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REVIEW

The Who, What, Why, When, How and Where of Vasospastic Angina

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Ischemic heart disease involves both "structural" and/or "functional" disorders of the coronary circulation. Structural atherosclerotic coronary artery disease (CAD) is well recognized, with established diagnostic and treatment strategies. In contrast, "functional CAD" has received limited attention and is seldom actively pursued in the investigation of ischemic heart disease. Vasospastic angina encompasses "functional CAD" attributable to coronary artery spasm and this "state of the art" consensus statement reviews contemporary aspects of this disorder. Patients with vasospastic angina typically present with angina at rest that promptly responds to short-acting nitrates and is associated with transient ischemic ECG changes. Although spontaneous episodes may be documented, provocative spasm testing may be required to confirm the diagnosis. It is important to diagnose vasospastic angina because it may be associated with major adverse events that can be prevented with the use of appropriate vasodilator therapy (eg, calcium-channel blockers) and the avoidance of aggravating stimuli (eg, smoking). Future studies are required to clarify the underlying pathophysiology, natural history and effective treatments for patients refractory to conventional therapy. (*Circ J* 2016; **80:** 289–298)

Key Words: Coronary artery disease; Coronary spasm; Ischemic heart disease; Variant angina; Vasospastic angina

The structural and functional attributes of the coronary circulation are fundamental in understanding ischemic heart disease (IHD), the leading cause of death worldwide.[1] Over the past century our ability to clinically image the structural pathology involving these vessels has led to a greater understanding of coronary artery disease (CAD), as well as the evolution of key therapies such as revascularization. In contrast, the functional attributes of the coronary circulation are more challenging because these are dynamic in nature and may not be apparent with routine clinical investigations. Accordingly, evaluation of functional disturbances involving the coronary circulation requires a broader approach because many aspects still remain elusive.

As detailed in the **Figure**, IHD is an encompassing term that includes pathological processes involving the large coronary arteries (>0.5 mm diameter) and/or the coronary microvessels (<0.5 mm), resulting in myocardial ischemia. Because the large arteries can be clinically imaged, "structural CAD" and "functional CAD" can potentially be distinguished, whereas the inability to readily image the microcirculation makes it difficult to distinguish its structural and functional components, so these are considered in unison. As intimated by the intersecting circles in the **Figure**, there is significant overlap in these various components,[2] which must be considered and appropriately evaluated[3] in any clinical presentation.

The Coronary Vasomotion Disorders International Study Group (COVADIS) aims to unify nomenclature and define the "state of the art" of coronary vasomotor disorders in order to advance the clinical understanding and management of IHD. This consensus statement will exclusively focus on vasospastic angina, which is a clinical disorder primarily attributable to coronary artery spasm.

The approach in this consensus statement on vasospastic angina was that adopted at the inaugural COVADIS Summit held on 4–5 September 2013. It involves what is often referred to as the "Kipling Method", originating from Rudyard Kipling's

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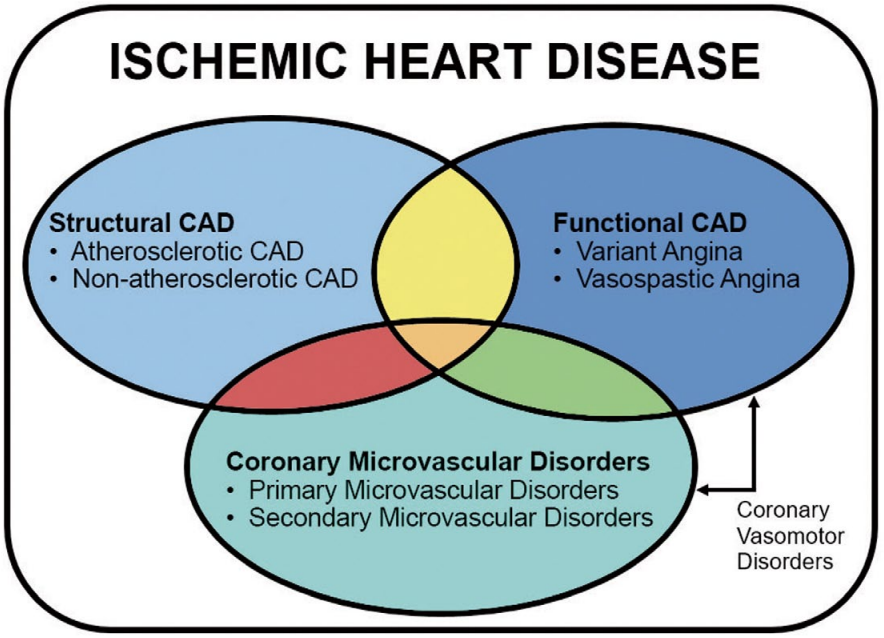

