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Functional disorders in non-culprit coronary arteries and their implications in patients with acute myocardial infarction☆

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ABSTRACT

Approximately 30-50% of patients with ST-segment elevation acute myocardial infarction have multivessel disease. The physiology of the non-culprit artery (NCA) is complex and represents a challenge to physicians as, while these plaques are presumably stable, clinical data show that they frequently lead to major adverse cardiovascular events. In addition the presence of microvascular and endothelial dysfunction may have prognostic implications and interfere with current physiological indices for stenosis severity assessment. In this review we aim to summarize current methods to study the microcirculation, discuss the evidence available regarding the endothelium and the microvascular compartment of the NCA; the best strategies to perform a complete revascularization based on proven ischemia; real limitations associated to hyperemic stenosis indices; and the potential role of novel resting-indices in this specific acute context.

Introduction

Acute coronary syndrome (ACS) is typically caused by the abrupt rupture of an atherosclerotic plaque [1,2]. This event results in intraluminal thrombus formation, leading to flow compromise and myocardial necrosis. ST-segment elevation acute myocardial infarction (STEMI) occurs when the culprit artery is completely occluded by the thrombus. However, coronary artery disease (CAD) frequently extends beyond the culprit artery. Thus, approximately half of the patients with STEMI have multivessel disease, which is associated with worse outcomes [1,2].

Coronary stenosis in the non-culprit artery (NCA) territory represents a challenge to physicians as, while these plaques are presumably stable, clinical data show that they frequently lead to major adverse cardiovascular events (MACE) [3,4]. Although ischemic lesions should be revascularized, many NCA stenoses are treated medically, while others are treated solely based on their angiographic appearance. Fractional flow reserve (FFR), the reference invasive physiologic index of severity, may improve classification and treatment decision for these lesions, facilitating a complete revascularization based on hemodynamic significance [5]. However, in the acute context of STEMI, with microvascular and endothelial dysfunction potentially present both in the culprit and NCA territories, FFR measurements may be altered, as a result of insufficient hyperemia. In this context, there is increasing interest in novel resting indices such as the instantaneous free-wave ratio (iFR), because of their independence from hyperemia [6,7].

In this article we aim to review the current knowledge of the NCA physiology, its prognostic implications, the best strategies to identify ischemia and the hypothetical limitations associated with currently available stenosis indices (central figure).

Microvascular dysfunction in the non-culprit artery

In normal conditions, coronary vessels $<500\,\mu$m –generally known as microcirculation–, are accountable for over 90% of the total coronary resistance [8]. These vessels autoregulate their resistance with the purpose of maintaining a blood flow adequate to myocardial demands. When the microcirculation is damaged, autoregulation fails; thus, microvascular dysfunction is a well-known cause of ischemia both in patients with and without obstructive CAD [9]. Mechanisms responsible are mainly microvascular

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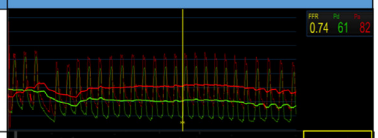
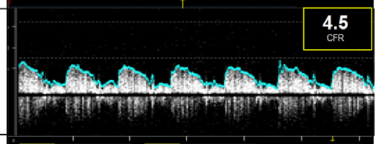
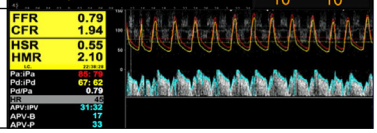
	Formula	Cutoff Value	Implications	Example
FFR	FFR = Pd/Pa	≤0.80	Functionally significant coronary stenosis	
CFR	APV_h/APV_b *Doppler Tmn_b/Tmn_h *Thermodilution	<2	Unspecific macrovascular and microvascular inability to increase flow	
IMR	IMR = Pd x Tmn_h *Thermodilution	>25	Specific microvascular dysfunction	
HMR	HMR = Pd/APV_h *Doppler	>2	Specific microvascular dysfunction	

Fig. 1. Invasive hyperemic indices used to study the microcirculation.
FFR (fractional flow reserve); Pd (distal pressure); Pa (aortic pressure); CFR (coronary flow reserve); APV (average peak velocity); H (hyperemia); B (baseline); IMR (index of microvascular resistance); Tmn (mean transient time); HMR (hyperemic microvascular resistance).

remodelling, endothelial dysfunction, reduced diastolic perfusion time and ventricular hypertrophy [9].

