

Invasive Assessment Of The Coronary Microcirculation In Reperfused STEMI Patients: Where Do We Stand?

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ABSTRACT

For patients presenting with an acute ST-segment elevation myocardial infarction (STEMI), the most effective therapy for reducing myocardial infarct (MI) size and preserving left ventricular (LV) systolic function is primary percutaneous coronary intervention (PPCI). However, mortality and morbidity remain significant. This is partly attributed to the development of microvascular obstruction (MVO), which occurs in up to 50% of STEMI patients post-PPCI, and it is associated with adverse LV remodeling and worse clinical outcomes. Although MVO can be detected by cardiac imaging techniques several hours post-PPCI, it may be too late to intervene at that time. Therefore, being able to predict the development of MVO at the time of PPCI may identify high-risk patients who might benefit from further adjuvant intracoronary therapies such as thrombolysis, vasodilators, glycoprotein IIb/IIIa inhibitors and anti-inflammatory agents that may reduce MVO. Recent studies have shown that invasive coronary physiology measurements performed during PPCI can be used to assess the coronary microcirculation. In this article, we provide an overview of the various invasive methods currently available to assess the coronary microcirculation in the setting of STEMI, and how they could potentially be used in the future for tailoring therapies to those most at risk.

INTRODUCTION

Prompt restoration of blood flow in the occluded epicardial coronary artery by primary percutaneous coronary intervention (PPCI), following an acute ST-segment elevation myocardial infarction (STEMI), is currently the gold-standard therapy for reducing myocardial infarct (MI) size and preserving left ventricular (LV) systolic function¹. However, although mortality due to STEMI has declined substantially since the introduction of PPCI, morbidity remains significant at one year.² This has been partly attributed to the detrimental effects of prompt restoration of coronary blood flow to the acutely ischemic myocardium, which itself can induce coronary microvascular injury and cardiomyocyte death, a phenomenon termed 'Reperfusion Injury (RI)'. There are 4 types of RI: myocardial stunning; reperfusion arrhythmias; coronary no reflow or microvascular obstruction (MVO); and 'lethal myocardial reperfusion injury'³ as illustrated in Figure 1. The first two are considered reversible, as they are usually transient or easily treated. To date, there is no effective therapy to prevent or minimize the burden of microvascular obstruction (MVO) and 'lethal myocardial reperfusion injury' and both are currently considered irreversible.

The phenomenon of MVO was first described in 1966 and it refers to the inability to reperfuse a previously ischemic myocardium in the presence of a patent epicardial coronary artery.⁴ MVO occurs in up to 50% of STEMI patients following PPCI and is associated with adverse LV remodeling and worse clinical outcomes.⁵ MVO can be detected at the time of PPCI by the presence of impaired myocardial blush grade (MBG) despite a patent epicardial coronary artery. It can be assessed non-invasively by electrocardiography, myocardial contrast echocardiography (MCE)⁶, myocardial scintigraphy⁷ and contrast-enhanced cardiovascular magnetic resonance (CMR)⁸ but these are typically performed a few hours or days post-PPCI.

Recent studies have shown that invasive coronary physiology measurements acquired during PPCI may be used to assess the coronary microcirculation at the time of PPCI. This may allow early implementation of adjuvant therapies via the intracoronary route to reduce MVO, whilst the patient is still in the cardiac catheterization laboratory. In this article, we provide an overview of the various invasive coronary physiology techniques to assess the coronary microcirculation in the setting of STEMI and explore their strengths and limitations, and how they could potentially be applied in the clinical setting to improve outcomes.