Figure. An overview of coronary disorders. CAD, coronary artery disease.

classic children's book, "Just so stories".[4]

I keep six honest serving-men (they taught me all I knew); Their names are What and Why and When and How and Where and Who.

As summarized in Table 1, these "Five W's (and one H)" are discussed in relation to the COVADIS Summit consensus on vasospastic angina and have been updated to include recent studies.

Who Is Likely to Have Vasospastic Angina?

To avoid the diagnosis being overlooked, it is paramount to elicit a relevant careful history detailing the key features in the clinical presentation and potential predisposing risk factors.

Clinical Presentation

The hallmark feature of vasospastic angina is rest angina (especially at night or in the early morning) that promptly responds to short-acting nitrates. Other features in relation to the anginal symptoms include precipitation by hyperventilation, preserved exercise tolerance (ie, no exertional symptoms), a diurnal variation (reflecting the diurnal variation in coronary spasm), and suppression of symptoms by calcium-channel blockers (CCBs).

Speculation that vasospastic angina is the coronary manifestation of a generalized vasomotor disorder has arisen from its reported association with Raynaud's phenomenon[5] and migraine.[5,6] These clinical associations have largely been implicated on the basis of case reports; however, more recent studies have suggested that the relationship is tenuous[6–8] and requires further investigation.

Predisposing Risk Factors

Several studies[8–13] have evaluated the associated clinical risk factors with inducible coronary artery spasm. Unlike structural atherosclerotic CAD, hypertension or diabetes do not predispose to coronary spasm. However, smoking was an important risk factor for coronary artery spasm in many of the studies. Moreover, smoking during coronary angiography has been shown to acutely induce spasm in susceptible individuals.[14] The role of dyslipidemia as a risk factor for coronary spasm is less clear, with most studies demonstrating no relationship with total cholesterol, although abnormalities in triglycerides[12] and high-density lipoprotein (HDL)[15] have been implicated in some studies. Thus, except for smoking, many of the conventional risk factors for atherosclerosis do not appear to be applicable to vasospastic angina.

There may also be ethnic or racial differences that predispose individuals to vasospastic angina, particularly in relation to Asian ethnicity. Although in the context of an acute ST-elevation myocardial infarction (MI) requiring reperfusion therapy, Japanese patients have been shown to have hyper-reactive vessels compared with Caucasians;[16] whether this translates to a greater propensity for vasospastic angina is uncertain. This underscores the difficulty in estimating the prevalence of vasospastic angina within a population, because there are international differences in (a) the awareness of this condition (and thus its potential diagnosis), (b) the routine use of provocative spasm testing, and (c) the definition of vasospastic angina. Within Asian populations where there is a high awareness of vasospastic angina, with provocative spasm testing routinely used and the diagnostic criteria standardized, the prevalence of this condition is estimated to be as high as 40% of patients with angina.[17] Unifying the vasospastic angina definitions will foster international studies regarding prevalence.

What Are the Diagnostic Criteria?

The Japanese Circulation Society was the first to develop comprehensive national guidelines specifically for vasospastic

