Review

Assessment of the coronary microcirculation in the cardiac catheterisation laboratory

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Abstract

The coronary microcirculation is a key determinant of blood supply to the myocardium and outweighs the epicardial arteries in its abundance and distribution. Recent studies have shown the clinical benefit of assessing the microcirculation, and this practice has now been given a recommendation within latest international guidelines and consensus statements. However, the uptake of assessing the microcirculation remains low. We continue to focus our efforts in diagnosing and managing epicardial coronary disease in the cardiac catheterisation laboratory, and mostly ignore the microvasculature. This is in large part due to the lack of familiarity with available tools to perform these assessments. This review aims to summarise the various techniques available to invasively assessing the coronary microcirculation in the catheterisation laboratory. The advantages, disadvantages, pitfalls and clinical implications of each method will be discussed.

Keywords: Coronary microvascular disease, microvascular angina, index of microcirculatory resistance, coronary physiology

INTRODUCTION

Assessment of coronary microcirculatory function in the cardiac catheterisation laboratory is valuable for both treatment of angina[2] and prognostication[3-5] and has recently been incorporated into European Society of Cardiology guidelines[6] as well as a consensus document by the European Association of Percutaneous Coronary Intervention[7]. The aim of this review is to provide a comprehensive review of the techniques of invasive assessment of coronary microvascular function in the cardiac catheterisation laboratory.

Indications for assessment of coronary microvascular function include, but are not limited to, ischemia and no obstructive coronary artery disease (INOCA)[2], myocardial infarction with non-obstructive coronary arteries (MINOCA)[8], ST-elevation myocardial infarction (STEMI)[4] and those with stable coronary artery disease[6].

ANATOMY, FUNCTION AND DYSFUNCTION OF THE MICROCIRCULATION

The coronary microcirculation is broadly defined as vessels smaller than 300 microns, or more generally through pre-arterioles, arterioles, capillaries and venules[9]. In addition to serving as capacitance vessels holding 90% of the myocardial blood volume, the microcirculation is the major source of regulation of myocardial blood flow, a role which becomes vital in the presence of a stenosis where coronary autoregulation is required to maintain flow [10]. In the absence of a stenosis, the microvasculature acts in the same way to regulate flow in response to varying physiological demands such as exercise[11].

Microvascular dysfunction is an umbrella term which encompasses multiple possible pathologies including vascular wall infiltration, extraluminal compression, sympathetic dysfunction and altered remodelling. However, the exact pathophysiological chain remains poorly understood[12]. There are now an increasing number of in vivo experimental models of coronary microvascular dysfunction which are useful in elucidating the pathophysiology of coronary microvascular dysfunction and may identify future therapeutic targets[13].