THE DETERMINANTS AND CLINICAL SIGNIFANCE OF MVO

Five major factors have been shown to contribute to the development of MVO namely⁹: pre-existing coronary microvascular dysfunction; the extent of ischemic injury; the presence of RI; distal coronary micro-embolization; and individual susceptibility (genetic factors such as 1976T.C polymorphism of the adenosine 2A receptors gene predisposing certain patients to the development of MVO; the presence of pre-infarct angina in certain patients may protect against the development of MVO)⁹. The pre-existence of coronary microvascular dysfunction and individual susceptibility are non-modifiable. The extent of ischemic injury is dependent on the symptom onset-to-door and door-to-balloon times, the area-at-risk, Thrombolysis in Myocardial Infarction (TIMI) flow pre-PPCI and collateral flow. Efforts have already been made to reduce the onset-to-balloon time to a minimum since the introduction of PPCI. Therefore, the main focus of research to minimize the burden of MVO has been to target both RI and distal coronary micro-embolization. A number of mechanisms have been described to contribute to the occurrence of MVO and these include external compression of capillaries by interstitial and/or cellular edema, by swollen cardiomyocytes and endothelial cells; the release of thrombogenic and

vasoactive substances; neutrophil plugging; capillary damage with extravasation of red blood cells (leading to intramyocardial hemorrhage - IMH); impaired coronary vasodilation; coronary micro-embolization from the atherosclerotic plaque, in-situ thrombosis and platelet micro-thrombi as illustrated in Figure 2.¹⁰ IMH has been shown to be a consequence of the process of reperfusion itself.¹¹ MVO is closely linked with the development of IMH¹² and clinical studies have supported the notion that MVO precedes the development of IMH in a subset of patients and is considered a more severe form of microvascular injury due to RI.^{13, 14}

The presence of MVO following PPCI as assessed by TIMI flow post-PPCI¹⁵, a combination of ST-segment resolution and MBG¹⁶, MCE¹⁷ and CMR¹⁸ have all strongly been linked with worse outcomes.⁹ In a recent meta-analysis⁵ of more than 1025 STEMI patients reperfused by PPCI and with a CMR performed within the first week, MVO was associated with the occurrence of a composite of cardiac death, congestive heart failure, and myocardial re-infarction with a hazard ratio of 3.74 (95% confidence interval of 2.21 to 6.34) whereas MI size was not, in a multivariate Cox regression analysis, after adjusting for confounders.

Despite having a patent epicardial coronary artery post-PPCI, those patients with MVO have areas of ongoing hypoperfusion at the microcirculation level and achieving patency of the microcirculation may theoretically reduce MVO, prevent IMH and limit MI size. Recently, high dose intra-coronary adenosine and sodium nitroprusside failed to reduce MVO and MI size in a cohort of 247 reperfused STEMI patients.¹⁹ However 67% of those patients had MVO by CMR and it is likely that those drugs failed to reach the microcirculation in two third of the patients. Therefore, another approach that would more likely improve outcomes in these patients might be to identify those patients at risk of MVO at the time of PPCI and subject them to low dose intracoronary thrombolysis²⁰ first, to achieve patency of the

microcirculation, and they treated with an infusion of adenosine or sodium nitroprusside, that would then be more likely to reach the microcirculation.¹⁹

NON-INVASIVE DETECTION ON MVO

The current techniques for identifying MVO are mainly via non-invasive tests (summarized in Table 1) and these are usually performed 3-5 days post-PPCI, when it may be too late to intervene. Figure 3 shows an example of a patient with a left anterior descending coronary artery occlusion, reperfused by PPCI with TIMI flow 3, but with extensive areas of MVO (red arrows) on the delayed enhancement CMR images performed on day 3. This imaging modality cannot be performed in most centers immediately post-PPCI, and it may be too late to intervene by the time MVO is detected using this modality..

The coronary microvascular circulation can also be assessed in the cardiac catheterization laboratory with TIMI flow grade²², corrected TIMI frame count (cTFC)²³, TIMI myocardial perfusion grade (TMPG)²⁴ and MBG²² (Table 1). However, these indexes are semi-quantitative and can be subjective²⁵, although automated software are available.²⁶ Furthermore, capillary permeability, microvascular spasm and capillary resistance under resting conditions may influence these indices.²⁷ Therefore, the utility and accuracy of these angiographic methods to detect MVO after primary PCI have limited their clinical application.

