Microvascular resistance reserve: a reference test of the coronary microcirculation?

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The diagnostic evaluation of coronary microvascular function is a 'hot topic' in cardiology. Coronary microvascular dysfunction is implicated in the pathogenesis of multiple cardiovascular conditions including diabetes[1], ischaemic heart disease (stable angina[2], post-percutaneous coronary intervention (PCI)[3], acute myocardial infarction[4]), infiltrative cardiomyopathy[5], cardiotoxicity[6], heart failure with preserved ejection fraction[7], and after cardiac transplantation[1]. The pathophysiological consequence of microvascular dysfunction is a myocardial blood supply: demand mismatch leading to regional or global ischaemia, ischemic symptoms, and an adverse cardiovascular prognosis[1], including in the absence of epicardial coronary artery disease[8].

While fractional flow reserve (FFR) and derived resting indexes are being increasingly used in clinical practice (Figure 1), they are focused on the epicardial coronary arteries and on the potential benefit of coronary revascularisation[9–11]. On the other hand, coronary flow reserve (CFR), traditionally assessed during maximal hyperaemia using a Doppler guidewire, does not discriminate between the epicardial vessels and the microcirculation, and CFR is affected by resting hemodynamics. The index of microcirculatory resistance (IMR)[12], which can now be measured directly using a diagnostic guidewire or indirectly using angiography, is not affected by the severity of an epicardial stenosis or resting conditions. The resistance reserve ratio (RRR) is a related estimate of the microvascular vasodilator reserve. However, these indices provide an indirect estimate of coronary blood flow and they are derived using a bolus (3 ml) intracoronary injection of saline, hence potentially affected by the operator and by the sensor location within the artery.

To overcome these limitations, De Bruyne et al.[13] recently proposed the novel microvascular resistance reserve (MRR) index measured using continuous thermodilution. MRR represents the extent to which hyperaemic microvascular resistance would decrease if the epicardial coronary artery were to be normal. Indeed, MRR corrects the CFR for the functional effect of

47 epicardial coronary atherosclerosis (assessed by FFR) and for the effect of pharmacological
48 vasodilatation on perfusion pressure (expressed by the ratio of resting to hyperemic aortic
49 pressure), according to the formula: MRR = (CFR/FFR) x (Pa_{rest}/Pa_{hyper}), where Pa_{rest} and
50 Pa_{hyper} represent aortic pressure during resting conditions and maximal hyperaemia,
51 respectively.

52 In this issue of the European Heart Journal, Boerhaut et al. [REF] report the results of a
53 multicenter, retrospective registry (ILIAS) in which the MRR was "extracted" by using either
54 doppler-derived CFR or bolus thermodilution-derived CFR in 1481 patients undergoing
55 coronary angiography and invasive physiologic assessment for chronic ischaemic heart
56 disease. The authors investigated both diagnostic performance of the new index, as compared
57 to CFR and non-invasive stress tests, and its prognostic role on the occurrence of major adverse
58 cardiovascular events and target vessel failure at a median follow up of 3.6 years.

59 The authors of the ILIAS study observed a moderately strong between MRR and CFR (R=0.87,
60 $p<0.005$). This is not surprising since CFR is incorporated in the MRR formula. The study also
61 confirmed a previous observation by De Bruyne et al. that the lower the FFR value, the greater
62 the difference between MRR and CFR. This finding supports the notion that MRR specifically
63 reflects microvascular function, whereas CFR reflects macrovascular atherosclerosis and
64 microvascular function.

65 The authors proposed an optimal MRR cut-off to identify reversible myocardial perfusion
66 abnormalities in a subgroup of patients who underwent non-invasive stress tests before
67 coronary angiography (n=503). Although the derived cut-off value of 3.0 was consistent in
68 sensitivity analyses, including when restricted to subgroups determined as having functionally
69 non-obstructive coronary artery disease, or having been assessed using single-photon emission
70 computed tomography (SPECT), or a Doppler wire, the overall diagnostic performance of
71 MRR was suboptimal (AUC 0.51).

The ILIAS study also investigated the prognostic role of MRR on the occurrence of major adverse cardiovascular events (MACE, n=163), including all-cause death (n=61), acute myocardial infarction (target vessel) (n=23) and urgent revascularization (n=149), and also target vessel failure (TVF) post-PCI (including cardiac death (n=46), acute myocardial infarction (target vessel) (n=23), and urgent revascularization (target vessel) (n=81), during a 5-year follow-up period. The authors found that MRR was independently associated with both MACE and TVF. When stratifying the study population by the presence of functionally important, intermediate, or functionally non-significant epicardial disease, only MRR was independently associated with MACE at follow-up in this group, whereas both MRR and CFR were predictors of events in the other subgroups. Despite being initially validated with continuous thermodilution, MRR seems to preserve its diagnostic and prognostic value even if calculated using alternative methodologies like Doppler- or bolus thermodilution. In other words, the diagnostic and prognostic value of MRR appears to be independent of the method.

These findings are remarkable considering the limitations that were acknowledged by the authors. The limitations include the post-hoc design, the retrospective selective inclusion of studies and participants, the heterogeneity between these studies, the lack of standardization in CFR definition and acquisition, the paucity of clinical and procedural data (especially regarding the angina burden), and site-adjudication of clinical events. Furthermore, some relevant data that would have been helpful to characterize the study population, including multivessel coronary disease, left ventricular function and the proportion of patients who underwent PCI during the index procedure, and the minimum FFR values, were not reported. Finally, no comparative data were provided on the diagnostic performance of MRR as compared to RRR, which is also a specific measure of microvascular function and currently displayed in commercially available software. Notwithstanding, in this study by Boerhout et al[REF], MRR

appeared to be a reliable diagnostic and prognostic index able to complement the assessment of epicardial coronary atherosclerosis.