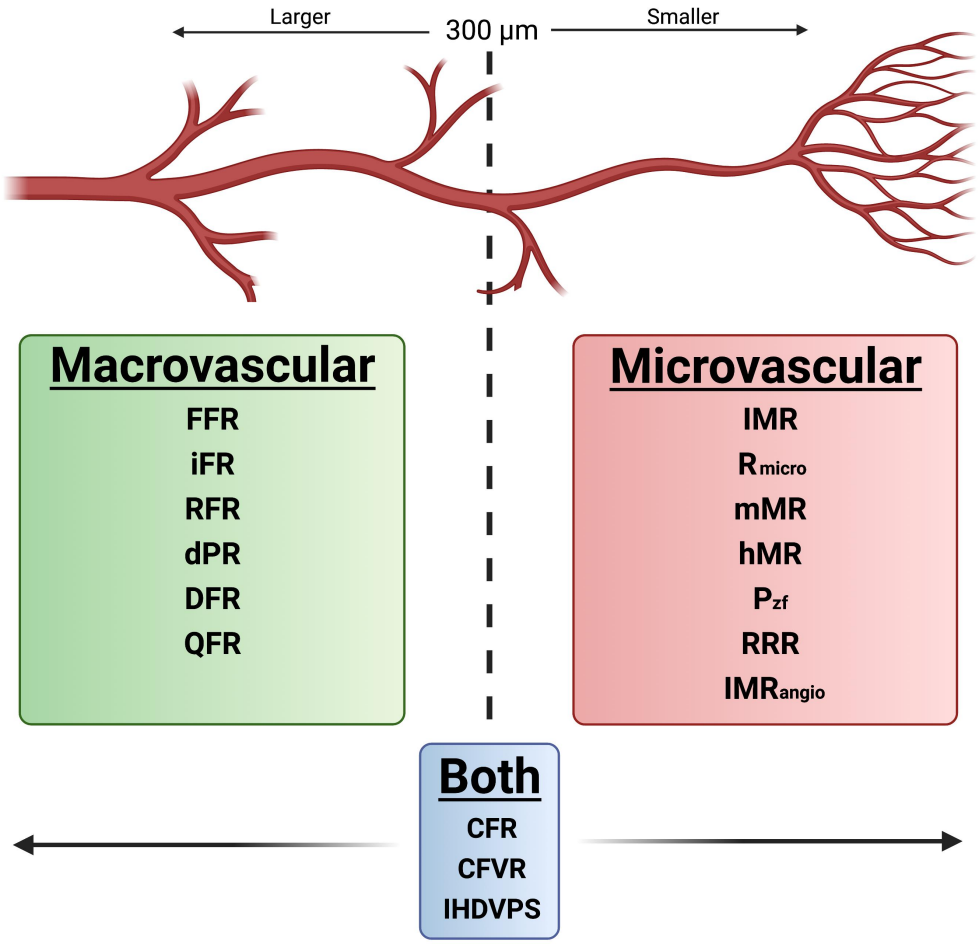

Figure 1: Coronary physiology measurements in the cardiac catheterisation laboratory. FFR: Fractional flow reserve; iFR: instantaneous wave-free ratio; RFR: Resting full-cycle ratio; dPR: Diastolic pressure ratio; DFR: Diastolic hyperaemia-free ratio; QFR: Quantitative flow ratio; IMR: Index of microcirculatory resistance; R_{micro}: Microvascular resistance (derived by continuous thermodilution); mMR: Minimal microvascular resistance; hMR: Hyperaemic microvascular resistance; P_{zf}: Zero-flow pressure; RRR: Resistive reserve ratio; IMR_{angio}: Angiography-derived index of microcirculatory resistance.

NON-INVASIVE METHODS

A number of non-invasive modalities can be used to assess the coronary microcirculation. These include positron emission tomography (PET), magnetic resonance imaging (MRI), single-photon emission computed tomography (SPECT), myocardial contrast echochardiography[10] and computed tomography (CT) perfusion[14]. These modalities can be used to quantify myocardial blood flow both at rest and during hyperaemia using various hyperamic agents. By then comparing resting perfusion to hyperaemic perfusion, a coronary

flow reserve (CFR) is able to be calculated. Unlike invasive angiography, these methods are not able to directly visualise the coronary artery (except for CT) and hence cannot distinguish between causes of a low CFR incuding focal epicardial stenosis, diffuse epicardial stenosis and microvascular dysfunction, and this limits their capacity to reliably diagnose coronary microvascular dysfunction. As listed in Table 1, there are now a variety of invasive methods available to evaluate the coronary microcirculation that will be discussed in this review.

Table 1. Techniques to assess for coronary microvascular dysfunction in the cardiac catheterisation laboratory

Index	Ease	Method	Normal range	Advantages	Disadvantages
IMR[15]	+++	Thermodilution	<25	-Specific to the microcirculation -Reproducible -Independent of haemodynamic perturbations - Predictive of subsequent death or rehospitalisation in STEMI patients - Predictive of subsequent MACE in patients undergoing elective PCI	-If FFR < 0.45, requires wedge pressure for correction
CFR[16]	++	Thermodilution	>2.0	-Predicts all-cause death	-Cannot distinguish between macrovascular and microvascular disease
RRR[17]	++	Thermodilution	>3.5	-Predicts cardiac death in a wide range of patients -More specific to the	-Influenced by extrinsic factors like CFR