INVASIVE ASSESSMENT OF THE CORONARY MICROCIRCULATION

The coronary circulation can be divided into the epicardial vessels, the microcirculation and the venous circulation²⁸ (Figure 2). Under normal resting physiological conditions, coronary blood flow is maintained at near constant levels

over a wide range of perfusion pressures by autoregulation.²⁹ However, disturbances in the autoregulatory process and/or impaired microvascular vasodilatory function due to disruption in the coronary microcirculation occurring in the presence of prolonged ischemia and MVO can be detected by invasive measures of coronary microcirculation. This can be divided into flow-based and resistance-based parameters (although flow remains an important component in the derivation of the latter parameters) as below:

1. Flow - based parameters

- a. Coronary flow velocity reserve (CFVR)
- b. Deceleration time of diastolic coronary flow velocity
- c. Presence of systolic flow reversal

2. Resistance - based parameters

- a. Index of microvascular resistance (IMR)
- b. Hyperemic microvascular resistance (HMR)
- c. Coronary zero flow pressure (Pzf)

Flow – based parameters

a) Coronary flow velocity reserve

CFVR is an index providing information on both the epicardial and coronary microvascular compartment. It can be derived by using both the Doppler²⁹ and thermodilution³⁰ techniques. CFVR is defined as the ratio of hyperemic to resting coronary blood flow.²⁹ CFVR has been used to assess the coronary microcirculation in the absence of epicardial stenosis. CFVR can also be derived using the thermodilution principle [CFVR = Tmn at rest/ Tmn at hyperemia]³⁰. A ratio of ≥ 2.0 is considered normal.⁸ A value of <2.0 has recently been shown to have a sensitivity of

79% for MVO and 80% for IMH but with a low specificity of 34% for the detection of both MVO and IMH in a large single-center study of 283 patients.⁸

Several studies have shown that CFVR measured in the reperfused infarct-related artery to be a potential prognostic marker for LV recovery following STEMI³¹⁻³⁴ (online appendix Table 1). CFVR has also shown to correspond well with the extent of MVO by CMR³⁵ and was found to be a better marker than TIMI flow, cTFC and MBG to predict recovery of LV function.³⁴ An increase in CFVR from the end of PPCI to 24 hours later was associated with higher myocardial salvage index, whereas a reduction in CFVR at 24 hours was associated with MVO and IMH.³⁶ A CFVR of <2.1 has also been shown to be associated with increased mortality at 10 years.³⁷

b and c) Diastolic deceleration time and systolic flow reversal

Rapid deceleration time of coronary diastolic flow velocity (diastolic deceleration time < 600 msec) and the presence of early systolic flow reversal in intracoronary Doppler recordings obtained after successful PPCI were shown to be associated with larger extent of MVO and poor long-term outcome after reperfusion.^{35, 38, 39}

Resistance – based parameters

Intraluminal obstruction (athero-embolization, cellular and humoral factors etc.) in combination with extravascular compressive pathologies (edema and IMH) impact on the increase in microvascular resistance after successful reperfusion achieved by PPCI. Microvascular resistance indices (IMR, HMR and Pzf) are therefore extremely well suited to determine the extent of the microvascular impairment after PPCI where acute changes in microvascular resistance are expected to be the most dramatic. Moreover, these parameters are specific for the coronary microcirculation during peak hyperemia or zero flow assumptions and are less likely to be influenced by

hemodynamic perturbations such as microvascular tone and resistance⁴⁰, heart rate⁴¹ and infusion of sodium nitroprusside and dobutamine.⁴¹

a) Index of microvascular resistance (IMR)

IMR is derived from the thermodilution principle⁴² using a guide wire with a pressure and a temperature sensor, and is defined as the distal coronary pressure (Pd) divided by the inverse of the mean transit time (Tmn) during hyperemia, or more simply, Pd multiplied by the Tmn (mm Hg · seconds, or units [U]).⁴² The wire sensor is usually positioned in the distal one third of the vessel (> 6cm from guide catheter tip). The average of 3 transit times of 3ml of room temperature normal saline solution during peak hyperemia is used to calculate Tmn⁴³ and the variability among the 3 readings should be <20%. An IMR value < 25U is indicative of normal microvascular perfusion.⁴⁴

