International standardization of diagnostic criteria for microvascular angina

Article *in* International Journal of Cardiology · September 2017

DOI: 10.1016/j.ijcard.2017.08.068

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International standardization of diagnostic criteria for microvascular angina☆

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ARTICLE INFO

Article history:
Received 6 February 2017
Received in revised form 13 July 2017
Accepted 24 August 2017
Available online 8 September 2017

Keywords:
Coronary artery disease
Ischaemic heart disease
Coronary artery spasm
Coronary microvascular dysfunction

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.

☆ The manuscript has been handled by the Guest editor Prof. Peter Schwartz.

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https://doi.org/10.1016/j.ijcard.2017.08.068
0167-5273/

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

standard criterion for MVA is the documentation of a reduced CFR [18] and/or the occurrence of microvascular spasm [19](Table 2). The choice of testing modality relates to availability and expertise, and suspected mechanism. For the assessment of CFR, noninvasive myocardial blood flow measurements using PET [8], assessment of myocardial perfusion with CMR [20] during maximal hyperemia induced by administration of vasodilators, or coronary flow velocity measurements using transthoracic Doppler echocardiography, can also be used [21]. The latter is measured by pulsed wave Doppler echocardiography, using a sample volume of ~3–4 mm^3 positioned on the colour signal of the artery. The measurements are usually done in the distal part of the left anterior descending coronary artery as this portion of the vessel allows proper visualization due to the proximity of the artery to the chest wall. The pattern of coronary blood flow velocity is biphasic, with a larger diastolic than systolic component; for this reason, only the diastolic component is usually measured [22]. PET allows determination of CFR by quantification of myocardial blood flow per gram of tissue both at rest and during pharmacological vasodilatation [20]. Measuring myocardial blood flow using PET can be done using different tracers such as oxygen-15 labelled water, nitrogen-13 labelled ammonia or the potassium analogue rubidium-82 [23,24].

Many patients with CMD will undergo invasive coronary angiography and this provides the opportunity for the assessment of flow reserve using invasive techniques normally available in the catheterization laboratory. These include measurement of coronary flow velocity reserve using a Doppler flow wire or of coronary blood flow reserve using a combined pressure/thermodilution wire [25,26]. These techniques have been extensively validated [27] and have been shown to be safe [28]. Independent of the technique used, CFR values below or equal to 2.0 or 2.5, depending on the methodology used, are indicative of CMD [29]. Recently, Doppler-derived hyperemic microvascular resistance and thermodilution-derived index of microvascular resistance have emerged as new techniques for assessment of CMD [30]. The guarded prognosis of patients with confirmed CMD justifies an invasive approach to establish an unequivocal diagnosis of this condition [31].

Coronary microvascular spasm, which is different from focal epicardial coronary artery spasm (as seen in Prinzmetal's variant angina) [32], can be inferred during angiographic studies in patients with chest pain despite angiographically unobstructed coronary arteries using intracoronary acetylcholine testing [33]. Investigation is needed to determine the sensitivity and specificity of microvascular spasm using acetylcholine as several reports have shown a high sensitivity and specificity (i.e. 90% and 99%, respectively) for intracoronary acetylcholine testing in patients with suspected epicardial spasm [34]. In patients with non-diagnostic acetylcholine-test results for microvascular spasm (e.g. reproduction of symptoms during the test without signs of ischemia or signs of ischemia without symptoms [26]), transient metabolic alterations (e.g. coronary sinus lactate production, low oxygen saturation) may be indicative of CMD. An alternative indirect approach evaluates the delayed flow of angiographic contrast, which reflects an increased distal coronary resistance and is known as the “coronary slow flow phenomenon” [35], using the established semi-quantitative TIMI frame count method [36] and diagnostic criteria for the method have been reported previously [37].