				microcirculation than CFR	
CFVR[18]	++	Doppler	>2.0	-Predicts all-cause death	-As with CFR, but additionally there are the technical issues associated with Doppler signal acquisition
hMR[19, 20]	+++	Doppler	<3.0	-Does not require correction provided FFR is above 0.6	-Technical issues associated with Doppler signal acquisition -Limited prognostic data
R_{micro}[21]	++	Continuous thermodilution	<500 Woods Units	-Does not require adenosine, as the saline infusion induces hyperaemia	-Equipment not yet widely available -Currently unclear how to correct for the presence of a stenosis - Limited prognostic data
mMR[22]	N/A	Doppler	Unknown	-Does not require hyperaemia	-Requires further validation given only one study available to date, published in 2016 -Limited prognostic data
IHDVPS[23]	+	Doppler	Not defined	-Correlates with histological microvascular abnormalities -Not generally altered by most haemodynamic parameters	-Difficult to interpret in the presence of a stenosis -Time consuming -Limited prognostic data
P_{zf}[24]	+	Doppler	< 42	-Can indicate extrinsic	-As with IHDVPS with

			mmHg	microvascular compression in STEMI	the addition that data for use is limited to STEMI -Limited prognostic data
TFC[25]	+++ +	Angiography	<21	-No guidewire required	-Qualitative -Limited accuracy and reproducibility
MBG[26]	+++ +	Angiography	2-3	-No guidewire required	-Qualitative -Limited accuracy and reproducibility
IMR$_{angio}$[27]	-	Angiography	As per IMR	-No guidewire required	-Calculated on PC post-procedure -Steep learning curve, difficult to perform -Needs further validation -Limited prognostic data
PB-CFR [28]	++	Arterial Pressure	>2	-Can be derived from pressure alone	-Poor accuracy -Limited prognostic data

IMR: Index of microcirculatory resistance; STEMI: ST-elevation myocardial infarction; MACE: Major adverse cardiovascular events, PCI: Percutaneous coronary intervention; CFR: Coronary flow reserve; RRR: Resistive reserve ratio; CFVR: Coronary flow velocity reserve; hMR: Hyperaemic microvascular resistance; R_{micro}: Microvascular resistance (derived using continuous thermodilution); mMR: Minimal microvascular resistance; IHDVPS: Instantaneous hyperaemic diastolic velocity–pressure slope; Pzf: Zero-flow pressure, TFC: TIMI frame count; MBG: Myocardial blush grade, IMRangio: Angiography-derived index of microcirculatory resistance; PB-CFR: Pressure-bounded coronary flow reserve.

ANGIOGRAPHIC METHODS

Coronary angiography-based techniques have historically been used to assess the status of the microvasculature with methods such as the TIMI myocardial perfusion grading system and myocardial blush grade providing an indirect, qualitative measures of the state of the microvasculature. Whilst being simple, angiographic methods have poor reproducibility and accuracy[29] and are of limited utility in the modern era with the advent more advanced techniques as discussed below.

THERMODILUTION METHODS

Index of Microcirculatory Resistance (IMR)

The index of microcirculatory resistance (IMR) represents the minimum achievable microvascular resistance of the circulatory bed being interrogated and hence relates directly to the amount of microvascular dysfunction present. It is measured using both pressure and thermodilution during hyperaemia and hence requires a wire which can measure both distal pressure and temperature, such as the Pressurewire X (Abbott Vascular, Illinois, USA). The IMR is a simple and highly reproducible measure that remains stable in the presence of varying haemodynamic conditions including pacing at 110bpm, infusion of nitroprusside and infusion of dobutaine[30].

1) Zero the guide and pressure wire pressures
2) Advance wire to the tip of the guiding catheter
3) Inject 100-200 mg of glyceryl trinitrate into coronary artery
4) Equalise wire pressure with aortic pressure
5) Advance the wire at least 6cm, into the distal third of the culprit vessel, and at least 3 cm downstream from the target lesion
6) Administer intracoronary glyceryl trinitrate at a dose of 100-200 micrograms.
7) Administer intravenous infusion of adenosine (140 µg/kg/min).
8) Once steady state hyperaemia is achieved, record the mean aortic pressure (Pa) and mean distal pressure (Pd)
9) Flush the guide catheter with room catheter saline to clear all contrast
10) Using a 3mL Leuer-lock syringe, briskly inject a 3mL bolus of room temperature saline, repeating this step 3 times and recording the average of 3 injections as the mean transit time (Tmn_{hyp})
11) The IMR is then calculated using the formula hyperaemic Pd x Tmn_{Hyp}. If software such as Coroflow (Coroventis Research AB) is used, the corrected IMR will also automatically be calculated (calculated IMR [IMR_{calc}] = PaxTmnHypx 1.35 x [Pd/Pa] - 0.32). The corrected IMR formula is required in the presence of significant epicardial stenosis to adjust for its physiological effects[1].

