Coronary Functional Tests in the Catheterization Laboratory
– Pathophysiological and Clinical Relevance –

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Coronary angiography has long been the only diagnostic tool for the invasive assessment of coronary artery disease. Yet it does not allow establishing the functional severity of epicardial stenoses or vasomotor disorders of the epicardial arteries or coronary microcirculation. Functional tests in the catheterization laboratory have recently emerged as an important adjunct to coronary angiography for providing a comprehensive evaluation of the coronary circulation. In this review, we will describe and interpret the key functional tests used in current clinical practice in different clinical settings. (Circ J 2015; 79: 676–684)

Key Words: Coronary microvascular disease; Endothelial dysfunction; Epicardial coronary arteries; Functional assessment

Functional tests based on the use of several vasoactive stimuli (Table) and on the measurement of several hemodynamic indexes have recently emerged as standard diagnostic modalities in the contemporary armamentarium of the interventional cardiologist during cardiac catheterization of patients with suspected coronary artery disease (CAD). The functional assessment of coronary circulation is important because it affects the management of patients with CAD. This field has recently evolved thanks also to the substantial advances over the past few years in our knowledge of coronary vasomotion abnormalities. In this review, we will describe and interpret the most important functional tests used in different clinical settings (Figure 1).

Functional Tests for the Assessment of Endothelial Dysfunction in Asymptomatic Subjects

Classically, endothelial dysfunction represents the first step of atherosclerosis. The functional approach to evaluating endothelial dysfunction consists in the assessment of coronary vasomotion in response to endothelium-dependent vasodilators such as acetylcholine (ACh), bradykinin, serotonin or substance P or in response to nitric oxide synthase inhibitors.3–5

Briefly, a Doppler-tipped guide wire is placed in the proximal segment of a coronary artery, through a guiding catheter, and Doppler coronary blood flow velocity is continuously recorded. Volumetric coronary blood flow is calculated with the formula validated by Doucette et al.6 Drugs are selectively infused through the guiding catheter and endothelial function is evaluated by measuring changes in epicardial coronary diameter assessed by quantitative coronary angiography (CAG) and/or of coronary blood flow velocity in response to increasing doses of drug. Most of the information currently available on coronary endothelial dysfunction is based on the utilization of low doses of ACh (usually, 0.182 and 18.2 μg/ml, 2 ml infused over 3 min). Epicardial coronary arteries with an intact endothelium respond to ACh with vasodilation, whereas vessels with endothelial dysfunction show a variable degree of constriction as result of direct activation of muscarinic receptors on vascular smooth muscle cells.7,8 Similarly, coronary microvascular endothelial dysfunction is usually defined as an increase in coronary blood flow <50% in response to ACh. Several studies in the past few years have convincingly shown that coronary endothelial dysfunction of epicardial coronary arteries and/or of coronary microcirculation has a worse outcome as compared with patients who have normal endothelial function.9 It is not well established, however, whether the assessment of coronary endothelial dysfunction improves risk stratification based on the assessment of risk factors. Furthermore, its invasive nature limits clinical applicability. Alternatively, endothelial dysfunction can be investigated in the peripheral circulation by intra-arterial infusion of ACh or by measuring flow-mediated dilation of the brachial artery by use of high-resolution ultrasound during reactive hyperemia.8,9 Although the latter has the advantage of being noninvasive, the degree of correlation between endothelial dysfunction in the peripheral and coronary circulations is not well established.

Functional Tests in Patients With Stable CAD

Intermediate Stenoses

The benefit of percutaneous coronary intervention (PCI) as an initial treatment strategy in patients with stable CAD is still a much debated issue in interventional cardiology.10 Indeed, the efficacy of myocardial revascularization strictly depends on the extent and severity of myocardial ischemia.11,12 Coronary
mediate stenosis partially proposed for assessing the functional severity of inter-
administration) to mean peak flow velocity at rest, was ini-
distal coronary peak flow velocity during maximal hyperemia 
flow velocity reserve (CFVR), defined as the ratio of mean 
baseline or hyperemic flow velocity.

