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SPECIAL ARTICLE

# International standardization of diagnostic criteria for vasospastic angina

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The *Coronary Vasomotion Disorders International Study Group* (COVADIS) was established to develop international standards for the diagnostic criteria of coronary vasomotor disorders. The first symposium held on the 4–5 September 2013 addressed the criteria for vasospastic angina, which included the following (i) nitrate-responsive angina, (ii) transient ischaemic electrocardiogram changes, and (iii) documented coronary artery spasm. Adoption of these diagnostic criteria will improve the clinical diagnosis of this condition and facilitate research in this field.

**Keywords** Coronary artery disease • Ischaemic heart disease • Coronary artery spasm • Vasospastic angina

More than 55 years ago, Prinzmetal detailed the clinical and electrocardiographic manifestations of a disorder thought to be due to epicardial coronary artery spasm, which he referred to as variant angina.[1] Subsequently, these patients were shown to have inducible coronary artery spasm and the term vasospastic angina (VSA) was coined. Except for the recently published Japanese Circulation Society guidelines[2,3] and a brief summary in the European Society of Cardiology Stable Coronary Artery Disease Guidelines,[4] there are no universal diagnostic criteria for VSA, which has impaired the progress in understanding and diagnosing this disorder. The objective of this paper is to establish international diagnostic criteria for VSA, to improve clinical diagnosis and facilitate research.

The term VSA should be considered as a broad diagnostic category including both documented spontaneous episodes of angina pectoris produced by coronary artery spasm as well as those induced during provocative spasm testing protocols. Although it may potentially co-exist with coronary microvascular disorders and/or structural coronary artery disease, VSA is a clinical entity that is centred on the hyper-reactivity of large coronary arteries to vasoconstrictor stimuli.[5] The importance of diagnosing VSA relates to: (i) the major adverse events associated with this disorder including sudden cardiac death,[6] acute myocardial infarction,[7] and syncope,[8] which may occur before the diagnosis of VSA is considered[9]; (ii) the potential to prevent these adverse events by avoiding potential coronary artery spasm precipitants (e.g. vasoconstrictors) and the use of established effective therapies (calcium channel blockers and nitrates).

*Table 1* summarizes the diagnostic criteria as proposed by the *Coronary Vasomotion Disorders International Study Group* (COVADIS). This group was established to internationally unify the diagnostic criteria for coronary vasomotor disorders, with the first COVADIS symposium held on the 4–5 September 2013 to address the VSA criteria. As detailed in *Table 1* and discussed further, VSA diagnosis involves three considerations: (i) classical clinical manifestations of VSA, (ii) documentation of myocardial ischaemia during spontaneous episodes, (iii) demonstration of coronary artery spasm, while the extent of evidence sub-classifies VSA into either 'definitive' or 'suspected' VSA (*Table 1*).

## Clinical manifestations

The hallmark feature of VSA is rest angina that promptly responds to short-acting nitrates. The anginal symptoms may exhibit a circadian pattern, be precipitated by hyperventilation but not usually exertion, and typically suppressed by calcium channel blockers (*Table 1*). Smoking is an established predisposing risk factor for VSA, whereas diabetes and hypertension do not play a role, and the relationship with dyslipidaemia is unclear.[10,11] Previous reports have suggested

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**Table 1 Coronary Artery Vasospastic Disorders Summit diagnostic criteria for vasospastic angina[a]**

Vasospastic angina diagnostic criteria elements

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

[a]'Definitive vasospastic angina' is diagnosed if nitrate-responsive angina is evident during spontaneous episodes and either the transient ischaemic ECG 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 ECG changes are equivocal or unavailable and coronary artery spasm criteria are equivocal.

**Table 2 Indications for provocative coronary artery spasm testing**

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 coronary artery disease
  - Unresponsive to empiric therapy
- 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
- Documented spontaneous episode of VSA to determine the 'site and mode' of spasm

Class IIb (controversial indications).
- Invasive testing for non-invasive diagnosed patients responsive to drug therapy

Class III (contra-indications)
- Emergent acute coronary syndrome
- Severe fixed multi-vessel coronary artery disease including left main stenosis
- Severe myocardial dysfunction (Class IIb if symptoms suggestive of vasospasm)
- Patients without any symptoms suggestive of VSA

that VSA is associated with the Raynaud's phenomenon and migraine, as part of a generalized vasomotor disorder[12]; however, systematic studies have found the relationship tenuous.[13] Japanese patients have been shown to have hyper-reactive vessels compared with Caucasians[14] but it is uncertain whether this translates to a greater propensity for VSA.