Figure 2: Measurement of IMR (and FFR). Note that steps 1-8 are common to both FFR and IMR measurement. Steps 9-11 are additional steps required to measure IMR. IMR: Index of microcirculatory resistance. IMR: Index of microcirculatory resistance; FFR: Fractional flow reserve.

The normal range for IMR is <25[31]. In stable patients, IMR has been used to identify those with microvascular angina, or INOCA. These allows for targeted therapy that has been shown to improved chest pain measures and quality of life[2] that was sustained at 1 year[32]. Furthermore, an abnormal IMR prior to elective percutaneous coronary intervention (PCI)

can be used to identify those at risk of periprocedural myocardial infarction (MI) with an abnormal IMR being associated with a 23-fold risk of periprocedural MI[3].

In the setting of ST-elevation myocardial infarction (STEMI), IMR has been shown to predict outcomes and identify patients that may benefit from further intervention. Post-STEMI IMR has been shown to predict death[4], peak creatine kinase (CK), echocardiographic wall motion score at 3 months[5], infarct size[33], microvascular obstruction (MVO) on magnetic resonance imaging (MRI)[33], left ventricular ejection fraction[34] as well as myocardial salvage[34]. Fahrni et al showed an elevated IMR to be associated with in increased risk of cardiac complications included but not limited to cardiac death, cardiogenic shock and pulmonary oedema[35].

Following primary PCI for STEMI, IMR improves appropriately in approximately two thirds of patients, however, De Maria et al identified one-third of patients where IMR did not improve as being either poor-responders or non-responders[36]. These non-responders have recently been targeted as a potential population which may benefit from further therapies[37] as an adjunct to primary PCI. Intracoronary thrombolysis has been investigated for this purpose[38]. Sezer et al administered intracoronary thrombolysis following primary PCI and showed that thrombolysis was associated with a reduction in IMR, a reduction in infarct size and preservation of left ventricular function. The RESTORE-MI trial is an ongoing randomised controlled which aims to enrol patients with IMR >32 after primary angioplasty to intracoronary tenecteplase or placebo (NCT03998319).

With an abundance of data exhibiting the value of IMR in the setting of MI and stable coronary artery disease, as well as many other clinical scenarios including a hypertrophic cardiomyopathy[39], Takotsubo cardiomyopathy[40] and allograft vasculopathy[41], IMR has now been included in the European Society of Cardiology (ESC) guidelines for diagnosis of microvascular dysfunction and is recommended for patients with angina and mild or no epicardial stenosis[6].

Coronary Flow Reserve (CFR)

Coronary flow reserve (CFR) is a comparison of flow at maximal hyperaemia to flow during rest. A normal CFR is above 2, meaning a doubling of flow from baseline to maximal hyperaemia[16]. CFR generally refers to thermodilution-derived CFR whereas doppler-derived CFR is generally referred to as coronary flow velocity reserve (CFVR). Unlike IMR, CFR is

also affected by the macrocirculation as well as resting haemodynamics. Prior to the advent of fractional flow reserve (FFR), CFR was mainly used to determine severity of coronary stenoses. However, it was identified as early as 1985 that a low CFR with a normal coronary angiogram could be due to many different causes including polycythaemia, anaemia, hypoxia and previous myocardial infarction[42]. CFR is understood to be affected by processes affecting the ability to increase flow from rest to hyperaemia. Microvascular dysfunction, or an inability of the microcirculation to vasodilate in response to hyperaemic stimuli such as adenosine, is one of these causes.