Moreover, a recent meta-analysis by Johnson et al
making regarding coronary stenoses of intermediate angio-
larization in patients presenting with multivessel disease,
benefit of FFR-guided vs. CAG-guided myocardial revascu-
olerance, NO release 2 min Headache, hypotension

| Endothelial-independent vasodilators | Dose range | Mechanisms of action | Approximate half-life | Side effects |
|-------------------------------------|------------|----------------------|----------------------|-------------|
| Adenosine                           | 60–600μg i.c. 140μg·kg⁻¹·min⁻¹ i.v. | A2 receptors stimulation | 10 s | Bradycardia, bronchoconstriction |
| Papaverine                          | 8–20mg i.c. | PDE inhibition (less adenosine degradation) | 2 h | Ventricular arrhythmias, hepatic toxicity, somnolence-vertigo |
| Nitrates                            | 200μg i.c. | Vasodilation of smooth muscle cells | 2 min | Headache, hypotension |
| Sodium nitroprusside                | 0.3–0.9μg/kg i.c. | NO release | 2 min | Headache, hypotension, cyanide toxicity |

| Endothelial-dependent vasodilators   | Dose range | Mechanisms of action | Approximate half-life | Side effects |
|-------------------------------------|------------|----------------------|----------------------|-------------|
| ACh*                                | 0.364–200μg i.c. over 2–3 min | Muscarinic receptor activation, NO release | 2 min | Bradycardia, hypotension bronchoconstriction |
| Substance P**                       | 0.7–22.4 pmol/min i.c. | NK1 receptor activation, NO release | 1.5 min | Bronchoconstriction, hypotension |
| Bradykinin**                        | 0.2–2μg/min i.c. | B1 and b2 receptor activation, NO release | 2 min | Hypotension, angioedema, cough |

| Vasococstrictor                      | Dose range | Mechanisms of action | Approximate half-life | Side effects |
|-------------------------------------|------------|----------------------|----------------------|-------------|
| Ergonovine                          | 2–60μg i.c. 50–300μg i.v. | Serotonin receptor activation | 30 min | Hypertension during i.v. administration |

*Direct vasconstrictor effect on smooth muscle cells. **No direct vasococstrictor effect on smooth muscle cells. ACh, acetylcholine; i.c., intracoronary; i.v., intravenous; NO, nitric oxide; PDE, phosphodiesterase.

Flow velocity reserve (CFVR), defined as the ratio of mean distal coronary peak flow velocity during maximal hyperemia (usually obtained by intracoronary or intravenous adenosine administration) to mean peak flow velocity at rest, was initially proposed for assessing the functional severity of intermediate stenosis13–17 (Figure 2). However, CFVR is deeply influenced by variations in physiological conditions that alter baseline or hyperemic flow velocity. Moreover, highly variable parameters such as heart rate and cardiac workload, in addition to sex and age, importantly influence CFVR. More importantly, a reduced CFVR can be caused by a significant epicardial stenosis, coronary microvascular dysfunction or both. Finally, from a practical point of view, measurement of an accurate Doppler flow velocity signal is more time-consuming than measurement of an accurate intracoronary (i.c.) pressure signal. For these reasons, in the latest years, fractional flow reserve (FFR), defined as the ratio of hyperemic distal coronary pressure to hyperemic aortic pressure (Figures 2,3),19 has emerged as a useful and reliable tool for clinical decision-making regarding coronary stenoses of intermediate angiographic severity in patients with stable angina. Of note, FFR and CFVR are complementary parameters, and may be discordant in the evaluation of the same coronary lesion, because of the relative contribution of epicardial stenoses and coronary microvascular dysfunction.21

Landmark studies have introduced FFR in the clinical practice. The FAME study has convincingly shown a clinical benefit of FFR-guided vs. CAG-guided myocardial revascularization in patients presenting with multivessel disease, using a cutoff of 0.80,23,24 and the FAME 2 study has recently demonstrated that, in patients with stable CAD, FFR-guided PCI as compared with medical therapy alone, improves the outcome principally by a lower rate of urgent revascularization in the PCI group (4.0% vs. 16.3%; hazard ratio (HR): 0.23; 95% confidence interval (CI): 0.14 to 0.38; P<0.001). Moreover, a recent meta-analysis by Johnson et al6 including 9,173 studies with 6,961 lesions showed a continuous and independent relationship of FFR values with subsequent outcomes, suggesting that as for every parameter used in decision-making, cutoff points should be evaluated together with global risk assessment. Interestingly, they also pointed out that the measurement of FFR immediately after stenting also exhibited an inverse relation with prognosis (HR: 0.86; 95% CI: 0.80 to 0.93; P<0.001), likely from both residual diffuse disease and imperfect stent deployment, which may prime future events.23,25

Recently, the NASCET27 and the RINASCET28 studies proposed a useful algorithm based on sequential utilization of contrast medium (which can be utilized more quickly), i.c. and i.v. adenosine (which is the gold standard, but more time-consuming) to obtained maximal coronary vasodilation (Figure 4). The use of this algorithm in daily practice could help in achieving a physiology-based approach to treatment of coronary artery stenosis, limiting the use of i.c. or i.v. adenosine for obtaining FFR to equivocal cases only.