Additionally, in the context of acute myocardial infarction (AMI), transient microvascular dysfunction may take place as a result of luminal obstruction (mainly microembolization by plaque and thrombus debris), inflammation and myocardial edema and necrosis, especially when no-reflow phenomenon takes place [10]. Contrarily to common belief, this microvascular damage is not limited to the culprit vessel but may extend to the NCA territory too [11]. This may have prognostic implications, and also interfere with the measurement of stenosis severity indices.

Microvascular dysfunction can be measured directly by invasive estimation of coronary flow and resistance (Fig. 1). In short, this can be achieved using an intracoronary Doppler wire to determine blood flow velocity or a thermodilution wire, which calculates the mean transient time as a surrogate of blood flow. Since absolute blood flow measurement and interpretation is complex, instead two other methods are used to describe coronary flow: coronary flow reserve (CFR) and microvascular resistance:

- CFR is defined as the ratio between coronary blood flow at maximal hyperemia and at baseline, and is considered normal if above 2 [8,9]. It expresses the capacity of the coronary circulation to increase blood flow in response to a hyperemic stimulus. CFR, however, has two main limitations: it does not help differentiate between epicardial and microvascular flow limitation; and it is very dependent on the baseline hemodynamics, which presumably can be altered in the STEMI context.
- For this reason, coronary resistance indices were developed (Fig. 1): the hyperemic microvascular resistance (HMR), which is calculated using the Doppler wire, is considered abnormal when above 2 [8]; and the index of microvascular resistance (IMR), which is derived from the thermodilution method, and is considered altered above 25 [8–10]. In contrast with CFR, IMR and HMR selectively express microvascular function and are less dependent on the hemodynamic situation [12]. It should be noted that CFR, IMR and HMR mainly express endothelium-independent microvascular function, as adenosine (which causes endothelium-independent vasodilation) is usually used to induce hyperemia.

Alternatively, microvascular function can be estimated by non-invasive methods. In the context of STEMI, cardiac magnetic resonance (CMR) has emerged as an accurate tool for microvascular obstruction (MVO) and infarct size quantification [10], and has been shown as an independent predictor of all-cause mortality [10,12,13].

Microvascular function indices have been used in the culprit territory after successful primary percutaneous coronary intervention (PCI) to predict outcomes. In this sense, an IMR>40 has been shown as an independent predictor of all-cause mortality [14] and MVO [10]. Of note, IMR in the culprit territory tends to decrease during follow-up [15], indicating the potentially transient pattern of the microvascular dysfunction.

The study of the microcirculation in the NCA territory is, however, limited, and mainly contemporary (Table 1). We studied the physiology of the NCA early after primary PCI, and found a mean CFR of 2.6, and a value below 2.0 in 37% of patients [16]. Similarly, Mejia-Renteria et al. found even lower CFR values, and lower than those of stable patients with CAD (1.77 vs 2.44; $p = 0.018$) [17]; another two recent studies found values similar to ours (2.9) [18,19]. Last, another study using positron emission tomography found a mean CFR of 2.5 as compared to 4.2 in healthy control subjects ($p < 0.001$) [20]. In sum, CFR values seem to be lower in the NCA than in patients with stable CAD, and are importantly decreased (CFR < 2) in approximately one third of the patients [21].