IMR has been used as a surrogate to invasively assess the coronary microcirculation in STEMI patients for more than a decade (online appendix Table 1). High IMR values at the time of PPCI have been associated with larger MI size by cardiac enzymes⁴⁵, less wall motion recovery at follow-up by echocardiography^{45, 46}, less viability by 18F-fluorodeoxyglucose positron emission tomography (FDG PET).⁴⁶ Factors predisposing to high IMR values have not been well studied but in a small study of 113 STEMI patients, Baek et al⁴⁷ found age and symptom-to-balloon time to be major predictors of high IMR.

Several studies have correlated IMR at the time of PPCI and CMR findings. Patients with high IMR were more likely to have MVO⁴⁸⁻⁵², IMH⁵³, larger MI size⁴⁸, less myocardial salvage⁵³ on the acute scan performed within a week and worse LV function at follow-up.⁴⁸ However not all studies^{54, 55} have shown that the IMR at the end of the PPCI procedure could predict MVO on CMR and this was recently summarized in a meta-analysis of studies reporting mean IMR values only.⁵⁶ These

studies individually were small and lacked power but after combining data from 6 studies (246 patients) reporting mean IMR values, those with MVO had significantly higher IMR ($49 \pm 33U$, 99%CI 41-57U) than those without MVO ($27 \pm 22U$, 99%CI 22-32U). In a recent single-center study of 283 patients by Carrick et al⁸, IMR was shown to be more closely associated with MVO, IMH and adverse LV remodeling by CMR and clinical outcomes than TMPG or CFR.

Data on serial IMR measurements post-STEMI is limited. Sezer et al⁵⁷ showed that >33% improvement in IMR in the infarcted territory at 5 months was associated with a 50% reduction in MI size assessed by single photon emission computed tomography in a small cohort of 35 reperfused STEMI patients. Cuculi et al⁵⁴ showed that, in 30 patients with CMR data at 6 months, those with MVO had a lower CFVR immediately post-PPCI and at 24 hours and a trend towards higher IMR. At 6 months, there was no difference in IMR and CFVR between these 2 groups of patients, despite a larger chronic MI size in the MVO group. However, unlike Sezer et al⁵⁷, they did not explore the reduction in MI size in those with an improvement in IMR. Most recently, Hoole et al⁵⁵ showed in 41 patients that those with an IMR <32U pre-stenting had a significant increase in IMR post-stenting and this was attributed to iatrogenic microvascular injury. Serial IMR measurements can improve our understanding of the microcirculation post-STEMI, but due to its invasive nature, getting patients back for repeat invasive measurements in the convalescent/chronic phase is challenging as highlighted by the Cuculi et al⁵⁴ (almost half of the patients dropped out at 6 months).

Fukunaga et al⁵² (88 patients) found that the shape of the thermodilution-derived temperature recovery curve following saline injection could be characterized into three categories. Patients in the “bimodal group” had higher prevalence of MVO on CMR and were at higher risk of death and rehospitalization for heart failure when compared to those in the “narrow unimodal” and “wide unimodal groups”. However

the impact of the speed of hand injections and the inter-observer reproducibility of these bimodal curves were not assessed and needs further validation.

Another approach explored by Park et al⁵⁸ (89 patients) has been to stratify STEMI patients according to both IMR and CFVR values. They found that those patients with CFVR<2 and IMR>27U did not show an improvement in wall motion score index by echocardiography. Ahn et al⁵⁰ (40 patients) showed that a combined high IMR (>36U) and low CFVR (<1.7) were highly predictive of MVO by CMR after PPCI. However, Carrick et al⁵⁹ recently showed that combining IMR >40U with CFR ≤2.0 did not add prognostic value in 283 patients. All these 3 studies used different cut-off values for IMR and CFR and although Carrick et al⁵⁹ had the largest number of patients, it was not powered for clinical outcomes.