## Ischaemic electrocardiogram manifestations

In Prinzmetal's original description,[1] spontaneous episodes of rest angina were associated with transient ST elevation that promptly resolved with short-acting nitrates. Subsequent studies have also demonstrated transient ST depression and U wave changes during spontaneous VSA episodes. If a spontaneous episode of rest angina is associated with transient ischaemic electrocardiogram (ECG) changes and there is no other cause identified for the ECG changes, then coronary artery spasm is presumed to be responsible and a definitive diagnosis of VSA may be made without formal documentation of coronary artery spasm (*Table 1*). However, documenting ischaemic ECG changes during spontaneous episodes of rest angina occurs infrequently so that coronary artery spasm provocative testing is often required.

## Coronary artery spasm manifestations

Coronary artery spasm provocation testing has been clinically used for >40 years although in contemporary cardiology practice, it is largely restricted to specialized centres. Multiple spasm testing protocols have been developed including non-invasive methods and these are discussed in detail in other papers.[3] The discussion in this paper is restricted to the gold standard approach.

### Method

The gold standard method for provocative spasm testing involves the administration of a provocative stimulus (typically intracoronary acetylcholine but alternatively intracoronary or intravenous ergonovine may be used) during invasive coronary angiography with the monitoring of patient symptoms, ECG and angiographic documentation of coronary artery spasm. A positive provocative test for coronary artery spasm must induce all of the following in response to the provocative stimulus: (i) reproduction of the usual chest pain, (ii) ischaemic ECG changes, and (iii) >90% vasoconstriction on angiography. The test result is considered equivocal if the provocative stimulus does not induce all three components. The consensus from the COVADIS symposium was that >90% vasoconstriction is the angiographic threshold to diagnose inducible spasm. Furthermore, this total/subtotal vasoconstriction may occur within the confines of one isolated coronary segment (focal spasm) or in ≥2 adjacent coronary segments (diffuse spasm).[10,15] Validation studies have demonstrated a high sensitivity and specificity for both the ergonovine (91 and 97%, respectively[16]) and acetylcholine (90 and 99%, respectively[17]) protocols relative to the diagnosis of spontaneous VSA.

## Risks

Non-invasive bedside provocative spasm testing has been associated with significant adverse events including death,[18] because detection and alleviation of the induced spasm is delayed. In contrast, invasive provocative spasm testing allows rapid detection and treatment of the induced spasm. Accordingly, there are no reported deaths and a similar risk profile to other invasive coronary procedures,[15,19,20] although there is 6.8% incidence of cardiac arrhythmias (i.e. comparable with that observed during spontaneous coronary artery spasm episodes).[20]

## Indications

Considering the risks associated with provocative spasm testing, the procedure should be performed by personnel experienced with the protocol in patients where the risk and benefits have been carefully evaluated. *Table 2* outlines recommended indications for provocative spasm testing. These are ranked into the conventional Class I–III categories, based upon the relative risks and benefits of the investigation.

## Conclusion

There are no universal diagnostic criteria for VSA, which has impaired the progress in understanding and diagnosing this disorder. Adoption of these diagnostic criteria will improve the clinical diagnosis of this condition and facilitate research in this field. Future directions for COVADIS involve the establishment of an international coronary vasomotor disorder clinical registry for diagnostic, prognostic, and therapeutic research.

## Funding

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# Appendix

## Coronary Artery Vasospastic Disorders Summit Attendees

The following international participants attended the inaugural Coronary Artery Vasospastic Disorders Summit held in Amsterdam on 4–5 September, 2013.

## Steering Committee

Bairey Merz, Noel—United States (Co-chair)
Beltrame, John—Australia (Co-chair)
Crea, Filippo—Italy
Kaski, Juan Carlos—United Kingdom
Ogawa, Hisao—Japan
Ong, Peter—Germany
Sechtem, Udo—Germany
Shimokawa, Hiroaki—Japan

## Summit Attendees

Baek, Sang Hong–South Korea
Bugiardini, Raffaele—Italy
Camici, Paolo—Italy
Conti, Richard—United States
Di Fiore, David—Australia
Lanza, Gaetano—Italy
Marzilli, Mario—Italy
Maseri, Attilio—Italy
Matsumoto, Yasuharu—Japan
Mehta, Puja—United States
Nihei, Taro—Japan
Nishimiya, Kensuke—Japan
Sueda, Shozo—Japan
Tremmel, Jennifer—United States
Uzuka, Hironori—Japan

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