Local availability and experience will dictate which investigation is performed and it may be necessary to perform more than one test to establish the diagnosis of MVA due to the heterogeneity of underlying mechanisms. The routine use of noninvasive or invasive coronary flow reserve measurements in patients with chest pain, evidence of ischemia, and no evidence of obstructive epicardial disease would address the majority of patients who have MVA and are currently discharged as having non-cardiac chest pain. Camici and Crea have proposed a diagnostic flowchart for the screening of patients with suspected microvascular angina which is based on the use of a combination of noninvasive and invasive tests [38].

6. Standardized diagnostic criteria

As outlined in Table 2, the diagnosis of MVA can be established if patients present with symptoms of myocardial ischemia, e.g. effort and/or rest angina, angina equivalents (i.e. shortness of breath) in the absence of relevant epicardial CAD (<50% diameter reduction or FFR >0.80). Furthermore, there should be objective evidence of myocardial ischemia as well as evidence of impaired coronary microvascular function. The latter may be documented by (a) an impaired coronary flow reserve (cut-off values depending on methodology use between ≤2.0 and ≤2.5) or (b) coronary microvascular spasm, defined as reproduction of symptoms, ischemic ECG shifts, but no epicardial spasm during acetylcholine testing or (c) abnormal coronary microvascular resistance indices (e.g. IMR > 25) or (d) coronary slow flow phenomenon, defined as TIMI frame count >25.

7. Benefit of establishing a diagnosis of MVA due to CMD

Overall, standard criteria for investigation of MVA due to CMD in patients with symptoms and signs of myocardial ischemia despite normal coronary angiograms, has the following benefits: (1) standardized criteria provide an investigative structure for mechanistic studies that will help gaining insight into therapeutic targets; (2) diagnostic strategies can be tested, including non-invasive and invasive balancing feasibility, safety, accuracy and cost; (3) investigation of prognostic indices/markers via registries which use standardized criteria should allow a better understanding of the problem and better comparisons among different international registries; (4) clinical trial studies can be designed to develop the evidence base needed for guidelines in this growing patient population.

8. Conclusions

Patients with signs and symptoms of myocardial ischemia in the absence of flow-limiting epicardial coronary artery stenosis currently represent a heterogeneous group and there is a need for the use of standard criteria for communication of investigations of MVA due to CMD as the underlying pathogenic mechanism. 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.

Disclosures

COVADIS was established in 2012 by a group of independent international clinician scientists with expertise in coronary vasomotor abnormalities. COVADIS has no relationship with industry and received unrestricted medical education grant support from non-for-profit organizations including The Hospital Research Foundation (Australia), Japanese Heart Foundation, DFG (Germany), St George Hospital University of London (UK) and the Barbra Streisand Women's Heart Center (USA).

Author	Industry relationship in past 2 years (all honoraria < $10,000)
CN Bairey Merz	Gilead (CME lectures), Amgen (consulting), Pfizer (consulting)
JF Beltrame	Servier (speaker, conference), Bristol Meyers Squibb & Pfizer (speaker), AstraZeneca (research grant)
PG Camici	Servier (Consultant), Menarini (Speaker)
F Crea	none to declare
JC Kaski	Menarini (speaker, conference), Servier (Advisory Board), Sanofi (Advisory Board)
P Ong	Berlin-Chemie/Menarini (speaker)
U Sechtem	None to declare
H Shimokawa	Japan Heart Foundation

Appendix 1. Coronary Artery Vasospastic Disorders Summit (COVADIS) attendees

The following international participants attended the second and third Coronary Artery Vasospastic Disorders Summit held in Barcelona on September 3–4th, 2014 and London on September 2–3rd, 2015.