The effect of IMR on clinical outcomes post-PPCI has been investigated in a large multi-center study of 253 STEMI patients. Fearon et al⁶⁰ found that patients with an IMR >40U, measured immediately after PPCI, was the only independent predictor of death (hazard ratio 4.3, P 0.02) after a median follow-up of 2.8 years. A recent meta-analysis⁵⁶ showed that patients with an IMR >41U at the end of the PPCI procedure were more likely to have MVO on the CMR. Most recently, in a single-center study of 283 STEMI patients, Carrick et al⁵⁹ also showed that an IMR >40U was a multivariable associate of adverse LV remodeling by CMR at 6 months, and was a better predictor of all-cause death or heart failure than the duration of ischemia, ST-segment resolution, TMPG and CFR after a median follow-up of 845 days.

However IMR remains an indirect measure for the coronary microvascular resistance and uses the inverse of transit time as a surrogate for flow. Furthermore, the manual injections of normal saline to obtain the transit times are prone to inter

and intra-observer variability and not all groups^{54, 55} have shown IMR could differentiate between patients with or without MVO.

b) Hyperemic microvascular resistance (HMR)

HMR is defined as the Pd divided by mean Doppler flow velocity at peak hyperemia simultaneously measured using a coronary guide wire with a combined pressure sensor and Doppler transducer^{61, 62} and measured in mm Hg cm⁻¹ s. A guide wire with dual pressure and Doppler flow sensor is placed in the distal one third of the infarct-related artery. This dual - sensor guide wire has a Doppler crystal at the tip and a pressure sensor at 1.5 cm from the tip. At hyperemia, phasic coronary flow velocities are obtained from 3 consecutive cardiac cycles and used to calculate the average hyperemic flow velocity.

The role of HMR in STEMI has been less well studied compared to IMR (summarized in the online appendix Table 1). The availability of a dual pressure and flow sensor wire allows simultaneous pressure and flow measurements within the coronary artery thereby making the measurement of HMR easier. HMR has been shown to be as good as CFVR and diastolic deceleration time at predicting regional wall motion recovery⁶³ and the transmural extent of MI⁶¹, but superior to CFVR to predict LV remodeling at 8 months.⁶⁴ In a small single-center study of 48 patients, an HMR value >2.5 mm Hg cm⁻¹ s has been shown to be indicative of MVO by CMR (sensitivity of 71% and specificity of 63%) and reduced myocardial blood flow on PET. In a larger cohort of 145 STEMI patients⁶⁵, an HMR value >2.82 mm Hg cm⁻¹ s was a strong predictor of a composite of death and re-hospitalization for heart failure. However, HMR was measured using the mean aortic pressure rather than the pressure distal to the coronary lesion in that study and more work with larger number

of patients are required to confirm the prognostic significance of HMR immediately post PPCI.

HMR also remains an indirect measure for the microvascular resistance and uses half the peak Doppler-derived velocity as a surrogate for flow. Additionally, detecting an adequate flow signal using a guide wire tipped with both a Doppler flow and a pressure sensor can be technically difficult.

c) Zero flow pressure (Pzf)

Pzf is defined as the distal coronary pressure when hypothetically there would be no flow in the coronary artery. Data from several cardiac cycles are used to plot Pd against the peak velocity. There are automated algorithms that can then sample the resultant pressure–velocity loop at the mid-diastolic period of the averaged cardiac cycle. A regression can then be drawn automatically from the diastolic data points, and Pzf is the pressure at which this line crosses the x-axis. This is the extrapolated distal coronary pressure at which flow would cease in the infarct-related artery.⁴⁰ It provides comprehensive assessment of the microvascular compartment as it assesses coronary flow over a range of pressures, irrespective of cardiac contractility and may reflect vascular tone.⁶⁶ In the context of STEMI, it also provides information on the effect of the interstitial myocardial pressure on the coronary microcirculation.⁶⁶ Pzf is derived from pressure-velocity loop analysis⁶⁷ and it informs the operator on the effect of intra-ventricular and interstitial myocardial pressure (external forces) over collapsible elements (capillaries) of the microcirculation. Therefore, Pzf measured after PPCI can be expected to be dependent mainly on the extent of external microcirculatory compression by edema and IMH. After PPCI, microvascular impairment may be partly attributed to decrease in total cross-sectional microvascular area by compressive effect generated by edema and/or IMH. Additionally, in patients with STEMI, increased diastolic filling pressures due to