The resting component of CFR is most prone to external influence and hence is the cause of most false positive CFR results. In the presence of increased resting flow due to various haemodynamic states, the CFR may be abnormal even though the microcirculatory resistance remains low and the IMR remains normal. Hence, factors extrinsic to the coronary arteries which affect resting haemodynamics such as renal failure[43], cirrhosis[44] and aortic stenosis[45] are all causes of a low CFR. Given that CFR is non-specific, it is not surprising that whilst CFR does predict cardiovascular death, it also predicts death from cancer and death from non-cardiovascular and non-cancer causes[46]. Furthermore, even in the setting of coronary disease, a low CFR is unable to distinguish diffuse epicardial disease from microvascular dysfunction.

Resistive Reserve Ratio (RRR)

The Resistive Reserve Ratio (RRR) represents the ratio between an estimate of baseline microcirculatory resistance and hyperaemic microcirculatory resistance ([PdRest x TmnRest]/[PdHyp x TmnHyp])[17]. As with CFR, this measure also compares rest to hyperaemia. However, by utilising resting Pd divided by hyperaemic Pd, it attempts to correct for disease in the epicardial vessel and is thus somewhat more specific to the microvasculature than CFR. However, because it still takes into account resting transit time (TmnRest), it is thought to be prone to extrinsic and haemodynamic factors. In a large prospective registry, comprised mostly of patients with stable coronary disease (~90%) combined with some patients with non-culprit ACS (~10%), RRR was shown to predict all-cause death, cardiac death and death or myocardial infarction[47].

Absolute Coronary Blood Flow and Myocardial Resistance (R_{micro})

Continuous coronary thermodilution is a novel technique to determine absolute coronary blood flow[48] and in turn myocardial resistance (R_{micro})[49]. Using the same setup as FFR or IMR, a pressure-temperature sensing wire is placed into the distal vessel as described in Figure 1. However, instead of utilising a hyperaemic agent such as adenosine, a specialised monorail microcatheter (Rayflow, Hexacath, Paris) is used to infuse room temperature saline at a constant rate using a dedicated infusion pump. This saline infusion induces hyperaemia and the change in temperature caused by the saline is then detected and measured by the thermistor on the pressure wire in the distal vessel. This allows for calculation of absolute coronary blood flow and by dividing Pd by the flow rate, R_{micro} can be calculated[50]. A slower rate of saline infusion which does not lead to hyperaemia can also be used to obtain resting flow and resistance[51] which can be used to calculate CFR and even RRR.

The main advantage of continuous thermodilution over IMR is that it is less operator dependent because saline is administered via an infusion pump rather than by 3mL bolus injections in the case of IMR, CFR or RRR. Continuous thermodilution has been shown to be safe, feasible and simple to perform, even in the context of STEMI[49]. Furthermore, continuous thermodilution derived low flow (Q) or high R_{micro} has been shown to be associated with severe angina[52]. However, there are limitations associated with this method of microvascular assessment. Firstly, because of its relatively recent advent, outcome data are lacking. Secondly, there is a requirement for a specialised microcatheter. Finally, there is significant interpatient variability in Q and R_{micro} during hyperaemia owing to the difference in vascular territory supplied and hence correction for myocardial mass using computed tomography may be needed[53] and no well-accepted normal values are available.

DOPPLER BASED MEASURES

Overview

The ComboWire XT (Philips, Hamburg, Germany) is able to measure intracoronary doppler velocity in addition to intracoronary pressure. This allows for measurement of velocity and hence the calculation of coronary flow, without the requirement for intracoronary saline injection. While thermodilution measures flow over the whole vessel by measuring transit time from to guide to the distal wire, doppler wires calculate vessel flow by measuring single point velocity at the level of the sensor which is usually located at the tip of the wire in the distal vessel. The average peak velocity (APV) is then taken to be equivalent to flow,

assuming that the wire tip remains in the centre of the vessel and there is laminar, parabolic flow at the location of measurement.