Table 1. Synopsis of Vasospastic Angina

Key Points
1. *Who* is likely to have vasospastic angina?
· Clinical presentation – rest angina promptly resolving with nitrates
· Predisposing risk factors – smoking, Japanese ethnicity
2. *What* are the diagnostic criteria?
· Spontaneous episode – nitrate-responsive angina + ischemic ECG changes
· Inducible spasm – provoke chest pain + ischemic ECG + >90% constriction
3. *Why* diagnose vasospastic angina?
· Prevent major adverse events (death, myocardial infarction, arrhythmias)
· Promptly initiate readily available effective therapy
· Avoid inappropriate therapy
4. *When* should provocative spasm testing be performed?
· Only if potential benefits > risks.
· Benefits – validated technique with prognostic implications
· Risks – very good safety record with acetylcholine provocation in trained labs
5. *How* should patients be managed?
· Lifestyle changes – smoking cessation
· First-line pharmacological therapy – calcium-channel blockers
· Avoid vasospastic agents – β-blockers, ergots, sympathomimetics
· Percutaneous coronary interventions have very limited role
6. *Where* are the knowledge gaps?
· Defining prevalence, risk factors and prognosis
· Elucidating the mechanisms of vascular smooth muscle hyper-reactivity
· Establishing the optimal diagnostic approach
· Developing novel therapies

Table 2. COVADIS Diagnostic Criteria for Vasospastic Angina*

Vasospastic Angina Diagnostic Criteria Elements
1. **Spontaneous Episode** – document following:
a. ***Nitrate-responsive angina***, with at least one of the following:
i. Rest angina – especially between night and early morning
ii. Marked diurnal variation in exercise tolerance – reduced in morning
iii. Hyperventilation can precipitate an episode
iv. Calcium-channel blockers (but not β-blockers) suppress episodes
and
b. ***Transient ischemic ECG changes***, including any of the following in at least 2 contiguous leads:
i. ST segment elevation ≥0.1 mV
ii. ST segment depression ≥0.1 mV
iii. New negative U waves
OR
2. **Inducible *coronary artery spasm*** – in response to provocative stimulus:
a. ***Transient total or subtotal coronary artery occlusion*** (>90% constriction), **and**
b. ***Chest pain provoked, and***
c. ***Transient ischemic ECG changes provoked*** (as above)

*Definitive vasospastic angina defined as: (i) nitrate-responsive angina during spontaneous episodes and (ii) either transient ischemic ECG changes during spontaneous episodes or inducible coronary artery spasm criteria are all fulfilled. Suspected vasospastic angina defined as: (i) nitrate-responsive angina during spontaneous episodes and (ii) either equivocal/unavailable ischemic ECG changes during spontaneous episode, and equivocal inducible coronary artery spasm criteria. COVADIS, Coronary Vasomotion Disorders International Study Group.

angina[18] (also referred to as coronary spastic angina by some Japanese researchers), which have been subsequently updated.[17] More recently, COVADIS published international diagnostic criteria.[19] The term "vasospastic angina" should be considered a broad diagnostic category encompassing both documented spontaneous episodes as well as induced episodes of coronary artery spasm. Although it may potentially coexist with coronary microvascular disorders[2] and/or structural CAD (**Figure**), it is a clinical entity that is centered on the hyper-reactivity of large coronary arteries.

Fundamental to the diagnosis of vasospastic angina is a history of rest angina that promptly responds to short-acting

Table 3. Coronary Spasm Association Risk Score

Clinical determinant	Hazard ratio (95% CI)	Assigned score
Out-of-hospital cardiac arrest	3.79 (1.61–8.94)	4
Significant organic stenosis	2.24 (1.33–3.78)	2
Rest angina alone	1.71 (1.08–2.72)	2
Smoking	1.71 (1.04–2.79)	2
Multivessel spasm	1.69 (1.03–2.78)	2
ST elevation during angina attack	1.54 (0.95–2.50)	1
Use of β-blockers	2.00 (0.88–4.54)	1

The Japanese Coronary Spasm Association (JCSA) Risk Score[24] (score 0–9) predicts the risk of MACE (cardiac death, non-fatal myocardial infarction and appropriate implantable cardioverter-defibrillator shocks) in patients with VSA, scored as: Low risk (0–2) 0.5% MACE/5 years; Intermediate risk (3–5) 0.8% MACE/5 years; High risk (6–9) 3.1% MACE/5 years. CI, confidence interval; MACE, major adverse cardiac events; VSA, vasospastic angina.

nitrates, that is, "nitrate-responsive angina" (Table 2). The absence of nitrate-responsive angina suggests that a diagnosis of vasospastic angina is unlikely.[17]

In the event of an ECG being recorded during a spontaneous vasospastic episode, the demonstration of transient diagnostic ischemic ECG changes during the nitrate-responsive angina episode is confirmatory evidence of "definite vasospastic angina" (Table 2) and provocative spasm testing is not required.[17] However, if the ischemic ECG changes are equivocal, then provocative spasm testing is required and a positive test would be indicative of "definite vasospastic angina" whereas a negative test in this context warrants a diagnosis of "suspected vasospastic angina" (Table 2).