With respect to IMR, a better marker of the microcirculation, no significant differences have been observed in the NCA when compared to patients with stable CAD [17, 18]. Mean IMR values in these studies were in general normal (17.9 ± 10.5 [18]; 15.6 (IQR 10.4-21.8) [17]; 18 (IQR 13.5-27) [19]). In the FISIOIAM study mean IMR values were slightly superior (24.4 ± 19), but only 27,7% of patients had an IMR above 25 [16]. This is in line with another study reporting IMR values in the NCA of 14 patients with STEMI, which only found an abnormal IMR in 21% of the cases [22].

Finally, there is little evidence on how microvascular function changes over time: on one hand CFR, with the limitation of its epicardial component and its dependence on baseline flow, has been described to increase during follow-up after AMI (2.9 vs 4.1 [19]; 2.5 vs 2.85 [20]); on the other hand, evidence on IMR modifications are contradictory, as one study showed a non-significant

Table 1
Main studies assessing the microcirculation in the non-culprit artery.

Study	Study design	*n*	CFR	IMR
Teunissen et al. [20]	• CFR calculated using [(15)O]H2O positron emission tomography 1 week after successful primary PCI and 3 months later. • Compared with age and sex matched sane subjects.	44	• **NCA 2.5 ± 0.8** vs 4.16 ± 1.45 in control group ($p < 0.001$). • CFR changed to 2.85 ± 0.7 3 months later in the NCA.	–
de Ward et al. [21]	• Doppler study after successful primary PCI • Compared to 40 stable patients without obstructive CAD	40	• **NCA 2.0 ± 0.7** vs 2.8 ± 0.7 in control arteries. • Lower CFR in patients with larger STEMI (1.7 ± 0.5 vs 2.3 ± 0.8), $p = 0.02$.	–
Choi et al. [18]	• Thermodilution study after successful primary PCI • Compared with 203 patients with stable CAD	100	• **NCA 2.88 ± 1.38** vs 3.16 ± 1.31 in stable CAD ($p = 0.208$).	• **NCA 17.9 ± 10.5** vs 18.5 ± 11.4 in stable CAD; $p = 0.693$. • NCA Tmn_b 0.80 ± 0.41 vs 0.82 ± 0.11 ($p = 0.406$) • NCA Tmn_h 0.30 ± 0.16 vs 0.30 ± 0.16 ($p = 0.971$)
Mejia-Renteria et al. [17]	• Staged thermodilution study (mean time to 2nd procedure 5.92 ± 4 days) • Compared with a matched control group of 46 stable angina patients	49	• **NCA 1.77** (**IQR 1.25-2.76**) vs 2.44 (IQR 1.63-4.00) ($p = 0.018$).	• **NCA 15.6** (**IQR 10.4-21.8**) vs 16.7 (IQR 11.6-23.6); $p = 0.559$. • Tmnb 0.58 (0.32–0.83) vs 0.65 (0.39–1.20); $p = 0.045$ • Tmn_h 0.26 (0.20–0.42) vs 0.26 (0.18–0.35); $p = 0.783$.
Diez-Delhoyo et al. [16]	• Staged thermodilution study [median time to 2nd procedure 2 days (IQR 2-4)]. • No control group	82	• **NCA 2.6 ± 1.3** • 37.3% of the patients had a CFR<2	• **NCA 24.4 ± 18.8**. • 27.7% of the patients had an IMR>25. • Mean RRR 3.2 ± 1.5. • Tmn_b 0.85 ± 0.48. • Tmn_h 0.39 ± 0.26.
van der Hoeven et al. [19]	• Thermodilution study after successful primary PCI and one month later • No control group	73	• **NCA 2.9 ± 1.4** • CFR increased to 4.1 ± 2.2 during follow-up • 22% of the patients had a CFR < 2 in the acute phase vs 16,7% 1month later ($p = 0.56$)	• **NCA 18 (IQR 13.5-27)** • Mean RRR 3.4 ± 1.7 in the acute phase vs 5.0 ± 2.7 ($p < 0.001$) during follow-up
Ntalianis et al. [22]	• Thermodilution study after successful primary PCI and 35 ± 4 days later. • No control group	14	–	• No significant changes in baseline **IMR (20 ± 3)** vs follow-up IMR (24 ± 6) • IMR>25 in 21% of the patients in the NCA

CFR (coronary flow reserve); PCI (percutaneous coronary intervention); CAD (coronary artery disease); NCA (non-culprit artery); IMR (index of microvascular resistance); Tmn (mean transient time; $_b\rightarrow$ baseline; $_h\rightarrow$ hyperemia); RRR (resistive reserve ratio).

increase in a small sample [22], while another found a nearly significant decrease [19].