increased cardiac muscle stiffness caused by cellular and interstitial edema may also decrease intramyocardial vascular capacitance and limits coronary flow in late diastole. Therefore, the transmitted increase in intra-cavity and interstitial pressures contribute to external compression of microcirculation and result in increased Pzf.

In small proof-of-concept studies, Pzf was a better predictor of viability by FDG PET than CFVR (27 patients)⁶⁷; was associated with higher left ventricular filling pressures (68 patients)⁶⁶ and adverse LV remodeling (48 patients)⁶⁸; and was a better predictor of chronic MI size by CMR than HMR and IMR (34 patients).⁴⁰ However, Pzf was not found to be superior to CFVR, Pzf and diastolic deceleration time in predicting the transmural extent of MI by CMR performed at 13 days (27 patients).⁶¹ So far, only one study has evaluated Pzf and MVO by CMR and a cut-off value of 42mmHg for Pzf did not differentiate those with and without MVO.⁴⁰

As summarized in table 2, Pzf requires off-line post-processing and the automated algorithms for its interpretation are not widely available yet. Therefore this index currently remains a research tool.

CURRENT APPLICATIONS

IMR has already been used as a surrogate endpoint in several proof-of-concept studies aiming to improve the coronary microcirculation in reperfused STEMI patients (summarized in the online appendix Table 2). The impact of strategies such as intracoronary streptokinase administered immediately after PPCI²⁰, nicorandil⁶⁹, sodium nitropruside⁷⁰, distal protection device⁷¹, thrombus aspiration⁵⁵ and a combination of intracoronary abciximab and aspiration thrombectomy⁵¹ on IMR has been investigated in small proof-of-concept studies and there are several other studies that are ongoing (summarized in the online appendix table 2). Of note, none of the randomized studies pre-selected patients based on high IMR values.

Hypothetically, in an ideal study, invasive coronary measurement with a reliable marker at the end of the PPCI procedure would identify those patients with MVO with high sensitivity and specificity. Given that MVO is due to a combination of factors, these patients would then be randomized to a combination therapy with intracoronary thrombolysis (to achieve patency of the microcirculation) and an intracoronary vasodilator with anti-inflammatory properties such as adenosine (which could be continued intravenously on the ward) or placebo. The primary endpoint of interest should ideally be hard clinical outcomes such as cardiovascular death and hospitalization for heart failure. However, such a study would require a large number of patients and endpoints such as the extent of IMH, MVO and MI size by CMR 3 days later and adverse LV remodeling at 6 months could be used as surrogates.

LIMITATIONS OF CURRENT INVASIVE MARKERS AND FUTURE DIRECTIONS

Table 2 summarizes the limitations of the current invasive markers to assess the microcirculation discussed so far. Future studies should aim at addressing these limitations in the first instance. Some examples would be:

To explore the possibility for an automated method (e.g. using a pump injector) to inject the 3ml of normal saline to minimize operator-related errors and improve inter-observer and inter-site reproducibility when performing IMR measurement.

Further validation work is required to assess the performance of HMR to detect MVO by CMR before it can be used to assess the effectiveness of therapies. Moreover, improvement in the delivery profile of the Doppler wire would increase the use of this technique in future studies.

The derivation of Pzf is based on the extrapolation from the pressure-velocity loop and the analysis techniques are time-consuming and are not available for immediate

read-outs of Pzf. Therefore, more work remains to be done to make the analysis of fully automated and the Pzf read-outs to be immediately available at the time of PPCI, before it can be widely used.