In the absence of a documented spontaneous vasospastic episode, provocative spasm testing can be performed in patients with nitrate-responsive angina, with a positive test confirming a diagnosis of definitive vasospastic angina whereas a negative test would qualify a diagnosis of suspected vasospastic angina (Table 2).

Prinzmetal Variant Angina

The terms "variant angina" (or "Prinzmetal variant angina") and "vasospastic angina" are often used interchangeably, but variant angina is a specific form of vasospastic angina that is diagnosed during a documented spontaneous vasospastic episode defined by (a) nitrate-responsive rest angina, associated with (b) transient ST segment elevation (≥0.1 mV in at least 2 contiguous leads). These concepts herald from the original work by Prinzmetal et al,[20] but the diagnostic subcategory should be perpetuated, considering the extensive published literature based on this definition. These early variant angina studies need to be interpreted in context, because many were undertaken when the use of coronary angiography was limited and CCBs were still emerging.

Why Diagnose Vasospastic Angina?

In contemporary clinical practice, the diagnosis of vasospastic angina is not often considered in patients presenting with chest pain. Consequently, the median time period for the diagnosis to be made following the initial presentation to a physician is 2 months.[21] Failure to make a diagnosis exposes the patient to (1) an unnecessary risk of major adverse cardiac events (MACE), (2) failure to institute effective therapy, and (3) the initiation of inappropriate therapy.

Major Adverse Cardiac Events

The prevalence of MACE (including death and MI) in vasospastic angina is difficult to define because of the variation in defining the disorder. Early studies[22] report a 3-year MACE rate of 5–37%, whereas more recent studies[23,24] describe a rate of 1% or less. Irrespective of the prevalence, it is disconcerting that MACE tend to occur within 3 months of symptom onset,[21] often when the diagnosis of vasospastic angina is yet to be made. The diagnosis especially needs to be considered early in patients presenting with acute coronary syndrome without a culprit lesion,[25–29] unexplained syncope[30] or those who survive sudden cardiac death.[31]

The Japanese Coronary Spasm Association has established a comprehensive vasospastic angina registry from which they have identified 7 independent clinical variables that predict the occurrence of MACE at 5 years (Table 3).[24] These MACE predictors require further validation because ethnicity,[22] sex,[32] and spasm type (diffuse vs. focal)[12] have also been shown to affect the long-term prognosis.

Effective Therapy Available

Prompt initiation of effective vasospastic angina therapy can avert the occurrence of MACE in these patients. CCBs are readily available and particularly effective, because their use has been shown to be an independent determinant of long-term infarct-free survival.[33]

Use of Inappropriate Therapy

An early diagnosis of vasospastic angina will avoid the initiation of inappropriate therapies such as revascularization and β-blockers. Although revascularization therapies are effective in obstructive atherosclerotic CAD, clinical decisions to undertake these interventions are often made without considering or assessing the dynamic nature of coronary stenoses.[34–36] For example, 21% of obstructive non-culprit lesions during angiography after acute MI are subsequently shown to be non-obstructive on follow-up angiography.[37] Similarly, β-blockers are effective in atherosclerotic CAD,[38] but of limited use in vasospastic angina, potentially predisposing to vasospastic episodes.[39]

When Should Provocative Spasm Testing Be Performed?

Documenting a spontaneous vasospastic episode can establish the diagnosis of vasospastic angina but they occur infrequently, thereby necessitating the use of provocative spasm testing. The indications for provocative spasm testing have been published in the JCS guidelines and are summarized in Table 4. However, determining the appropriateness of pro-