To summarize, according to IMR, microvascular function may not be importantly affected in the NCA, or at least no more than in patients with stable CAD. These studies highlight that some patients develop a certain degree of microvascular dysfunction, but its severity and prevalence may not be as important as previously believed, probably affecting around a quarter of the subjects. Indeed IMR has to be used as the preferred method to measure the microvascular function during STEMI, as the baseline hemodynamic changes that affect patients in this context alter CFR values.

Endothelial dysfunction in the non-culprit artery

The vascular endothelium, a major determinant of coronary resistance and flow, is a monolayer of cells that covers the internal lumen of blood vessels. In response to physiological triggers, the vascular endothelium regulates arterial smooth muscle tone through the release of vasodilators –mainly nitric oxide (NO)– and vasoconstrictors [23]. When the vascular endothelium is damaged, this function of coronary flow regulation is altered, which results in an insufficient vasodilation or paradoxical vasoconstriction. Endothelial dysfunction also promotes atherosclerosis and thrombosis, and thus may lead to ACS [23].

Although the endothelium has different roles, it is customary to measure its function by the study of its vasomotor activity. The gold-standard technique is to invasively assess this activity during coronary angiography using intracoronary acetylcholine [8,23]. A functioning endothelium releases NO in response to acetylcholine. In case of an impaired endothelial function, NO production is inappropriate, the direct muscarinic stimulation of the smooth muscle by acetylcholine becomes predominant, and vasoconstriction occurs. This is appreciated in the epicardial artery by angiography, and in the microvascular compartment by measuring the CFR. Alternatively, non-invasive methods, such as flow mediated dilation (FMD) and peripheral arterial tonometry (PAT), can also be used [23]. However, in the ACS context, FMD and PAT do not represent intrinsic NCA endothelial dysfunction, but a surrogate of the systemic endothelial status.

Endothelial dysfunction has been widely identified as a predictor of MACE in patients with non-obstructive CAD, stable angina and heart failure [23]. However, evidence in patients with ACS is limited. Using FMD, systemic endothelial dysfunction has been shown as an independent predictor of MACE [24,25]. Evidence regarding an invasive assessment of endothelial dysfunction is scarce, probably translating a safety concern related to acetylcholine administration within the acute phase of AMI. One study reported a 21% prevalence coronary spasm in response to ergometrine, half

of which affected the NCA [26]. However, the procedure was not performed during the acute phase, but at least 2 weeks after the index AMI; and moreover, the physiologic meaning of these responses is uncertain, not being specifically endothelial. Elbaz et al. did study endothelial function in patients with non-ST segment elevation myocardial infarction (NSTEMI), and showed endothelial dysfunction in the NCA in 81% of patients [27]. Probably, the best evidence of endothelial function in the NCA comes from the recent FISIOIAM study [16]. We studied 84 patients a median of 48 h after primary PCI, and found a 60% prevalence of macrovascular endothelial dysfunction, and a 44% prevalence of microvascular endothelial dysfunction. Interestingly, macrovascular vasoconstriction affected the NCA plaque in 80% of the cases when a positive response was observed. Globally, 70% of the subjects had an altered endothelial study. This endothelial dysfunction selectively affecting the NCA plaque may explain, at least in part, why some of these lesions are prone to plaque rupture on follow-up.

Endothelial dysfunction in the course of AMI may improve over time. In the study by Elbaz, which excluded STEMI patients, 77% of vasomotion abnormalities during invasive assessment improved after 6 months [27]. Normalization of endothelial function has also been described by FMD, and has been found a predictor of lower risk for MACE [24,25].

