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International standardization of diagnostic criteria for microvascular angina☆

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ABSTRACT

Standardization of diagnostic criteria for ischemic symptoms due to coronary microvascular dysfunction (CMD) is needed for further investigation of patients presenting with anginal chest pain consistent with "microvascular angina" (MVA). At the annual *Coronary Vasomotion Disorders International Study Group* (COVADIS) Summits held in August 2014 and 2015, the following criteria were agreed upon for the investigative diagnosis of microvascular angina: (1) presence of symptoms suggestive of myocardial ischemia; (2) objective documentation of myocardial ischemia, as assessed by currently available techniques; (3) absence of obstructive CAD (<50% coronary diameter reduction and/or fractional flow reserve (FFR) >0.80) (4) confirmation of a reduced coronary blood flow reserve and/or inducible microvascular spasm. These standardized criteria provide an investigative structure for mechanistic, diagnostic, prognostic and clinical trial studies aimed at developing an evidence base needed for guidelines in this growing patient population. Standardized criteria will facilitate microvascular angina registries and recruitment of suitable patients into clinical trials. Mechanistic research will also benefit from the implementation of standardized diagnostic criteria for MVA.

1. Introduction

Myocardial ischemia that develops in the absence of hemodynamically significant coronary artery stenoses continues to puzzle physicians worldwide and a large proportion of patients with this condition are discharged from specialty medical attention with a diagnosis of "non-cardiac chest pain". A recent U.S. study in over 400,000 individuals undergoing diagnostic coronary angiography for suspected obstructive epicardial coronary disease showed that 59% had either normal coronary arteriograms or non-obstructive (<50% stenosis) coronary artery disease (CAD) [1]. Of importance, the arterial coronary tree comprises not only the epicardial arteries, but also smaller arteries and arterioles (<500 μm). The latter feed the capillaries and represent an important part of the coronary microcirculation, namely the main site of regulation of myocardial blood flow. The term coronary microvascular dysfunction (CMD) was proposed to cover a large number of clinical scenarios characterized by evidence of a reduced Coronary Flow Reserve (CFR) in the absence of obstructive epicardial disease [2]. Several studies have demonstrated coronary microvascular dysfunction (CMD) in a large proportion of patients with non-obstructive CAD (~30–50%) even after exclusion of epicardial spasm using provocative testing with acetylcholine [3,4]. COVADIS, the *Coronary Vasomotion Disorders International Study Group*, was established to develop standardized criteria for coronary vasomotor disorders thereby facilitating the clinical diagnosis of affected patients and promoting international collaborative research endeavors to improve our understanding of these elusive disorders. This paper focuses on the standardization of criteria for microvascular angina (MVA) attributable to CMD, in patients presenting with angina pectoris or ischemic-like symptoms

Abbreviations: CAD, coronary artery disease; CMD, coronary microvascular dysfunction; CMR, cardiac magnetic resonance imaging; COVADIS, Coronary Vasomotion Disorders International Study Group; CTA, computed tomography angiography; FFR, fractional flow reserve; MVA, microvascular angina; PET, positron emission tomography.

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in the absence of flow-limiting CAD (i.e. type 1 CMD according to the original classification proposed by Camici and Crea [2], Table 1). This seems timely as COVADIS has identified several knowledge gaps in this area, including the need for a better understanding of MVA with regard to: (1) absolute prevalence, (2) optimized diagnostics, (3) efficacy of pharmacologic and other therapeutic strategies and (4) impact on prognosis. To meaningfully address these knowledge gaps clinical registries by COVADIS and other groups have been established and clinical trials are being formulated.

2. Symptoms and clinical manifestations

Similar to patients with obstructive, epicardial CAD, those with MVA due to CMD may present with typical angina pectoris, atypical symptoms, or angina-equivalent symptoms. Albeit CMD may occur in asymptomatic subjects, these individuals will be identified only opportunistically given the absence of symptoms [5]. Characteristically, patients with MVA often present with effort-induced retrosternal oppressive chest discomfort or pain, and/or dyspnea, although in many patients, the symptoms can develop not only during, but also or mainly after the exercise has ceased [6]. In addition, patients with MVA may experience episodes of chest pain at rest. These episodes may have variable duration and, not infrequently, the chest pain is atypical in character and duration, i.e. prolonged, oppressive discomfort or stabbing like pain. Compared to patients with angina due to obstructive CAD, patients with angina caused by CMD appear to respond less dramatically to the administration of sublingual or oral nitrates [7]. Although the clinical presentation can be similar in men and women with CMD, studies have consistently shown an increased female prevalence (especially postmenopausal women) [8,9,19]. Cardiovascular risk factors in patients with MVA are similar to those in CAD and a pathogenic role -via the induction of microvascular dysfunction- has been suggested for these risk factors in subgroups of patients with MVA [10]. It is important to stress the fact that the diagnosis of MVA cannot be established based on symptoms alone.