Table 4. Indications for Provocative Spasm Testing
Class I (Strong Indications)
• History suspicious of VSA without documented spontaneous episode, especially if:
· Nitrate-responsive rest angina, and/or
· Marked diurnal variation in symptom onset/exercise tolerance, and/or
· Rest angina without obstructive coronary artery disease
• Acute coronary syndrome 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-invasive diagnosed patients unresponsive to drug therapy
Class IIb (Controversial Indications)
• Documented spontaneous episode of variant angina
• Invasive testing for non-invasive diagnosed patients responsive to drug therapy
Class III (Contra-indications)
• Emergent acute coronary syndrome
• Severe fixed multivessel CAD including left main coronary artery stenosis
• Severe myocardial dysfunction (Class IIb if symptoms suggestive of vasospasm)
• Patients without any symptoms suggestive of VSA

*Adapted with permission from Beltrame JF, et al.[19] CAD, coronary artery disease; PCI, percutaneous coronary intervention; VSA, vasospastic angina.

vocative spasm testing for a particular patient not only requires an understanding of the methods involved but also careful consideration of the potential benefits and risks, as discussed next.

Spasm Testing Methods

Provocative spasm testing involves (i) the use of a provocative stimulus, either pharmacological (acetylcholine or ergonovine) or non-pharmacological (hyperventilation±TRIS buffer infusion or cold pressor testing), and (ii) an assessment modality to evaluate the vasomotor response, which may include angina symptoms, ischemic ECG changes, reversible perfusion defect, reversible regional wall motion abnormality, or subtotal/total vessel occlusion on angiography.[40] Noninvasive approaches to provocative spasm testing have included bedside hyperventilation testing with ECG monitoring[41] or intravenous ergonovine/ergometrine testing with ECG/echocardiographic monitoring.[40,42] However, the gold standard approach uses invasive coronary angiography to directly image coronary spasm, with intracoronary acetylcholine the most commonly used provocative stimulus (particularly as ergonovine is not available in many countries).

As detailed in **Table 2**, an invasive provocation test for inducible coronary artery spasm is considered positive when all of the following have been documented in response to the provocative stimulus: (a) chest pain, (b) ischemic ECG changes, and (c) ≥90% vasoconstriction on angiography. The test result is considered equivocal if the provocative stimulus does not induce all 3 components. Although earlier studies have used a lower threshold, the ≥90% vasoconstrictor response threshold has been established by expert consensus,[17,18] with the rationale based on hemodynamic studies demonstrating ≥90% vessel obstruction is required to impede resting blood flow. Importantly, catheter-induced spasm is not considered as a positive test for inducible spasm.

Benefits

Because vasospastic angina is diagnosed by documentation of spontaneous episodes alone in less than one-quarter of cases,[32] without the use of provocative spasm testing many cases would be missed. Importantly, both ergonovine[43] and acetylcholine[44] provocative testing have been validated against spontaneous episodes of vasospastic angina and found to have a sensitivity ≥90% and specificity ≥97%. Furthermore, vasospastic angina studies have demonstrated similarities in the clinical characteristics of induced and spontaneous vasospastic episodes,[45] as well as confirming the reproducibility of provocation testing.[46] The prognostic implications of a positive provocative spasm test have recently been demonstrated in the VA Korean Registry, with 4.2% of the patients experiencing a cardiac event during the subsequent 2 years.[47]

Risks

Provocative spasm testing has had a precarious history following early experience with bedside ergot testing undertaken with ECG monitoring alone and managed primarily with sublingual nitrates when ST elevation occurred. This hazardous approach was abandoned when a case series reported MACE in 5 patients during spasm testing, including 3 deaths.[48] With the evolution of coronary angiography and invasive provocative spasm testing, the safety of this investigation has markedly improved, because of early identification of spasm and prompt potent treatment. Intracoronary acetylcholine provocative spasm testing has particularly been shown to be safe, with no reported deaths in large studies.[49,50] However, significant adverse events can occur during testing, including cardiac arrhythmias,[49–51] coronary artery dissection, ST-elevation MI,[52] and shock.[49,51] Although some of these hazards relate to the invasive angiography procedure, others are inherent to coronary spasm and best managed in a medically supervised environment rather than exposing the undiagnosed patient to these conditions. This relative risk of undertaking acetylcholine testing is well illustrated by Wei et al,[52] in whose study the risk

of MACE during testing was 2.4% but over the next 4 years the risk of MACE was 14.5%, including a 2.7% mortality risk. Accordingly, those authors conclude that the use of provocative testing by experienced operators for diagnostic and prognostic purposes was beneficial in these at-risk patients.[52]

How Should Patients Be Managed?