In summary, endothelial dysfunction itself, or as a marker of cardiovascular disease, is a strong predictor of MACE in a wide variety of clinical scenarios. In patients with STEMI, endothelial dysfunction affecting the NCA is a common finding, and it may have a transient pattern. In any case, more evidence is required to define the exact role of endothelial dysfunction assessment in patients with STEMI, and the potential treatment implications of a positive test.

Assessment of epicardial obstruction in the non-culprit artery

The decision to treat the NCA stenosis has been a matter of debate in the last years. Initial observational studies suggested that angiography-guided NCA revascularization was an independent predictor of all-cause mortality during short-term follow-up [28]. Accordingly, 2012 European Society of Cardiology and 2013 ACC/AHA clinical guidelines recommended that PCI should be limited to the culprit vessel with the exception of cardiogenic shock. However the PRAMI and CvLPRIT randomized trials recently showed that a preventive-PCI strategy was associated with a lower rate of MACE than a single culprit-vessel strategy [3,4]. The PRAMI trial was prematurely stopped after a benefit in MACE was observed in the preventive PCI arm (HR 0,32; $p < 0{,}001$). Of note, NCA PCI was performed right after primary PCI [3]. In the CvLPRIT trial, revascularization could be performed during primary PCI or in a second procedure; at 12 months, the composite primary endpoint occurred in 10% of the complete revascularization group versus 21,2% in the culprit-only group (HR 0.45; $p = 0.009$) [4]. On the other hand, in the context of cardiogenic shock, the CULPRIT-SHOCK randomized trial found that preventive PCI in patients with STEMI and multivessel disease was associated with a higher relative risk of death (HR 0.84; $p = 0.03$) [29].

In our opinion this paradigm change is based on at least three physiological reasons that may explain the benefit of NCA revascularization in stable patients: first, some of these lesions are hemodynamically significant despite asymptomatic, hence associated to worse outcomes [5]; second, other lesions will tend to disrupt due to local endothelial dysfunction and the systemic pro-inflammatory environment associated to STEMI; and last some lesions are actually unstable plaques despite an angiographically intact endothelium. This is supported by the fact that MACE curves in studies comparing single culprit-lesion versus multivessel PCI start to separate from the very early phase after STEMI [3,4]. In fact this rationale may not be helpful in patients with cardiogenic shock, who probably require short and neat PCI procedures, avoiding prolonged revascularization-times and large amounts of contrast, that may increase patient instability and need for renal-replacement therapy [29].

Accordingly, current clinical guidelines support a routine complete revascularization in stable patients [1,2]. Pending a randomized trial assessing the best timing for revascularization of the NCA stenosis, current evidence supports a staged revascularization strategy [30], with the second procedure preferably performed before discharge [2], or at least not delayed more than 1–2 weeks [3,4]. Of note, in both PRAMI and CULPRIT trials, the decision to undergo PCI was based on the angiographic severity appearance. Next, we discuss the potential additional value of hyperemic and non-hyperemic physiology indices of obstruction to guide NCA revascularization (Fig. 2).

Theoretical and real limitations of an FFR-guided revascularization strategy

FFR is an index of the physiological significance of a coronary stenosis and is defined as the ratio of maximal blood flow in a stenotic artery to theoretical maximal flow for such artery without the stenosis. It can be easily estimated calculating the ratio of distal coronary pressure to aortic pressure during maximal steady hyperemia (Fig. 1) [5]. Typically, hyperemia is achieved using adenosine, although other drugs such as papaverine, regadenoson or nitroprusside can also be employed [8,9].