The estimation of flow by measurement of doppler derived APV has technical challenges[31]. It is not known whether the presumed parabolic flow profile remains constant at different flow rates[54]. In vessels with non-significant stenoses, the hyperaemic APV was shown to be numerically more variable than resting APV with a standard deviation of 13 cm/s vs 5 cm/s[55]. In the same patients, hyperaemic mean transit time as measured by thermodilution had a narrower range than resting mean transit time (0.15 s vs 0.65 s). The quality of doppler data is also variable, and the same study showing 84% of thermodilution traces measurements being labelled as "good" vs only 57% of doppler derived measurements. Doppler measurements also have poor reproducibility[56]. Finally, in vessels with significant tortuosity, wire bias may lead to the tip of the wire not being in the centre of the vessel leading to an altered flow profile. Similar perturbations to flow profiles can be expected around branches and stenotic segments. When practically compared to thermodilution, doppler is more time consuming, has a steeper learning curve and is more likely to produce inaccurate results[57].

Hyperaemic Microvascular Resistance (hMR)

hMR is a Doppler derived minimum microvascular resistance index. It is similar to IMR. But uses doppler derived velocity rather than thermodilution to calculate resistance. The steps to measure the doppler based hMR overlaps with IMR significantly (Figure 2, steps 1-8), but without the additional steps of saline bolus injection (Figure 2, steps 9-11)[19]. hMR is calculated with the formula Pd/APV_{Hyp} with no routine correction for stenosis or collateral flow performed[58].

While being equivalent to IMR theoretically, significant practical differences are present with at most a modest correlation in one study (rho 0.41)[59]. Hence, outcome data from IMR cannot be generalised to hMR. Data for hMR is somewhat limited as compared to IMR. In the post-STEMI setting, while one study showed no association with left ventricular function[60], a number of studies do show prognostic significance. It has been shown that an elevated hMR predicts MRI measured microvascular injury[61], infarct size[62] and LV remodelling at 8 months[63], as well as a composite endpoint of death and hospitalisation for heart failure but neither of those endpoints alone[20].

The aforementioned technical issues with doppler measurement may be exaggerated during hyperaemia given the higher flow rates,[54] potentially causing inaccuracies, particularly in larger vessels[64]. Given the limited data and technical issues, hMR is generally reserved for research rather than clinical usage[57].

Coronary Flow Velocity Reserve (CFVR)

Coronary Flow Velocity Reserve is the hyperaemic velocity divided by the resting velocity and is similar to CFR as measured by thermodilution. In an open-chest pig model, CFR_{thermo} correlated better with the directly measured CFR than $CFR_{Doppler}$ (CFVR) did. Everaars et al showed that $CFR_{Doppler}$ was superior CFR_{thermo} in terms of agreement with the current gold standard of CFR measurement which is positron emission tomography (PET)[55,65]. This contradictory study has certain limitations. Firstly, a significant number of patients had a very rapid resting transit time (below 0.25 seconds) and yet were able to an appropriate hyperaemic response with hyperaemic transit times as quick as 0.10 seconds - the combination of these two findings usually represents the wire being too close to the guide, and hence the distance too short for accurate thermodilution. Another limitation of this study includes exclusion of 14% of doppler traces due to poor quality, from a site recognised as having expertise in doppler measurement[65], a number which would likely be amplified in non-expert sites. Barbato et al showed that an optimal CFR_{thermo} could be obtained in 97% of patients whereas an optimal $CFR_{Doppler}$ could only be obtained in 69% of patients and found a relatively good correlation between CFR_{thermo} and $CFR_{Doppler}$ ($r = 0.79$, $p<0.0001$)[66].

Despite the abovementioned issues, CFVR, like CFR, has multiple studies which highlight its utility as a powerful prognostic tool. A low CFVR was found to predict revascularisation[67], major adverse outcomes[68], all-cause death and cardiac mortality[18].

Minimal Microvascular Resistance (mMR)

Minimal microvascular resistance is a novel index calculated by measuring the hMR in the wave-free period[22]. More specifically it is calculated during hyperaemia by multiplying the APV by Pd in the period starting 25% of the way into diastole and ending 5ms before diastole. As opposed to hMR, mMR has been shown to be unaffected by obstructive stenoses. As with the corrected IMR, mMR may be used in future scenarios where microvascular resistance needs to be measured in the presence of a stenosis but given its relatively recent advent, further studies are required to assess its clinical utility.