The conventional management of vasospastic angina involves lifestyle changes, use of established pharmacological therapies, avoidance of aggravating factors and possibly the use of percutaneous coronary intervention (PCI) for associated fixed obstructive CAD. In some patients with refractory vasospastic angina, these therapies have limited efficacy, so that alternate approaches are warranted.

Lifestyle Changes

Smoking cessation efforts are essential in patients with vasospastic angina, given that smoking is a major risk factor for coronary artery spasm. Moreover, smoking cessation in vasospastic angina patients is associated with a reduction in both angina symptoms[53] and cardiovascular events.[15] Aerobic exercise training has also been shown to reduce angina episodes in patients with vasospastic angina.[54] In contrast, the role of lipid-lowering therapy is less clear, although statin therapy has been shown to suppress acetylcholine-induced spasm.[55]

Pharmacological Therapies

CCBs are the first-line therapy for vasospastic angina. These agents have been shown to reduce symptomatic angina episodes,[56–62] suppress inducible coronary spasm,[60] and most importantly are an independent determinant of preventing MACE in vasospastic angina patients.[33,63]

Nitrates have been used since the first description of vasospastic angina and are effective in reducing anginal episodes,[57] although their efficacy in reducing MACE is not evident.[64,65]

Nicorandil is a potassium-channel opener with nitrate-like effects that is extensively used in Japan for the treatment of vasospastic angina. It is also available in other countries, but not in the USA. The parenteral preparation has been shown to ameliorate acute vasospastic episodes[66] and the oral form prevents inducible vasospastic episodes,[67] as well as reducing angina frequency.[68]

Fasudil is a rho kinase inhibitor that is only available in Japan at present. The rho kinase pathway has an important role in the pathogenesis of coronary spasm[69,70] and its inhibition has been shown to acutely alleviate severe coronary vasospasm,[71] as well as prevent inducible spasm in patients with vasospastic angina.[72]

Other pharmacologic therapies that have been shown to suppress inducible coronary artery spasm and thus may be of benefit in the treatment of coronary artery vasospastic disorders include statins,[55] cilostazol,[73] pioglitazone,[74] magnesium,[75] estrogen replacement therapy in postmenopausal women[76] and possibly vitamin C therapy.[77]

Avoid Vasospastic Agents

Certain medications may precipitate a vasospastic episode and should be used with caution. Beta-blockers have been shown to produce vasoconstriction[78] and precipitate coronary spasm;[39] however, in combination with vasodilator therapy they may be safe[79] and useful in patients with concomitant atherosclerotic structural CAD.[18] Although the 3rd generation β-blockers (eg, nebivolol) should be less likely to induce vasospasm, because of their vasodilating properties, a recent case report described nebivolol-associated vasospasm.[80] Ergot compounds found in some antimigraine medications[81] and obstetric preparations[82] may precipitate a vasospastic episode. Sympathomimetic agents such as epinephrine[83,84] and cocaine[85] may produce coronary spasm. Serotonergic compounds are found in some antimigraine therapies[86–89] and some antidepressants, and thus must be used with caution. General anesthesia may induce episodes of coronary spasm,[90–92] although it is often difficult to determine the exact precipitating medication. Chemotherapeutic agents, including 5-fluorouracil,[93–95] capecitabine[96,97] and sorafenib,[98,99] have been reported to precipitate coronary vasospastic episodes. Alcohol ingestion may precipitate vasospastic angina episodes,[100–103] but the literature is conflicting because episodes have also been reported to be alleviated by alcohol consumption[104,105] and aggravated during alcohol withdrawal.[106] These apparent inconsistencies may in part be explained by variations in the aldehyde dehydrogenase-2 genotype in East Asians. Approximately 30–50% of Japanese, Korean and Chinese populations (but not within Caucasian or African populations) have aldehyde dehydrogenase-2 deficiency that results in increased production of reactive aldehydes and oxidative stress that predisposes to coronary artery spasm.[107]