The theoretical FFR in a normal coronary artery is 1. A cutoff value of 0.75 accurately predicts inducible ischemia, and a cut-off of 0.8 is used for safe deferral of coronary intervention [5]. However, the ischemic risk of a lesion is inversely proportional to FFR, as a continuous rather than dicotomic function. This fact is of paramount importance, indicating that lower FFR values receive larger absolute benefits from revascularization [31]. A so-called “grey-zone” with values between 0.75 and 0.80 has been described [8], in which binary agreement is logically lower. In this borderline FFR values, keeping a clinical perspective and weighing risks/benefits of revascularization is mandatory. As previously pointed out, the presence of microvascular dysfunction and its limitation to hyperemia may overestimate FFR values, leading to significant stenosis being left untreated. Moreover, FFR values are inversely proportional to the amount of myocardium supplied and may in this case overestimate stenosis severity in case the NCA is supplying blood to the culprit territory [32].

In the context of STEMI, significant microvascular dysfunction and stunned myocardium are common findings in the culprit artery [10,13–15]. Measuring FFR in the culprit stenosis does not have a clear rationale, but it may occur that another stenosis different than the culprit is present in the same infarct-related territory. In this context, major limitations for interpretation of FFR have been reported. First studies in STEMI patients showed a severely decreased vasodilatory capacity [33,34]. Tamita et al. found higher FFR values in STEMI-related arteries compared to those of stable patients, after adjusting for stenosis severity (0.95 ± 0.04 vs. 0.90 ± 0.04; $p = 0.002$) [35]. Also, FFR has been found to decrease 6-months after STEMI in the culprit vessel, especially in patients with microvascular obstruction ($\Delta -0.08 \pm 0.07$) [15]. Considering all this evidence, FFR is not a reliable index of coronary severity in culprit vessels in STEMI, at least in the first weeks after an AMI when microvascular dysfunction is maximal.

As previously exposed, the extent of microvascular dysfunction in the NCA territory is lower and may only affect around 25% of the arteries [15–21]. Some studies have pointed out that patients with ACS following an FFR-guided PCI strategy may have worse