Of note, in order to simplify the use of functional tests for the assessment of intermediate stenoses, new adenosine-free indexes are emerging. For instance, the instantaneous wave-free ratio (iFR) is a recently proposed index of stenosis severity, which uses a translesional pressure ratio as a measure of functional stenosis severity. It is not based on the use of vasodilators, but rather on measurement of i.c. pressure during the diastolic “wave-free” period, a period in the cardiac cycle when intrabead microvascular resistance is inherently stable and minimized. This wave-free window provides a phase in which microvascular resistance is significantly lower than that over the whole cardiac cycle, and coronary hemodynamics are most suited for assessment of the hemodynamic effects of a stenosis.29

It can be calculated using conventional pressure guidewires and differs fundamentally from FFR because it does not require vasodilators such as adenosine for its calculation.29 Recently, the ADVICE trial assessed the role of iFR measurement in patients undergoing invasive functional assessment of
The so-called "hyperemic flow reserve" (HFR) represents the ratio of the mean distal coronary pressure to the mean distal flow velocity during maximal hyperemia. HFR is a measure of the ability of the coronary arteries to dilate in response to increased metabolic demand.

In the presence of a coronary artery stenosis, HFR is reduced compared to normal vessels. This reduction in HFR is due to the combination of decreased flow and increased resistance to flow caused by the stenosis. The extent of the reduction in HFR can be used to estimate the severity of the stenosis.

A lower HFR indicates a more severe stenosis, whereas a higher HFR indicates a less severe stenosis. Therefore, HFR can be used to assess the severity of coronary artery stenosis and guide interventional procedures such as stent placement.

In summary, HFR is a valuable tool for assessing the severity of coronary artery stenosis and guiding interventional procedures. It is a non-invasive and reliable method for assessing coronary artery stenosis and can be used in clinical practice to guide patient care.

**Figure 1.** Summary of the most useful functional tests used in the catheterization laboratory in various clinical settings. In asymptomatic subjects, functional tests can be used to assess endothelial dysfunction for risk stratification, usually by measuring the response of coronary diameter and of coronary blood flow to low-dose i.c. Ach. In patients with SCAD and obstructive CAD on angiography, the functional tests are mostly used in 2 different situations: assessment of (1) intermediate coronary stenoses and (2) diffuse coronary disease. Functional severity of a stenosis can be assessed using several indexes, including FFR (validated in large prospective studies) or IFR, BSR and HSR (which all need to be validated in large, prospective studies). CFVR can also be measured but an abnormal value does not allow establishing whether it is related to epicardial stenosis severity, coronary microvascular dysfunction or both, while IMR and HMR measurement allow specific assessment of the contribution of coronary microvascular dysfunction. In the case of diffuse coronary disease, the following functional indexes can be used to identify the contribution of individual stenoses: FFR and IFR during pullback pressure. Again, IMR and HMR can be measured to assess the contribution of coronary microvascular dysfunction. In the case of effort angina and no obstructive CAD, measuring CFVR, IMR or HMR using adenosine and Ach testing can be performed in order to test for the presence of impaired vasodilatory function or increased susceptibility to vasoconstrictor stimuli. Finally, a functional evaluation may be needed in patients with ACS and no obstructive CAD on coronary angiography. In particular, an i.c. ergonovine or Ach test is used to diagnose spasm of epicardial coronary artery, whereas microvascular coronary spasm causes symptoms and ischemic ST changes in the absence of epicardial spasm in response to i.c. Ach. *Any narrowing >50% diameter stenosis; **assessment of the contribution of coronary microvascular dysfunction. Ach, acetylcholine; ACS, acute coronary syndrome; BSR, baseline stenosis resistance; CAD, coronary artery disease; CFVR, coronary flow velocity reserve; ED, endothelial dysfunction; FFR, fractional flow reserve; HMR, hyperemic microvascular resistance; HSR, hyperemic stenosis resistance; i.c., intracoronary; iFR, instantaneous wave-free ratio; IMR, index of microvascular resistance; MVA, microvascular angina; SCAD, stable coronary artery disease; VSA, vasospastic angina.
Coronary stenoses deemed significant by FFR, the prevalence of inducible ischemia was significantly higher when HMR was high, even though FFR did not differ between HMR groups. Furthermore, the increase in HSR mirrored the increase in HMR and myocardial ischemia. Those findings suggest an interaction between epicardial and microvascular disease in the development of inducible ischemia that is not underscored by coronary pressure measurements only. Indeed, FFR is influenced by the magnitude of flow through the stenosis; with increasing coronary flow through a stenosis, distal coronary