Limited data are available regarding the strength of diastolic deceleration time and systolic flow reversal to identify MVO when compared to IMR, HMR and Pzf. Therefore, further, adequately powered, comparative studies using these parameters, using a multi-center approach to facilitate recruitment are needed.

These above steps would help to assess which of these markers would emerge as the most robust surrogate marker for predicting MVO at the end of the PPCI procedure. Early identification of these high-risk patients is important as already described above and early adjuvant intervention could then be started in the cardiac catheterization laboratory and administered via the intracoronary route and continued intravenously in the ward in needed. Therapies that may be beneficial in this setting would be glycoprotein IIb/IIIa inhibitors (e.g. abciximab²¹ to reduce platelet aggregation in the microcirculation); thrombolytics (e.g. half dose alteplase for lysis of distal embolization of thrombi); vasodilators (e.g. adenosine^{19, 72}, nicorandil⁶⁹ for spasm of the microcirculation due to release of vasoactive substances); and anti-inflammatory agents (e.g. methylprednisolone⁷³ to reduce reperfusion edema and relieve extrinsic compression of the microcirculation). Other treatments aiming to stabilize the endothelium with angiotensin-1 or tyrosine kinase inhibitors¹³ may help to reduce extravasation of red blood cells and the development of IMH. Using this approach would also avoid any adjuvant strategies be given to those patients who are unlikely to have MVO, and minimize their exposure to potential adverse events.

Figure 4 shows a hypothetical approach in future studies to identify and target those at high-risk at the end of the PPCI procedure using IMR as an example. Given that patients with an IMR of >40U has been shown to more likely have MVO⁵⁶ and worse

outcomes^{60 59}, this value could be used as a cut-off. Those patients with an IMR of >40U at the end of PPCI could then be targeted with further adjuvant therapies mentioned above and this approach may improve outcomes in this group of patients.

CONCLUSION

Invasive assessment of the coronary microcirculation at the time of PPCI is an exciting field that could provide us with the opportunity to interrogate the extent of the microvascular injury reliably in the cardiac catheterization laboratory at the end of the PPCI procedure despite having a patent infarct-related epicardial coronary artery. This approach would potentially identify those patients at high risk of MVO and target them with adjuvant therapies. However, more validation work remains to be done before one or a combination of these invasive markers described here could be used in therapeutic trials aiming to eventually improve outcomes in these patients.

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Table 1: Non-invasive assessment and angiographic assessment of MVO

Modality	Comments	Limitations
ECG	<p>ST-segment resolution of <70% at 60 to 90 minutes post-reperfusion in the presence of a patent epicardial coronary is suggestive of MVO⁷⁴.</p> <p>Inexpensive and portable.</p>	<p>Discrepancies have been documented between coronary angiographic indices of reperfusion and ST-segment resolution⁷⁵.</p> <p>There is a delay of at least one hour before it can be acquired for comparison.</p>
MCE	<p>Can detect the presence of MVO and can also quantify its severity.</p> <p>Inexpensive and can be portable.</p>	<p>Several factors such as labour-intensive data acquisition, sub-optimal images (especially of the lateral wall), difficulties with image interpretation, and safety concerns regarding the use of the micro-bubbles have hampered the widespread adoption in the clinical setting⁷⁶</p>
CMR	<p>CMR can differentiate between early MVO using first pass perfusion or early gadolinium enhancement and late MVO by late gadolinium enhancement.</p> <p>CMR is also the gold standard to assess MI size, LV volumes and ejection fraction.</p> <p>CMR can also quantify the extent of MVO accurately and differentiate between hemorrhagic and non-hemorrhagic MVO, thereby providing an additional layer of prognostic information⁷⁷.</p>	<p>Usually performed 2 to 7 days post-reperfusion when it may be too late to intervene.</p> <p>Not applicable to everyone – e.g. those with contra-indication to CMR will be excluded.</p> <p>Expensive and not yet widely available.</p>