Steering committee

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

Summit attendees

Agewall, Stefan – Norway
Akira, Suda – Japan
Baek, Sang Hong – South Korea
Conti, C. R – USA
Escaned, Javier – Spain
Elias–Smale, Suzette – The Netherlands
Figueras Bellot, Jaume – Spain
Freedman, Ben – Australia
Friedrich, Matthias – Canada
Gori, Tommaso – Germany
Handberg, Eileen – USA
Kaikita, Koichi – Japan
Komatsu, Masayasu – Japan
Lanza, G.A – Italy
Lerman, Amir – USA
Maas, Angela – The Netherlands
Marzilli, Mario – Italy
Maseri, Attilio – Italy
Mehta, Puja – USA
Nihei, Taro – Japan
Nishimiya, Kensuke – Japan
Odaka, Yuji – Japan
Ohyama, Kazuma – Japan
Park, Seong–Mi – South Korea
Plein, Sven – United Kingdom
Prescott, Eva – Denmark
Reynolds, Harmony – USA
Sharif, Behzad – USA
Sheikh, Abdul – Australia
Shim, Wan–Joo – South Korea
Sueda, Shozo – Japan
Takahashi, Jun – Japan
Tornvall, Per – Sweden
Tremmel, Jennifer – USA
Voigtländer, Thomas – Germany
Wei, Janet – USA

References

[1] M.R. Patel, E.D. Peterson, D. Dai, J.M. Brennan, R.F. Redberg, H.V. Anderson, R.G. Brindis, P.S. Douglas, Low diagnostic yield of elective coronary angiography, N. Engl. J. Med. 362 (2010) 886–895.

[2] P.G. Camici, F. Crea, Coronary microvascular dysfunction, N. Engl. J. Med. 356 (2007) 830–840.

[3] S.E. Reis, R. Holubkov, A.J. Conrad Smith, et al., WISE Investigators, Coronary microvascular dysfunction is highly prevalent in women with chest pain in the absence of coronary artery disease: results from the NHLBI WISE study, Am. Heart J. 141 (2001) 735–741.

[4] P. Ong, A. Athanasiadis, G. Borgulya, H. Mahrholdt, J.C. Kaski, U. Sechtem, 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. 59 (2012) 655–662.

[5] Task Force Members, G. Montalescot, U. Sechtem, S. Achenbach, F. Andreotti, C. Arden, A. Budaj, R. Bugiardini, F. Crea, T. Cuisset, C. Di Mario, J.R. Ferreira, B.J. Gersh, A.K. Gitt, J.S. Hulot, N. Marx, L.H. Opie, M. Pfisterer, E. Prescott, F. Ruschitzka, M. Sabaté, R. Senior, D.P. Taggart, E.E. van der Wall, C.J. Vrints, ESC Committee for Practice Guidelines, J.L. Zamorano, S. Achenbach, H. Baumgartner, J.J. Bax, H. Bueno, V. Dean, C. Deaton, C. Erol, R. Fagard, R. Ferrari, D. Hasdai, A.W. Hoes, P. Kirchhof, J. Knuuti, P. Kolh, P. Lancellotti, A. Linhart, P. Nihoyannopoulos, M.F. Piepoli, P. Ponikowski, P.A. Sirnes, J.L. Tamargo, M. Tendera, A. Torbicki, W. Wijns, S. Windecker, Document Reviewers, J. Knuuti, M. Valgimigli, H. Bueno, M.J. Claeys, N. Donner-Banzhoff, C. Erol, H. Frank, C. Funck-Brentano, O. Gaemperli, J.R. Gonzalez-Juanatey, M. Hamilos, D. Hasdai, S. Husted, S.K. James, K. Kervinen, P. Kolh, S.D. Kristensen, P. Lancellotti, A.P. Maggioni, M.F. Piepoli, A.R. Pries, F. Romeo, L. Rydén, M.L. Simoons, P.A. Sirnes, P.G. Steg, A. Timmis, W. Wijns, S. Windecker, A. Yildirir, J.L. Zamorano, 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. 34 (2013) 2949–3003.

[6] J.C. Kaski, G.M.C. Rosano, P. Collins, P. Nihoyannopoulos, A. Maseri, P.A. Poole-Wilson, Cardiac syndrome X: clinical characteristics and left ventricular function: long-term follow-up study, J. Am. Coll. Cardiol. 25 (1995) 807–814.