304

305 **Other Doppler Derived Measures - Instantaneous Hyperaemic Diastolic Velocity–**
306 **Pressure Slope (IHDVPS) and Zero-flow Pressure (P_{zf})**

307 The instantaneous hyperaemic diastolic velocity-pressure slope (IHDVPS) and Zero-flow
308 Pressure (P_{zf}) are both doppler derived measures which, like mMR are measured during
309 hyperaemia during diastole and have to be calculated offline post-hoc, as there are no
310 commercially available systems to calculate them automatically. IHDVPS represents
311 capacitance, which is the inverse of resistance and P_{zf} represents the backpressure of the
312 coronary circulation.

313

314 Calculation of these measures requires generation of pressure-flow loops with IHDVPS being
315 the slope of this curve in mid to late diastole and P_{zf} being the theoretical pressure at which
316 coronary flow would cease, and is the pressure obtained by following the IHDVPS slope
317 down to a velocity of 0 cm/second[23]. Automation is possible[24,69], but has not become
318 commercially available.

319

320 IHDVPS is primarily a tool for assessing stenosis severity but it has been shown to be
321 independent of many extrinsic factors such as aortic pressure and cardiac contractility [70]. In
322 the absence of a stenosis, while IHDVPS correlate with histological microvascular changes[71],
323 a normal IHDVPS still does not exclude microvascular dysfunction[70] and its actual value in
324 predicting microvascular dysfunction is controversial[23]. P_{zf} is sensitive to extravascular
325 compression and has hence been shown to be of prognostic value in assessing reperfusion
326 injury post STEMI[23]. IHDVPS and P_{zf} are technically challenging and time-consuming to
327 obtain and hence are primarily used in the research setting, even though both have been
328 conceived in the 1980s[72,73].

329

330 **PRESSURE-BOUNDED CFR**

331 Pressure-Bounded CFR (PB-CFR) is a method which attempts to estimate CFR from the
332 coronary pressure traces without the use of thermodilution or doppler velocity measurement.
333 This has been shown to have no prognostic utility in a large registry of patients with coronary
334 artery disease[28]. In our unpublished database, we found the true thermodilution derived CFR
335 to fall between the PB-CFR estimated limits less than 50% of the time. Given the
336 aforementioned issues, PB-CFR has no clinical utility.

337

ANGIOGRAPHY-DERIVED INDEX OF MICROCIRCULATORY RESISTANCE (IMR_{ANGIO})

Angiography-derived Index of Microcirculatory Resistance (IMR_{angio}) is a novel, wire-free method of estimating the IMR. Angiography images are acquired during hyperaemia and the hyperaemic Pa is noted. Then, off-line software QAngio® XA 3D (Medis, Leiden, Netherlands), is used to determine the quantitative flow reserve (QFR) as well as the "hyperaemic transit time" of the contrast by counting the number of frames taken for the contrast to travel from the guide to the distal vessel and dividing this by the number of frames per second. The hyperaemic Pa is then multiplied by the QFR to estimate the "hyperaemic Pd"[27]. IMR is then estimated using the formula IMR_{angio} = "hyperaemic Pd" x "hyperaemic transit time."

IMR_{angio} was validated in the post-STEMI setting and showed a better correlation with IMR in the infarct related artery post-primary PCI ($\rho = 0.88$, $p < 0.001$) than in the non-infarct related artery ($\rho = 0.64$, $p = 0.009$). Specific outcome data for IMR_{angio} is not yet available. Software of this nature is very operator dependant and has a steep learning curve. Although hyperaemia is still required, IMR_{angio} obviates the need for a guidewire and may become more widespread in the future.

CONCLUSIONS

Microvascular assessment is a vital tool in the cardiac catheterisation laboratory, especially after its inclusion in the ESC guidelines[6] and EAPCI consensus statement[7]. While many indices to measure microvascular status exist, only IMR, CFR and hMR have been included in these landmark documents. IMR currently appears to be the most specific and reliable. Future studies will further refine the clinical role and utility these methods.

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Authors' contributions

Wrote and review the manuscript: Ada C, Yong A

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Conflicts of interest

Both authors declare that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

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