Let's functionalize the myocardial flow reserve

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Quantitative myocardial blood flows (MBF) by PET are entering the practice of nuclear cardiology. Flow responses to pharmacologic vasodilation measured in absolute units together with myocardial flow reserves (MFR) have improved the detection of functionally obstructive coronary artery disease, especially in patients with multivessel disease. They also have become powerful predictors of major adverse cardiac events (MACE) including cardiac death, nonfatal myocardial infarction, acute coronary syndrome and hospital admission for heart failure. Applied globally to the myocardium, vasodilator-stimulated flows probe the responsiveness of the entire coronary circulation and provide a measure of its overall vascular health. The “global myocardial flow reserve (MFR)” as the ratio of global hyperemic to rest MBF therefore reflects the composite effects of coronary morphological and functional alterations that exert resistance to increases in coronary flow. A benchmark value of 2.0 for the MFR has emerged from multiple follow up investigations in patients after PET MPI and flow measurements, a threshold value that discriminates between high and low risk of cardiac death and of MACE.^{1–3}

MFRs of ≤ 2.0 in patients with obstructive coronary disease, visualized as inducible perfusion defects on MPI and verified by invasive or noninvasive coronary angiography, can guide decisions on treatment strategies. For example, event-free survival improved significantly more after early revascularization than on medical treatment alone in patients with severely reduced MFRs (i.e., 1.2 or lower), but did not differ between revascularization and medical treatment in patients with less severely reduced MFRs (i.e., > 1.4).³ Of note, some evidence exists for MFR as a guide to the

type of revascularization. For example, two studies report significantly better event-free survival outcomes after CABG than after PCI.^{4,5}

However, impaired MFRs without obstructive coronary disease remain therapeutically challenging because pathophysiologic mechanisms of the impaired vasodilator flow response are not fully understood. Impairments of MFR without obstructive disease are frequently present in patients referred to PET evaluation because of clinical signs of ischemia including angina and ischemic ECG changes. Nearly 50% of patients with normal stress MPI on PET and thus without evidence of obstructive CAD had global MFRs ≤ 2.0 or ≤ 1.8 and thus were at high risk for MACE including death.^{3,6} Defined broadly as coronary microvascular dysfunction (CMD) without obstructive disease, it is prevalent among patients with cardio-metabolic syndromes (i.e., obesity, pre-diabetes, diabetes mellitus), with chronic renal disease, or with heart failure with preserved ejection fraction (HFpEF) and occurs more frequently in women than in men.⁷ The underlying pathophysiology still awaits clarification. Whether functional or structural alterations confined to the microcirculation fully account for the MFR impairment has remained uncertain. In fact, a synergy of multiple adverse players may interfere with the normal coronary reactivity. Apart from structural alterations of the microcirculation like arteriolar remodeling and rarefaction, diffuse atherosclerosis or non-obstructive disease of the epicardial conduit vessel may also contribute to reducing the vasodilator-induced flow response. Depending on the reactivity of the downstream resistance vessels, a gradual distal-to-proximal coronary pressure gradient in diffusely diseased arteries may reach levels of ischemia with distal to proximal coronary pressure gradients of ≤ 8.0 , equivalent to FFRs for discrete but functionally significant stenoses. Their effect on MBF is seen on perfusion images as a gradual decline of flow in the base-to-apex direction.^{8,9} Purely functional disturbances may further add to the impairment of the flow response. For example, pharmacologic inhibition of NO synthesis in normal

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human volunteers attenuates the flow response to adenosine and thus the global MFR,¹⁰ emphasizing the role of endothelial dysfunction, both at the level of the microcirculation and the epicardial conduit vessel, as a major player of limiting the flow responses, an effect that often augmented by circulating vasoconstrictive substances.¹¹ Importantly, functional alterations may be amenable to therapeutic interventions with normalization of the flow reserve.^{12,13} Extravascular resistive forces can also oppose hyperemic flow responses when intra-myocardial pressures are high as for example in patients with systolic blood pressure or with elevated left ventricular filling pressures.¹⁴

Functional characterization of impaired flow responses can identify possible mechanisms and guide patient management. In the CarMicA (coronary microvascular angina) trial for example, management of patients with angina but no obstructive disease, stratified by findings made with functional testing, improved the patients' quality-of-life.¹⁵ Different from the invasiveness of functional characterization of microvascular reactivity in these studies using intracoronary acetylcholine and/or adenosine, measurements of MBF with PET offer a unique and broad platform for exploring pathophysiologic mechanisms of an impairment in vascular reactivity. They are non-invasive, are readily repeatable and can be "functionalized", that is, through measurements of changes in MFR in response to pharmacologic interventions that either target specific control points of coronary vasomotion or, alternatively, more system-wide determinants of coronary vasodilation. For example, an improvement in MFR after administration of L-arginine (as the substrate of NO synthesis) implicates NO unavailability and, possibly, the endothelium as likely participants in the impairment of vascular responsiveness;¹⁶ coronary flow responses to insulin as measured with PET could inform on vascular effects of insulin resistance in patients with cardiometabolic disorders including obesity.^{17,18} Effects of angiotensin converting enzyme (ACE)-inhibitors or angiotensin II receptor blockers (ARBs) on coronary vasodilator responses in hypertensive patients for example could shed new light on the complex interplay of system-wide regulatory mechanisms and coronary vasomotor control. Besides the potential of providing important mechanistic insights, a thus functionalized MFR could lead to developments of more targeted therapeutic strategies for raising the vasodilator capacity of the coronary circulation. If in fact MFR does outperform other variables like LVEF, size and severity of perfusion defects and metabolic evidence of myocardial viability in the prediction of MACE, as recently observed in patients with ischemic cardiomyopathy,⁵ then MFR becomes a highly critical determinant of the

clinical outcome. Accordingly, functionalizing the MFR in the search for targeted therapeutic strategies will be a worthwhile and therapeutically important goal, especially for meeting an unmet therapeutic need in patients with CMD without obstructive coronary disease.

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