[7] G. Russo, A. Di Franco, P. Lamendola, P. Tarzia, R. Nerla, A. Stazi, A. Villano, A. Sestito, G.A. Lanza, F. Crea, Lack of effect of nitrates on exercise stress test results in patients with microvascular angina, Cardiovasc. Drugs Ther. 27 (2013) 229–234.

[8] V.L. Murthy, M. Naya, V.R. Taqueti, C.R. Foster, M. Gaber, J. Hainer, S. Dorbala, R. Blankstein, O. Rimoldi, P.G. Camici, M.F. Di Carli, Effects of sex on coronary microvascular dysfunction and cardiac outcomes, Circulation 129 (2014) 2518–2527.

[9] I.A. Vermeltfoort, P.G. Raijmakers, I.I. Riphagen, D.A. Odekerken, A.F. Kuijper, A. Zwijnenburg, G.J. Teule, Definitions and incidence of cardiac syndrome X: review and analysis of clinical data, Clin. Res. Cardiol. 99 (2010) 475–481.

[10] T.R. Wessel, C.B. Arant, S.P. McGorray, B.L. Sharaf, S.E. Reis, R.A. Kerensky, G.O. Von Mering, K.M. Smith, D.F. Pauly, E.M. Handberg, S. Mankad, M.B. Olson, D.B. Johnson, C.N. Bairey Merz, G. Sopko, Coronary microvascular reactivity is only partially by atherosclerosis risk factors or coronary artery disease in women evaluated for suspected ischemia: results from the NHLBI Women's Ischemia Syndrome Evaluation (WISE), Clin. Cardiol. 30 (2007) 69–74.

[11] L. Smeeth, J.S. Skinner, J. Ashcroft, H. Hemingway, Timmis a; chest pain guideline development group. NICE clinical guideline: chest pain of recent onset, Br. J. Gen. Pract. 60 (2010) 607–610.

[12] S.D. Fihn, J.M. Gardin, J. Abrams, K. Berra, J.C. Blankenship, A.P. Dallas, P.S. Douglas, J.M. Foody, T.C. Gerber, A.L. Hinderliter, S.B. King 3rd, P.D. Kligfield, H.M. Krumholz, R.Y. Kwong, M.J. Lim, J.A. Linderbaum, M.J. Mack, M.A. Munger, R.L. Prager, J.F. Sabik, L.J. Shaw, J.D. Sikkema, C.R. Smith Jr., S.C. Smith Jr., J.A. Spertus, S.V. Williams, American College of Cardiology Foundation, American Heart Association Task Force on Practice Guidelines; American College of Physicians, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, Society of Thoracic Surgeons, 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American College of Physicians, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons, J. Am. Coll. Cardiol. 60 (2012) e44–e164.

[13] J.A. Panza, J.M. Laurienzo, R.V. Curiel, E.F. Unger, A.A. Quyyumi, V. Dilsizian, R.O. Cannon 3rd., Investigation of the mechanism of chest pain in patients with angiographically normal coronary arteries using transesophageal dobutamine stress echocardiography, J. Am. Coll. Cardiol. 29 (1997) 293–301.

[14] A. Maseri, F. Crea, J.C. Kaski, T. Crake, Mechanisms of angina pectoris in syndrome X, J. Am. Coll. Cardiol. 17 (1991) 499–506.

[15] C.W. White, C.B. Wright, D.B. Doty, L.F. Hiratza, C.L. Eastham, D.G. Harrison, M.L. Marcus, Does visual interpretation of the coronary arteriogram predict the physiologic importance of a coronary stenosis? N. Engl. J. Med. 310 (1984) 819–824.

[16] T.P. van de Hoef, M. Siebes, J.A. Spaan, J.J. Piek, Fundamentals in clinical coronary physiology: why coronary flow is more important than coronary pressure, Eur Heart J. 36 (2015) (3312-9a).