3. Objective documentation of myocardial ischemia

Current guidelines for the diagnosis of stable ischemic heart disease [5,11,12] recommend that symptomatic patients with an intermediate pre-test probability for the presence of obstructive CAD should undergo non-invasive diagnostic testing for detection of myocardial ischemia (Table 2). Objective demonstration of myocardial ischemia should be obtained with rest/stress electrocardiography and/or non-invasive imaging by assessing either myocardial perfusion with single photon emission computed tomography (SPECT), positron emission tomography (PET) or cardiac magnetic resonance (CMR) or cardiac function with stress echocardiography. During such testing, patients with MVA typically show ST-segment changes and angina, and approximately 20–30% of the patients exhibit transient perfusion defects [13]. A minority of patients only exhibit regional wall motion abnormalities. The dissociation between clinical and ECG signs of ischemia and mechanical alterations is possibly due to a patchy distribution of ischemia resulting from CMD and is in sharp contrast with the regional perfusion and/or wall motion abnormalities observed when myocardial ischemia is caused by flow-limiting epicardial stenoses [14].

Table 1
Classification of coronary microvascular dysfunction.

	Clinical setting	Main pathogenetic mechanisms
Type 1: Coronary microvascular dysfunction in the absence of myocardial diseases and obstructive coronary artery disease	Risk factors Microvascular angina	Endothelial dysfunction Smooth muscle cell dysfunction Vascular remodeling

Table 2
Clinical criteria for suspecting microvascular angina (MVA)*.

1. Symptoms of myocardial ischemia
   a. Effort and/or rest angina
   b. Angina equivalents (i.e. shortness of breath)
2. Absence of obstructive CAD (<50% diameter reduction or FFR > 0.80) by
   a. Coronary CTA
   b. Invasive coronary angiography
3. Objective evidence of myocardial ischemia
   a. Ischemic ECG changes during an episode of chest pain
   b. Stress-induced chest pain and/or ischemic ECG changes in the presence or absence of transient/reversible abnormal myocardial perfusion and/or wall motion abnormality
4. Evidence of impaired coronary microvascular function
   a. Impaired coronary flow reserve (cut-off values depending on methodology use between ≤2.0 and ≤2.5)
   b. Coronary microvascular spasm, defined as reproduction of symptoms, ischemic ECG shifts but no epicardial spasm during acetylcholine testing.
   c. Abnormal coronary microvascular resistance indices (e.g. IMR > 25)
   d. Coronary slow flow phenomenon, defined as TIMI frame count >25.

Table legend: ECG = electrocardiogram, CAD = coronary artery disease, CTA = computed tomographic angiography, FFR = fractional flow reserve, IMR = index of microcirculatory resistance, TIMI = thrombolysis in myocardial infarction.
*__Definitive MVA__ is only diagnosed if all four criteria are present for a diagnosis of microvascular angina.
__Suspected MVA__ is diagnosed if symptoms of ischemia are present (criteria-1) with no obstructive coronary artery disease (criteria-2) but only (a) objective evidence of myocardial ischemia (criteria-3), or (b) evidence of impaired coronary microvascular function (criteria-4) alone.

4. Absence of obstructive/flow-limiting coronary stenoses

The diagnosis of MVA requires – in the first instance – ruling out obstructive/flow limiting CAD as a cause of the ischemic symptoms. The latter is defined as stenoses causing >50% diameter reduction, assessed by conventional angiography or computed tomography angiography [CTA], and/or abnormal (<0.80) fractional flow reserve (FFR). Patients without obstructive CAD may have one of the following on diagnostic coronary angiography: normal or mildly diseased coronary arteries (0% to 30% diameter stenosis), stenosis of "intermediate" severity (30–50%) or diffusely diseased epicardial arteries. In many instances angiography alone may be insufficient to establish whether stenoses <50% are non-obstructive [15]. It is therefore necessary to demonstrate, objectively, that diffuse disease or stenoses of 'intermediate' severity are not flow-limiting and FFR should be measured to identify the hemodynamic relevance of these lesions. However, in some cases microvascular dysfunction may limit microvessel dilation leading to underestimation of physiological stenosis severity by FFR in this setting [16]. CTA is a useful tool to exclude significant epicardial disease. However, in patients with demonstrable epicardial disease on CTA invasive coronary angiography is often performed to assess the extent of disease. In such cases with diffuse disease or stenosis of "intermediate" severity (30–50%) FFR should be measured to assess the relevance of these lesions. CT-FFR is an appealing, emerging non-invasive technology for the assessment of flow-limiting stenoses, but it is probably not as yet sufficiently proven a methodology to be used for this purpose in routine medical practice [17]. In patients with CAD, but with FFR >0.80, or in those with angiographically normal coronary arteries, the presence of: (1) ischemia-like symptoms and (2) objective evidence of myocardial ischemia, should represent sufficient evidence for the clinician to consider CMD as a likely mechanism responsible for the patient's symptoms.

5. Confirmation of reduced coronary blood flow reserve and/or microvascular spasm causing myocardial ischemia

Currently available techniques do not allow direct visualization of the coronary microcirculation in vivo. Assessment of coronary microcirculatory function can be done invasively and non-invasively using techniques that rely on the functional integrity of the coronary microcirculation. A

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