation 1974;50:534—9.
[17] Miwa K, Igawa A, Miyagi Y, Nakagawa K, Inoue H. Alterations of autonomic nervous activity preceding nocturnal variant angina: sympathetic augmentation with parasympathetic impairment. Am Heart J 1998;135:762—71.
[18] Miyamoto S, Kawano H, Sakamoto T, et al. Increased plasma levels of thioredoxin in patients with coronary spastic angina. Antioxid Redox Signal 2004;6:75—80.
[19] Miwa K, Igawa A, Nakagawa K, Hirai T, Inoue H. Consumption of vitamin E in coronary circulation in patients with variant angina. Cardiovasc Res 1999;41:291—8.
[20] Ota Y, Kugiyama K, Sugiyama S, et al. Impairment of endothelium-dependent relaxation of rabbit aortas by cigarette smoke extract-role of free radicals and attenuation by captopril. Atherosclerosis 1997;131:195—202.
[21] Glueck CJ, Valdes A, Bowe D, Munsif S, Wang P. The endothelial nitric oxide synthase T-786c mutation, a treatable etiology of Prinzmetal's angina. Transl Res 2013;162:64—6.
[22] Yoo SY, Kim J, Cheong S, et al. Rho-associated kinase 2 polymorphism in patients with vasospastic angina. Korean Circ J 2012;42:406—13.
[23] Takaoka K, Yoshimura M, Ogawa H, et al. Comparison of the risk factors for coronary artery spasm with those for organic stenosis in a Japanese population: role of cigarette smoking. Int J Cardiol 2000;72:121—6.
[24] Miller D, Waters DD, Warnica W, Szlachcic J, Kreeft J, Theroux P. Is variant angina the coronary manifestation of a generalized vasospastic disorder? N Engl J Med 1981;304:763—6.
[25] Nakamura Y, Shinozaki N, Hirasawa M, et al. Prevalence of migraine and Raynaud's phenomenon in Japanese patients with vasospastic angina. Jpn Circ J 2000;64:239—42.
[26] Pristipino C, Beltrame JF, Finocchiaro ML, et al. Major racial differences in coronary constrictor response between japanese and caucasians with recent myocardial infarction. Circulation 2000;101:1102—8.
[27] Yeung AC, Vekshtein VI, Krantz DS, et al. The effect of atherosclerosis on the vasomotor response of coronary arteries to mental stress. N Engl J Med 1991;325:1551—6.
[28] Oda H, Suzuki M, Oniki T, Kishi Y, Numano F. Alcohol and coronary spasm. Angiology 1994;45:187—97.
[29] Kalsner S. Cocaine sensitization of coronary artery contractions: mechanism of drug-induced spasm. J Pharmacol Exp Ther 1993;264:1132—40.
[30] Beltrame JF, Crea F, Kaski JC, et al. International standardization of diagnostic criteria for vasospastic angina. Eur Heart J 2017;38:2565—8.
[31] de Luna AB, Cygankiewicz I, Baranchuk A, et al. Prinzmetal angina: ECG changes and clinical considerations: a consensus paper. Ann Noninvasive Electrocardiol 2014;19:442—53.
[32] Joint Working JCS Group. Guidelines for diagnosis and treatment of patients with vasospastic angina (Coronary Spastic Angina) (JCS 2013). Circ J 2014;78:2779—801.
[33] Montalescot G, Sechtem U, Achenbach S, et al. 2013 ESC guidelines on the management of stable coronary artery disease: the Task Force on the management of stable coronary artery disease of the European Society of Cardiology. Eur Heart J 2013;34:2949—3003.
[34] Tanaka A, Shimada K, Tearney GJ, et al. Conformational change in coronary artery structure assessed by optical coherence tomography in patients with vasospastic angina. J Am Coll Cardiol 2011;58:1608—13.
[35] Chahine RA, Feldman RL, Giles TD, et al. Randomized placebo-controlled trial of amlodipine in vasospastic angina. Amlodipine Study 160 Group. J Am Coll Cardiol 1993;21:1365—70.
[36] Rosenthal SJ, Ginsburg R, Lamb IH, Baim DS, Schroeder JS. Efficacy of diltiazem for control of symptoms of coronary arterial spasm. Am J Cardiol 1980;46:1027—32.
[37] Roffi M, Patrono C, Collet JP, et al. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). Eur Heart J 2016;37:267—315.
[38] Schroeder JS. Combination therapy with isosorbide dinitrate: current status and the future. Am Heart J 1985;110:284—91.
[39] Miwa K, Kambara H, Kawai C. Effect of aspirin in large doses on attacks of variant angina. Am Heart J 1983;105:351—5.
[40] Kim MC, Ahn Y, Park KH, et al. Clinical outcomes of low-dose aspirin administration in patients with variant angina pectoris. Int J Cardiol 2013;167:2333—4.
[41] Yasue H, Mizuno Y, Harada E, et al. Effects of a 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor, fluvastatin, on coronary spasm after withdrawal of calcium-channel blockers. J Am Coll Cardiol 2008;51:1742—8.
[42] Ishii M, Kaikita K, Sato K, et al. Impact of Statin Therapy on Clinical Outcome in Patients With Coronary Spasm. J Am Heart Assoc 2016:5.
[43] Tzivoni D, Keren A, Benhorin J, Gottlieb S, Atlas D, Stern S. Prazosin therapy for refractory variant angina. Am Heart J 1983;105:262—6.
[44] Winniford MD, Filipchuk N, Hillis LD. Alpha-adrenergic blockade for variant angina: a long-term, double-blind, randomized trial. Circulation 1983;67:1185—8.
[45] Masumoto A, Mohri M, Shimokawa H, Urakami L, Usui M, Takeshita A. Suppression of coronary artery spasm by the Rho-kinase inhibitor fasudil in patients with vasospastic angina. Circulation 2002;105:1545—7.
[46] Kishida H, Murao S. Effect of a new coronary vasodilator, nicorandil, on variant angina pectoris. Clin Pharmacol Ther 1987;42:166—74.

[47] Khatri S, Webb JG, Carere RG, Dodek A. Stenting for coronary artery spasm. Catheter Cardiovasc Interv 2002;56:16—20.

[48] Meisel SR, Mazur A, Chetboun I, et al. Usefulness of implantable cardioverter-defibrillators in refractory variant angina pectoris complicated by ventricular fibrillation in patients with angiographically normal coronary arteries. Am J Cardiol 2002;89:1114—6.

[49] Eschalier R, Souteyrand G, Jean F, et al. Should an implanted defibrillator be considered in patients with vasospastic angina? Arch Cardiovasc Dis 2014;107:42—7.

[50] Sueda S, Kohno H, Miyoshi T, Sasaki Y, Sakaue T, Habara H. Spasm provocation tests performed under medical therapy: a new approach for treating patients with refractory coronary spastic angina on emergency admission. Intern Med 2014;53:1739—47.

[51] Yasue H, Takizawa A, Nagao M, et al. Long-term prognosis for patients with variant angina and influential factors. Circulation 1988;78:1—9.

[52] Cho SW, Park TK, Gwag HB, et al. Clinical Outcomes of Vasospastic Angina Patients Presenting With Acute Coronary Syndrome. J Am Heart Assoc 2016;5 [e004336].