[17] E. Hulten, M.F. Di Carli, FFRCT: solid PLATFORM or thin ice? J. Am. Coll. Cardiol. 66 (2015) 2324–2328.

[18] M.J. Kern, A. Lerman, J.W. Bech, B. De Bruyne, E. Eeckhout, W.F. Fearon, S.T. Higano, M.J. Lim, M. Meuwissen, J.J. Piek, N.H. Pijls, M. Siebes, J.A. Spaan, American Heart Association Committee on Diagnostic and Interventional Cardiac Catheterization, Council on Clinical Cardiology, Physiological assessment of coronary artery disease in the cardiac catheterization laboratory: a scientific statement from the American Heart Association Committee on Diagnostic and Interventional Cardiac Catheterization, Council on Clinical Cardiology, Circulation 114 (2006) 1321–1341.

[19] P. Ong, A. Athanasiadis, G. Borgulya, I. Vokshi, R. Bastiaenen, S. Kubik, S. Hill, T. Schäufele, H. Mahrholdt, J.C. Kaski, U. Sechtem, Clinical usefulness, angiographic characteristics, and safety evaluation of intracoronary acetylcholine provocation testing among 921 consecutive white patients with unobstructed coronary arteries, Circulation 129 (2014) 1723–1730.

[20] L.E. Thomson, J. Wei, M. Agarwal, A. Haft-Baradaran, C. Shufelt, P.K. Mehta, E.B. Gill, B.D. Johnson, T. Kenkre, E.M. Handberg, D. Li, B. Sharif, D.S. Berman, J.W. Petersen, C.J. Pepine, C.N. Bairey Merz, Cardiac magnetic resonance myocardial perfusion reserve index is reduced in women with coronary microvascular dysfunction. A National Heart, Lung, and Blood Institute-sponsored study from the Women's Ischemia Syndrome Evaluation, Circ. Cardiovasc. Imaging 8 (2015) (pii:e002481).
[21] L. Galiuto, A. Sestito, S. Barchetta, G.A. Sgueglia, F. Infusino, C. La Rosa, G. Lanza, F. Crea, Noninvasive evaluation of flow reserve in the left anterior descending coronary artery in patients with cardiac syndrome X, Am. J. Cardiol. 99 (2007) 1378–1383.
[22] P. Meimoun, S. Sayah, J.C. Tcheuffa, T. Benali, A. Luycx-Bore, F. Levy, et al., Transthoracic coronary flow velocity reserve assessment: comparison between adenosine and dobutamine, J. Am. Soc. Echocardiogr. 19 (2006) 1220–1228.
[23] P.G. Camici, O.E. Rimoldi, The clinical value of myocardial blood flow measurement, J. Nucl. Med. 50 (2009) 1076–1087.
[24] K.L. Gould, N.P. Johnson, T.M. Bateman, R.S. Beanlands, F.M. Bengel, R. Bober, et al., Anatomic versus physiologic assessment of coronary artery disease. Role of coronary flow reserve, fractional flow reserve, and positron emission tomography imaging in revascularization decision-making, J. Am. Coll. Cardiol. 62 (2013) 1639–1653.
[25] E. Barbato, W. Aarnoudse, W.R. Aengevaeren, G. Werner, V. Klauss, W. Bojara, I. Herzfeld, K.G. Oldroyd, N.H. Pijls, B. De Bruyne, Week 25 study group, Validation of coronary flow reserve measurements by thermodilution in clinical practice, Eur. Heart J. 25 (2004) 219–223.
[26] B.K. Lee, H.S. Lim, W.F. Fearon, A.S. Yong, R. Yamada, S. Tanaka, D.P. Lee, A.C. Yeung, J.A. Tremmel, Invasive evaluation of patients with angina in the absence of obstructive coronary artery disease, Circulation 131 (2015) 1054–1060.