\[ \text{CFVR} = \frac{V \text{ during hyperemia}}{V \text{ during basal conditions}} \]

\[ \text{FFR} = \frac{P_d}{P_a} \text{ during hyperemia} \]

\[ \text{iFR} = \frac{P_d}{P_a} \text{ during "wave free period"} \]

\[ \text{IMR} = P_d \cdot \text{MTT} \]

\[ \text{HSR} = \frac{(P_a - P_d)}{V \text{ during hyperemia}} \]

\[ \text{HMR} = \frac{P_d}{V} \text{ during hyperemia} \]

\[ \text{BSR} = \frac{(P_a - P_d)}{V} \text{ during basal conditions} \]
pressure and, thus, FFR decreases. A low HMR implies that the impediment to coronary flow is relatively low, which may dictate a low FFR value despite the fact that the resistance to flow induced by the stenosis and microvasculature is low at maximal vasodilatation. With increasing HMR, flow through this fixed stenosis will decrease and FFR will increase, despite no alteration in resistance to flow resulting from the epicardial stenosis. However, there is no clinical cutoff value or normal range for HMR. Furthermore, it is debatable whether HMR should be corrected for the contribution of collateral flow to total myocardial blood flow, because its neglect may lead to an overestimation of true microvascular resistance by HMR, although the collateral flow contribution is known to be negligible in the setting of stable CAD of intermediate severity.

The stenosis resistance index during baseline conditions (ie, baseline stenosis resistance index [BSR]) has more recently been introduced, a notion based on the limited influence of hyperemia on HSR. This index is defined as the ratio of the pressure gradient across the stenosis to the distal flow velocity during baseline conditions (Figure 2) and has been shown to provide a diagnostic accuracy for inducible myocardial ischemia on noninvasive stress testing equivalent to that of FFR or CFVR. However, BSR is in need of further validation before its clinical adoption may be advocated.

In conclusion, the measurement of BSR, HSR and HMR provides more detailed information on the specific contribution of epicardial and microvascular disease to myocardial ischemia and these indexes are more predictive of myocardial ischemia on perfusion scans than FFR; yet, the clinical relevance of these indexes is limited by the lack of prospective studies exploring the effect of their measurement on outcome, which, in contrast, has well been defined for FFR.

Finally, in this clinical scenario, intravascular ultrasound (IVUS) and optical coherence tomography (OCT) are also relied on as alternative options, offering morphological non-functional insights. Yet again, there is not a single morphological parameter (by IVUS or OCT) that has hitherto been validated for deferring coronary revascularization.

**Diffuse Disease**

Although studies have documented the high diagnostic efficiency of physiological assessment in minimizing the number of vessels requiring treatment, it is widely recognized that interrogation of an individual stenosis in the presence of tandem lesions or diffuse disease under hyperemic conditions makes PCI planning complex and less practical. These difficulties are related to the hemodynamic interdependence of stenoses under conditions of hyperemia; indeed, hyperemic flow through 1 stenosis is limited by the presence of the other stenoses. Yet treating functionally relevant stenoses while deferring treatment of the nonfunctionally relevant stenoses might improve the outcome. In particular, this may be valuable when some lesions are considered to have higher procedural risk than others.

Another important issue is establishing whether in an anginal patient the myocardial ischemia is caused by moderate but diffuse disease responsible for a progressive pressure loss along an epicardial coronary branch or rather by coronary microvascular dysfunction; it is obvious that these 2 conditions need different treatments.

FFR measured during pullback of the pressure wire under maximal hyperemia can be helpful in the identification of functionally significant stenoses. Indeed, Kim et al found that FFR assessment during pullback pressure is safe and might help in determining target lesions for revascularization by PCI. In vessels with an FFR <0.8, they stented first the stenosis that caused the largest pressure step-up. In total, 116 stents were implanted and revascularization was deferred in 61.1% (182 of 298) of lesions. There were no events related to deferred lesions.