Should MRR become a unifying, reference invasive measure of microvascular disease? Currently, CFR and IMR represent distinct properties of the microcirculation (Figure 1). CFR reflects the vasodilator reserve of the coronary circulation including the epicardial artery and microcirculation, RRR specifically reflects the vasodilator reserve of the microcirculation, whereas IMR, hyperemic microvascular resistance (HMR) and absolute microvascular resistance (AMR) more specifically reflect microvascular resistance (rather than vasodilator reserve). Therefore, it remains to be clarified whether MRR is diagnostically sufficient as a single index to represent all of these parameters, or whether MRR may yet provide complementary information coupled with measures of actual microvascular resistance (IMR, HMR and AMR).

As matter of fact, epicardial and microvascular disease represent a continuum. Currently, a comprehensive assessment of microvascular function is feasible and recommended in European[14] and North American[15] chest pain guidelines when myocardial ischaemia with no obstructive coronary arteries (INOCA) is suspected. The authors should be commended for having provided the first multicentre data on the clinical significance of MRR. Their study should pave the way for future studies in cardiovascular conditions where coronary microvascular disease is implicated. Potentially, MRR may serve as a therapeutic target to guide therapy development for coronary microvascular disease.

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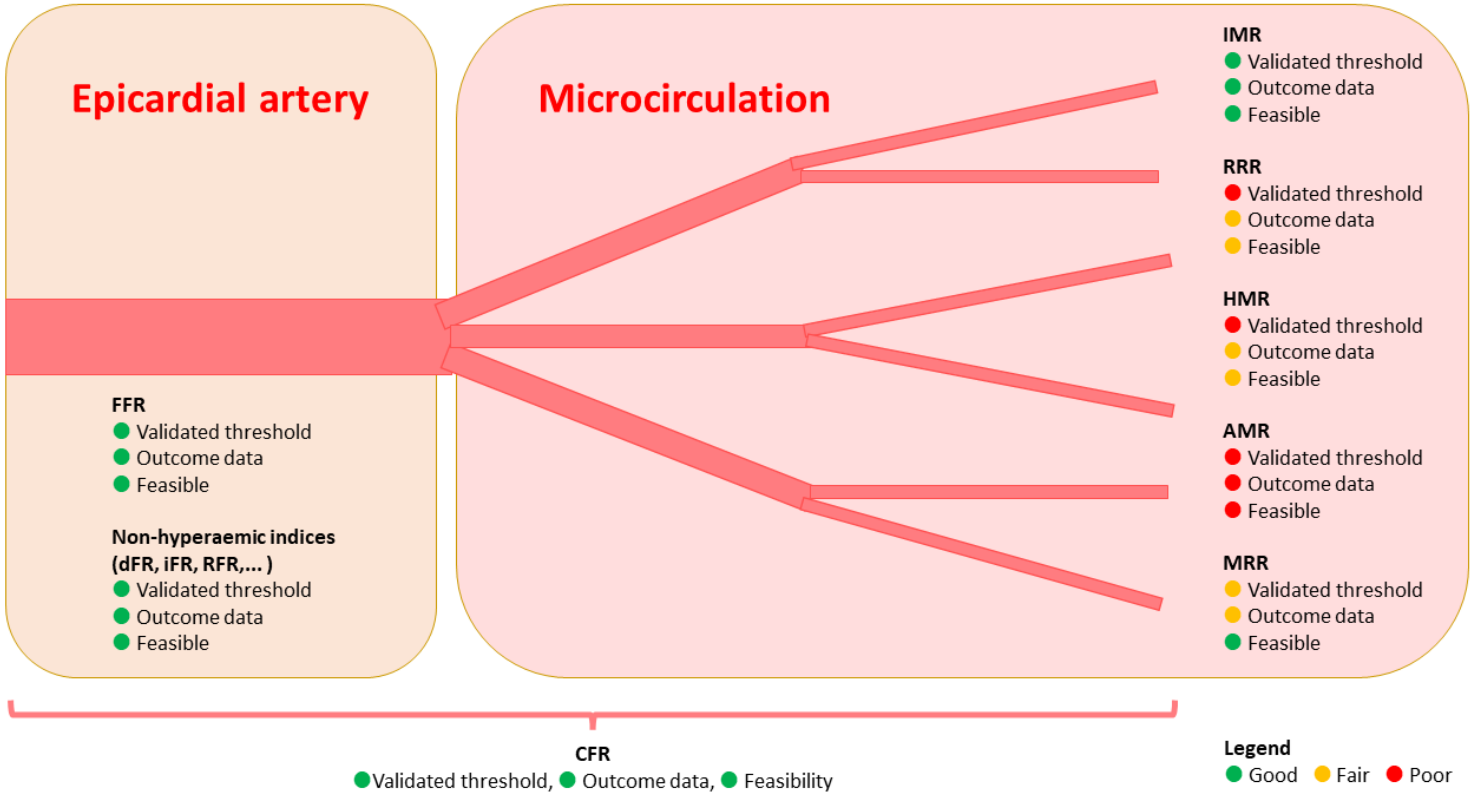
Graphical abstract

Diagnostic and prognostic characteristics of currently invasive coronary physiology indices.



FFR: fractional flow reserve; iFR: instantaneous wave-free ratio; RFR: resting full-cycle ratio; DFR: diastolic hyperaemia-free ratio; IMR: index of microcirculatory resistance; RRR: resistive reserve ratio; HMR: hyperaemic microvascular resistance; AMR: absolute microvascular resistance; MRR: microvascular resistance reserve.