[27] A.L. McGinn, C.W. White, R.F. Wilson, Interstudy variability of coronary flow reserve. Influence of heart rate, arterial pressure, and ventricular preload, Circulation 81 (1990) 1319–1330.
[28] J. Wei, P.K. Mehta, B.D. Johnson, B. Samuels, S. Kar, R.D. Anderson, B. Azarbal, J. Peterse, B. Sharaf, E. Handberg, C. Shufelt, K. Kothawade, G. Sopko, A. Lerman, L. Shaw, S.F. Kelsey, C.J. Pepine, C.N. Bairey Merz, Safety of coronary reactivity testing in women with no obstructive Coronary artery disease: results from the NHLBI-sponsored Women's Ischemic Syndrome Evaluation (WISE) study, J. Am. Coll. Cardiol. Intv. 5 (2012) 646–653.
[29] S.E. Reis, R. Holubkov, J.S. Lee, B. Sharaf, N. Reichek, W.J. Rogers, E.G. Walsh, A.R. Fuisz, R. Kerensky, K.M. Detre, G. Sopko, C.J. Pepine, Coronary flow velocity response to adenosine characterizes coronary microvascular function in women with chest pain and no obstructive coronary disease. Results from the pilot phase of the Women's Ischemia Syndrome Evaluation (WISE) study, J. Am. Coll. Cardiol. 33 (1999) 1469–1475.
[30] M.K. Ng, A.C. Yeung, W.F. Fearon, Invasive assessment of the coronary microcirculation: superior reproducibility and less hemodynamic dependence of index of microcirculatory resistance compared with coronary flow reserve, Circulation 113 (2006) 2054–2061.
[31] V.R. Taqueti, L.J. Shaw, N.R. Cook, V.L. Murthy, N.R. Shah, C.R. Foster, J. Hainer, R. Blankstein, S. Dorbala, M.F. Di Carli, Excess cardiovascular risk in women relative to men referred for coronary angiography is associated with severely impaired coronary flow reserve, not obstructive disease, Circulation (Nov 14) (2016) (pii: CIRCULATIONAHA.116.023266. Epub ahead of print).
[32] J.F. Beltrame, F. Crea, J.C. Kaski, H. Ogawa, P. Ong, U. Sechtem, H. Shimokawa, C.N. Bairey Merz, Coronary Vasomotion Disorders International Study Group (COVADIS), International standardization of diagnostic criteria for vasospastic angina, Eur. Heart. J. 38 (2017) 2565–2568.
[33] M. Mohri, M. Koyanagi, K. Egashira, H. Tagawa, T. Ichiki, H. Shimokawa, A. Takeshita, Angina pectoris caused by coronary microvascular spasm, Lancet 351 (1998) 1165–1169.
[34] K. Okumura, H. Yasue, K. Matsuyama, K. Goto, H. Miyagi, H. Ogawa, K. Matsuyama, Sensitivity and specificity of intracoronary injection of acetylcholine for the induction of coronary artery spasm, J. Am. Coll. Cardiol. 12 (1988) 883–888.
[35] J.F. Beltrame, S.B. Limaye, J.D. Horowitz, The coronary slow flow phenomenon - a new coronary microvascular disorder, Cardiology 97 (2002) 197–202.
[36] C.M. Gibson, C.P. Cannon, W.L. Daley, J.T. Dodge Jr., B. Alexander Jr., S.J. Marble, C.H. McCabe, L. Raymond, T. Fortin, W.K. Poole, E. Braunwald, TIMI frame count: a quantitative method of assessing coronary artery flow, Circulation 93 (1996) 879–888.
[37] J.F. Beltrame, Defining the coronary slow flow phenomenon, Circ. J. 76 (2012) 818–820.
[38] P.G. Camici, F. Crea, Microvascular angina: a women's affair? Circ. Cardiovasc. Imaging 8 (4) (2015, Apr) https://doi.org/10.1161/CIRCIMAGING.115.003252 (pii: e003252).