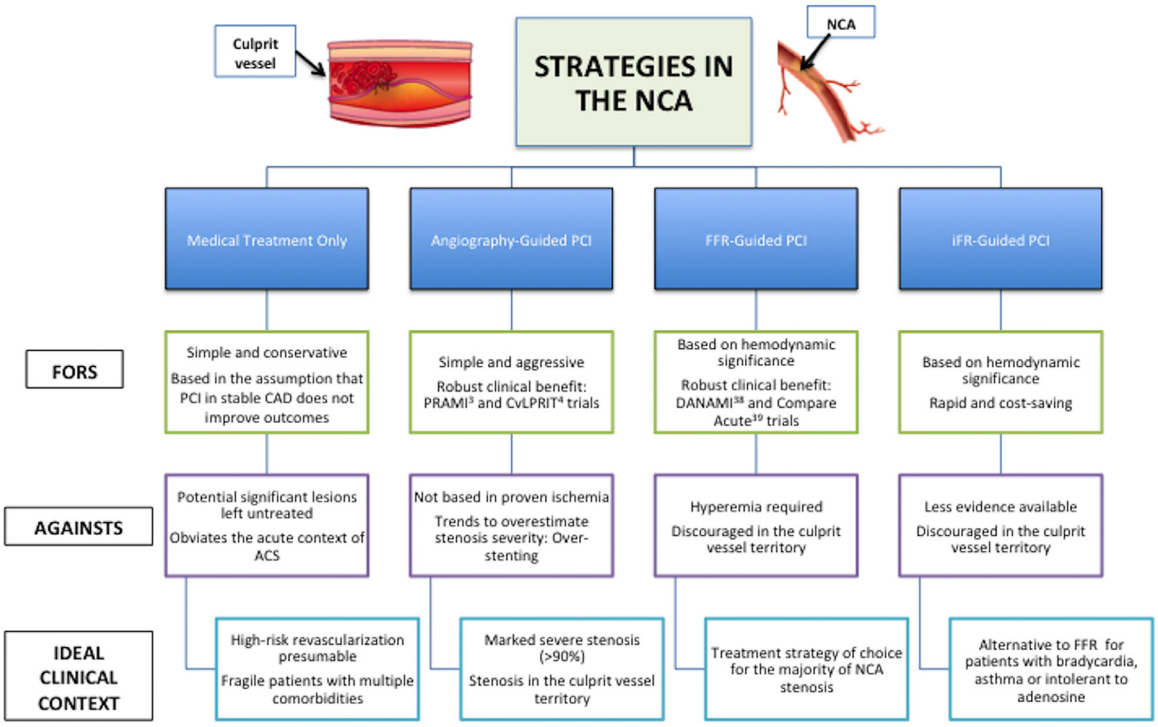


Fig. 2. Available strategies to treat patients with STEMI and multivessel disease.
NCA (non-culprit artery); PCI (percutaneous coronary intervention); CAD (coronary artery disease); ACS (acute coronary syndrome); FFR(fractional flow-reserve; iFR (instantaneous free—wave ratio).

outcomes than those with stable angina. In this sense, Mehta et al. found in ACS patients, but not in stable ones, that every 0.01 decrease in FFR was associated with higher rates of MACE (HR 1.08; 1.03-1.12; $p = 0.026$) [36]. Some authors have proposed an alternative cutoff of <0.84 as the best to predict MACE in ACS, rather than the standard cutoff of 0.8 in stable patients [37]. These studies do not invalidate the use of FFR in the setting of ACS, but translate the well-known worse outcomes associated to ACS as compared to stable CAD [38].

In fact, several studies have confirmed the reliability of FFR in this context. From a pre-clinical basis, in a recent study using a porcine model, IMR-FFR values were not modified in the circumflex artery after repeated injections of microspheres in the left anterior descending artery [39]. Importantly, in an observational study including 75 STEMI patients, FFR did not change in the NCA when assessed 35 days later (0.77 ± 0.13 vs. 0.77 ± 0.13; p = NS) [22]. More recently, 2 studies have reported slight increases in FFR values (Δ+0.02) when measured 1–2 months after STEMI [19,40]. Of note, in the study by Wood et al., only 3 patients moved from an FFR>0.80 to ≤0.80, translating an excellent discrimination power. In the study by Layland, a resistive reserve ratio (RRR; an index of the vasodilatory capacity of a microcirculation) of 2.46 in patients with NSTEMI was considered valid for FFR-guided PCI [34]. In this sense, in the FISIOIAM and in van der Hoeven's study mean RRR in the NCA was 3.2 and 3.4 respectively, far exceeding the preserved vasodilatory capacity cutoff [16,19]. Finally, in the recent study by Choi et al., FFR values of NCA stenosis were even lower than those of stable patients matched by coronary severity (0.80 ± 0.11 vs 0.82 ± 0.11) [18].

Accordingly, large randomized clinical trials have validated an FFR-guided complete revascularization strategy, which is associated to a lower incidence of MACE as compared to a single-culprit vessel strategy [41,42]. However, it should be noted that the clinical benefit is mostly driven by unplanned revascularization, and that these studies did not compare FFR-guided revascularization with angiography-guided revascularization. This comparison was performed in a substudy of the FAME-1 trial, showing that patients with acute coronary syndrome had the same risk reduction (19%) from an FFR-guided revascularization as patients with stable CAD [38].

In summary, the possibility of transient microvascular dysfunction in the NCA is a theoretical limitation of FFR in this context. This is certainly important in the culprit artery territory, while it seems more dubious in the NCA, where the vasodilatory capacity of the microcirculation is less impaired. Importantly, two trials have validated the clinical use of FFR-guided revascularization in the NCA.