PCIs

Although PCIs are generally inappropriate in patients with vasospastic angina who have no obstructive CAD, it may be considered in those with concomitant obstructive atherosclerotic CAD. PCI to ameliorate the obstructive atherosclerotic lesion can be safely performed in vasospastic angina patients,[108–111] although the reported efficacy is variable, with some studies finding an increased risk of restenosis following angioplasty,[108–110] but others demonstrating similar results to those without a propensity to vasospasm.[111] However, the procedure should be undertaken with the patient on maintenance CCB and nitrate therapy, which should be continued after the procedure to avoid vasospasm at other sites.[112]

Refractory Vasospastic Angina

This is defined as vasospastic angina episodes that are unresponsive to 2 coronary vasodilator medications at conventional doses (typically CCBs and nitrates). During an acute intractable episode of coronary artery spasm, intracoronary administration of nitrates[35,48,113] and/or verapamil[114] may be considered, but generally the problem has a more chronic nature. The management of chronic refractory vasospastic angina is largely empirical, with case reports suggesting the following strategies to be effective: (a) high-dose CCBs[115,116] (verapamil or diltiazem 960 mg/day and/or nifedipine 100 mg/day), (b) antiadrenergic drugs, including guanethidine and clonidine,[117] (c) fasudil,[71] (d) corticosteroids,[118,119] (e) left stellate ganglion blockade,[120] and (f) selective PCI.[121–128] Coronary artery bypass grafting with cardiac denervation has been used in the past but with unfavorable outcomes.[129,130]

Where Are the Knowledge Gaps?

Although considerable advances in the understanding and treatment of vasospastic angina have been made, the future is especially promising considering contemporary mechanistic and registry research. Knowledge gaps to be addressed include an improved understanding of the prevalence, prognosis, pathophysiology, diagnostic strategies and therapeutics.

Prevalence, Risk Factors and Prognosis

Through international clinical registries such as the Japanese

Coronary Spasm Association registry, large numbers of patients with common diagnostic criteria can be studied so that the prevalence, risk factors, and prognosis of vasospastic angina can be accurately determined. International collaboration to build on the Asian registries will provide a more global perspective.

Pathophysiology

Vascular smooth muscle hyper-reactivity is believed to be the primary pathophysiological mechanism responsible for coronary artery spasm, with endothelial dysfunction also potentially contributing.[69,131] Although the etiology of this vascular hyper-reactivity remains elusive, significant advances in the responsible molecular mechanisms have been made with the development of a miniature swine coronary artery vasospastic model.[69,132] However, further human studies are required to evaluate the clinical relevance of these mechanisms and explore novel therapeutic targets. In addition, coexisting coronary microvascular dysfunction in patients with vasospastic angina needs further evaluation, especially in relation to its prevalence and the clinical presentations implicating coexistence.

Diagnostic Strategies

Provocative spasm testing allows the diagnosis of vasospastic angina in the absence of a spontaneous vasospastic episode. A variety of invasive provocative spasm testing protocols are described, but the optimal protocol for safety and diagnostic efficacy needs to be defined.[40] The safety and diagnostic efficacy of noninvasive methods need further evaluation.

Therapeutics

The advent and use of CCBs has been associated with a significant reduction in MACE in vasospastic angina patients. However, these agents have limited effect in reducing symptoms, with only 38% of affected patients achieving complete resolution of anginal episodes.[133] Nicorandil and more recently fasudil were developed as antivasospastic agents, but their availability internationally is limited and their incremental benefits in improving symptoms and reducing major adverse events are yet to be defined. Thus, targeting new therapies at novel molecular pathways is needed. Moreover, the role of lifestyle factors, treatments directed at associated nonobstructive atherosclerotic CAD, and the use of devices such as implantable defibrillators in those with life-threatening vasospastic angina-associated arrhythmias, needs to be clarified.

Conclusions

Functional disorders of the coronary circulation are easily overlooked if not considered in the diagnostic evaluation of patients with suspected IHD. Vasospastic angina is one of the more easily defined coronary vasomotor disorders because the pathologic vessels can be imaged and effective therapies are available. Despite this, the diagnosis is often a latent consideration, so patients are unnecessarily exposed to MACE. Furthermore, substantial work is still required by clinical investigators to both improve our understanding of this disorder and develop novel therapies.

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Supplementary Files

Supplementary File 1

Coronary Artery Vasospastic Disorders Summit Attendees

Please find supplementary file(s);
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