Another possible approach is a stenosis severity assessment under resting conditions. Recently, Nijjer et al found that iFR measurements during continuous resting pressure wire pullback can provide a physiological map of the entire epicardial coronary branch and can predict the hemodynamic consequences of stenting specific stenoses before PCI, thereby facilitating the intervention and stenting strategy. However, it has to be taken into account that, in diffuse atherosclerotic disease, coronary microvascular dysfunction also might influence the FFR values. In this context, the index of microvascular resistance (IMR), a pressure-temperature-tipped guidewire-based quantitative measure of coronary microvasculature function, can be a useful tool for resolving doubtful cases. It is calculated by multiplying the distal coronary pressure by the mean transit time of a 3-ml bolus of saline at room temperature during coronary hyperemia induced by i.v. adenosine and it has been widely showed to be repeat-
able and independent of hemodynamic variations, including heart rate, blood pressure and myocardial contractility.\(^4\)

Of note, Echavarria-Pinto et al\(^5\) recently reported that integrating the results of FFR, CFR and IMR proved the presence of different patterns characterized by a variable combination of epicardial disease and microvascular dysfunction. In particular, in vessels with FFR >0.80 and CFR <2, IMR exhibited a wide dispersion, suggesting a combination of diffuse atherosclerotic narrowing and coronary microvascular dysfunction.

A further application of functional coronary assessment may be to assist surgical revascularization; identifying where a bypass graft can be placed in a diffusely diseased vessel may help to maximize the hemodynamic benefit. In this setting, preoperative FFR evaluation might also play a prognostic role in the prediction of graft patency. In particular, Botman et al\(^6\) studied 164 patients eligible for coronary artery bypass surgery who were not suitable for PCI and with at least 1 intermediate lesion. They measured FFR in all lesions to be grafted in order to establish whether a lesion was functionally significant. At 1-year follow-up, systematic CAG showed a 91% patency rate for bypass grafts to branches with functionally significant lesions and a 79% patency rate for bypass grafts to functionally nonsignificant lesions. A similar trend was observed at 2-year follow-up.\(^7\) At 3-year follow-up, the rate of graft occlusion was 4-fold lower for bypass grafts to branches with functionally significant lesions than in bypass grafts to functionally nonsignificant lesions.\(^8\)

IVUS and OCT are the actual imaging modalities being investigated for their ability to identify culprit lesions.\(^9\) However, the results of these imaging modalities not always are in keeping with those obtained using the better validated pressure-derived indexes.\(^10\)

**Microvascular Angina (MVA)**

In patients with angina and no obstructive coronary atherosclerosis, an important goal during CAG is to establish or confirm the diagnosis of MVA, which can be defined on the basis of the following criteria: (1) typical exercise-induced angina; (2) documented stress-induced myocardial ischemia; (3) absence of obstructive atherosclerotic CAD; (4) absence of organic nonatherosclerotic causes of epicardial CAD (including coronary aneurysms, bridging and anomalies); (5) absence of vasospastic angina (VSA; no epicardial vasospasm with ergonovine or ACh test); and (6) active demonstration of coronary microvascular dysfunction (positive ACh and/or adenosine test results).

In patients in whom the differential diagnosis between microvascular and VSA is uncertain, based on noninvasive testing, it is worth performing an ACh test. The most frequently used protocol to this end is the i.c. administration of incremental doses of ACh (20, 50 and 100\(\mu\)g into the left coronary artery and 20 and 50\(\mu\)g into the right coronary artery) over a period of 3 min each. A positive response for MVA is characterized by the onset of angina and typical ischemic ST-segment changes (usually depression) in the absence of focal epicardial spasm. Of note, a diagnosis of MVA based on ACh testing has been reported in approximately 50% of patients referred for CAG because of effort angina and found to have no obstructive atherosclerosis (Figure 5).\(^11\)

In patients with suspected MVA and absence of myocardial ischemia during ACh testing, it is worth performing an ACh test. The most frequently used protocol to this end is the i.c. administration of incremental doses of ACh (20, 50 and 100\(\mu\)g into the left coronary artery and 20 and 50\(\mu\)g into the right coronary artery) over a period of 3 min each. A positive response for MVA is characterized by the onset of angina and typical ischemic ST-segment changes (usually depression) in the absence of focal epicardial spasm. Of note, a diagnosis of MVA based on ACh testing has been reported in approximately 50% of patients referred for CAG because of effort angina and found to have no obstructive atherosclerosis (Figure 5).\(^11\)