Non-hyperemic indices in the non-culprit artery

In the last years, several non-hyperemic indices have been developed in order to avoid adenosine-dependent hyperemia and its concomitant transient side effects. The instantaneous wave-free ratio (iFR) is calculated by measuring the resting pressure gradient (Pd/Pa) across a coronary lesion during a specific part of the diastole [8]. Its measurement depends on the assumption that maximal flow and minimal resistance occur during a certain part of the diastole. A cutoff value of ≤0.89 has been set to identify ischemia [6,7]. Recently, 2 other resting indices have been introduced [43]: the resting full-cycle ratio (RFR) is based on the identification of the lowest Pd/Pa within the entire cardiac cycle; the diastolic pressure-ratio (dPR) is the averaged Pd/Pa ratio during the entire diastole. As these indices are novel, evidence supporting their use in ACS is limited. It is not unreasonable to think that these resting indices may not be affected by microvascular dysfunction, as microvascular vasodilation is not required. However baseline hemodynamics are altered after STEMI [21], and tachycardia and flow acceleration mostly affect the diastole. Hence, resting indices are not free of potential theoretical limitations in this context.

Preliminary data in AMI patients have shown slight changes in mean iFR values when measured during primary PCI and at follow-up (0.89 vs 0.91 [44]; 0.93 vs 0.94, $p = 0.12$ [19]). As previously described with FFR, iFR values were comparable in NCA versus stable lesions after adjusting by angiographic severity [18]. Concerning binary agreement in ischemic classification over time, the study by van der Hoeven did not find differences between FFR and iFR (FFR in the acute setting agreed with FFR on follow-up in 80.8%; for iFR it was 82.2%; $p > 0.99$).

There are limited data on the clinical use of iFR in the NCA. Recently, iFR-guided PCI has proven non-inferior to FFR-guided PCI in patients with stable CAD in two large randomized trials [6,7]. However, patients with STEMI were minimally represented in these trials. A subanalysis of patients with ACS from these two trials showed similar outcomes when PCI was deferred based on FFR or iFR [45]. To date, RFR and dPR have shown a good correlation with iFR, but no data are available regarding their use in STEMI patients [43].

In summary, non-hyperemic indices represent a promising alternative in patients with CAD, especially if avoiding adenosine is mandatory. iFR measurements appear to be minimally altered by microvascular dysfunction or other disturbed hemodynamics in STEMI. Although initial data suggest that the use of iFR in the NCA may be accurate and safe, more evidence is needed in this specific context to completely validate its widespread utilization.

Future perspectives

Despite major advances in recent years, in our opinion important gaps in evidence are relevant and more research seems warranted:

- The extent of microvascular dysfunction in the NCA and its prognostic implication remain incompletely understood. The same is true for its potential impact on the accuracy of FFR and non-hyperemic pressure indexes. Long-term follow-up studies comparing patients with and without microvascular dysfunction measured during the acute phase may help clarify these issues.
- Similarly, the precise role of endothelial dysfunction in the context of STEMI remains uncertain. In particular, we have yet to clarify how persistent it is over time after ACS, and whether it carries a higher risk of MACE. It is also uncertain whether the finding of endothelial dysfunction in this context warrants a specific treatment –for instance, withdrawal of betablockers or use of calcium channel blockers to prevent epicardial spasm.
- We currently know that both angiography-guided and FFR-guided multivessel PCI are superior to culprit-vessel only revascularization. However these 2 strategies have not been compared to date, which is fundamental to establish the gold-standard strategy in patients with STEMI and multivessel disease. The FRAME-AMI trial will shed light on this question [46]. Also, the precise timing for multivessel revascularization remains unknown. The MULTISTARS trial, currently recruiting, will probably provide robust evidence in this context [47].
- To completely validate the use of resting indices in patients with AMI, iFR will have to be compared to FFR. The INTERPRET trial will provide more evidence in this respect [48].

Conclusions

The physiology of the NCA is complex and represents a challenge. Endothelial dysfunction is common and its measurement using acetylcholine in the acute phase is safe. Microvascular dysfunction in the NCA seems to be mild, and its impact on FFR measurements, although real, has not been proven clinically relevant to date. Revascularization should be based on proven ischemia, and thus a physiology-guided strategy may be the most appropriate. Novel resting indices are a promising alternative and warrant further studies.

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