In patients with suspected MVA and absence of myocardial ischemia during ACh testing, it is important to assess CFVR using adenosine. A CFVR <2.5 is usually considered as diagnostic of coronary microvascular dysfunction.\(^12\) Because of some significant variability in healthy individuals, however, a cutoff of 2 might be more specific. Recent data indicate that among patients with MVA, a CFR <2 is associated with a worse outcome as compared with patients with CFR \(\geq\)2.\(^13\)

It is still unknown whether an abnormal response to ACh and an abnormal CFVR identify different subsets of patients with MVA.

**Functional Tests in Patients With Acute Coronary Syndrome**

Angina at rest with or without raised cardiac enzymes is usually caused by a dynamic and unexpected destabilization
of an unstable coronary plaque with superimposed coronary thrombosis.60 However, the introduction of high-resolution imaging modalities such as OCT has allowed the establishing that a subset of patients with rest angina exhibit epicardial stenoses with stable features, thus suggesting an important role for coronary vasomotor dysfunction.61 An extreme form of coronary vasomotor dysfunction in this setting is epicardial or microvascular spasm, which needs to be systematically investigated, particularly in patients with predominantly rest angina who do not exhibit obstructive atherosclerosis on CAG. In a recent study of patients with predominantly rest angina who underwent CAG and were found to have no obstructive lesions on CAG, ACh testing revealed epicardial or microvascular spasm in 49% of patients.62

VSA Numerous agents have been proposed for spasm provocation testing, including ergonovine, ACh, neuropeptide Y, histamine and dopamine.63–68 However, a large body of evidence supports utilization of ergonovine and ACh for clinical practice. A positive response to ACh (Figure 6)69 or ergonovine is defined as a transient occlusion (>90% narrowing) of a coronary artery branch with signs and symptoms of myocardial ischemia (angina/ST-segment changes).69,70 Various testing protocols using i.c. and i.v. ergonovine administration have been described (Table).70–74 Importantly, Hackett et al demonstrated that induction of coronary artery spasm (CAS) with i.c. ergonovine might be safer than that induced by i.v. administration.64 Furthermore, although i.v. ergonovine provocation testing has good sensitivity (100% with angina as part of the diagnostic criteria, and 94% with ST-segment elevation),71 reports show the frequency of provoked CAS with i.c. ergonovine to be 2.2–2.6-fold higher than with i.v. testing.74 Specificity of i.v. and i.c. ergonovine provocation testing are similarly high at >90%. Despite high sensitivity, a negative test cannot always exclude CAS. A recent observational study70 evaluated 1,244 patients with VSA who underwent different i.c. provocation tests (40% ergonovine, 57% ACh, 2% ergonovine+ACh, 1% other). The overall incidence of arrhythmic complications was 6.8%, which is comparable to 7.0% during spontaneous angina episodes. They reported a 5.5% major adverse cardiovascular event rate during the 32-month follow-up period. After multivariable analysis, mixed (focal and diffuse) multivessel spasm predicted major adverse cardiovascular events (adjusted HR: 2.84; 95% CI 1.43 to 6.03, P<0.01), whereas provocation-related arrhythmias (defined as ventricular tachycardia, ventricular fibrillation, and bradycardias) did not.79

Unstable MVA Coronary microvascular spasm is characterized by transient transmural myocardial ischemia, as indicated by ST-segment changes, during spontaneous or provoked angina, in the presence of normal epicardial coronary arteries. It may be considered as the unstable presentation of MVA.75 Approximately 25% of patients with acute coronary syndrome and no obstructive CAD have evidence of microvascular spasm, although an increase in the troponin concentration is infrequent.75 In this context, unstable MVA, similar to what we previously described for stable MVA, can be diagnosed when an i.c. ACh test reproduces the symptoms usually experienced by the patient and triggers ischemic ECG changes, in the absence of focal epicardial spasm (Figure 5).76

Conclusions Functional tests in the catheterization laboratory are emerging as important tools for epicardial and microvascular assessment. Importantly, their use should be coherently integrated in different clinical settings. Functional tests will probably lead to a more comprehensive assessment of CAD and guide treatment based on a full understanding of the underlying mechanism of disease.

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