MSCT	<p>MDCT performed immediately after PPCI could detect hypo-enhanced areas that were significantly associated with coronary angiographic no-reflow.⁷⁸</p> <p>MDCT performed without contrast reinjection immediately after PPCI for the identification of heterogeneous enhancement could also predict the occurrence of MVO and adverse LV remodeling by CMR.⁷⁹</p>	<p>This approach is logistically difficult to implement in most centers.</p> <p>Limited data from 2 studies so far and warrants further validation.</p>
TIMI flow	<p>A TIMI flow grade of <2 in the presence of a patent epicardial coronary artery is indicative of no-reflow.²²</p>	<p>Cannot be used to assess the microvascular circulation in those with TIMI flow 3.</p>
cTFC	<p>cTFC is a more robust method to assess the epicardial flow quantitatively²³ and is more reproducible.</p>	<p>Requires off line post-processing.</p>
MBG and TMPG	<p>MBG is a measure of maximum contrast intensity whereas TMPG is a measure of contrast washout time.</p> <p>MBG has also been shown to predict mortality in patients with TIMI 3 flow⁸⁰ and may be more practical.</p> <p>A normal TMPG has been shown to be a superior marker of death than a TIMI flow of 3 in the thrombolytic era²⁴</p>	<p>Capillary permeability, microvascular spasm and capillary resistance under resting conditions may influence these indices.²⁷</p>

ECG: electrocardiography; MCE: myocardial contrast echocardiography; MDCT: contrast-enhanced multi-detector computed tomography; TIMI: TIMI: thrombolysis in myocardial infarction; cTFC: corrected TIMI frame count; MBG: myocardial blush grade; TMPG: TIMI myocardial perfusion grade;

Table 2: Definitions of invasive markers to assess the microvascular circulation

	Comments	Limitations
CFVR	<ul style="list-style-type: none"> • Defined as the ratio of hyperemic to resting coronary blood flow²⁹ • CFVR can also be derived using the thermodilution principle [CFVR = Tmn at rest/ Tmn at hyperemia]³⁰ • A ratio of ≥ 2.0 is considered normal 	<ul style="list-style-type: none"> • The Doppler flow velocity tracings may not be consistent from beat to beat and could be a source of variability. • CFVR is unable to distinguish between relative epicardial and microvascular contribution to total coronary resistance • CFVR is dependent upon hemodynamic factors (i.e., blood pressure, heart rate, etc.). • When using the thermodilution technique, manual injection of the saline can be a source of variability. • Requires the achievement of hyperemia. In the STEMI setting, using adenosine may be ineffective in those patients who may have consumed caffeinated products.
IMR	<ul style="list-style-type: none"> • Defined as Pd divided by the inverse of the Tmn during hyperemia, or more simply, Pd multiplied by the Tmn (mm Hg · seconds, or units [U])⁴² • The wire sensor is usually positioned in the distal one third of the vessel (> 6cm from guide catheter tip) • The average of 3 transit times of 3ml of room temperature normal saline solution – the variability should be <20% - during peak hyperemia is used to calculate mean Tmn⁴³ • An IMR value < 25U is indicative of normal microvascular perfusion⁴⁴. • IMR has been shown to be more reproducible 	<ul style="list-style-type: none"> • Manual injection of the saline can be a source of variability. • Requires the achievement of hyperemia. In the STEMI setting, using adenosine may be ineffective in those patients who may have consumed caffeinated products.

	<p>than CFR and to be independent of hemodynamic influences (pacing at 110 bpm, nitroprusside infusion or dobutamine infusion)⁴¹.</p> <ul style="list-style-type: none"> • It is not affected by epicardial stenosis⁴² • In the presence of collaterals, corrected IMR (cIMR) using the formula $cIMR = Pa \times Tmn \times (Pd - Pw) / (Pa - Pw)$ is more accurate as this takes into account the contribution of collateral flow^{81 82}. 	
HMR	<ul style="list-style-type: none"> • HMR is derived as the ratio of distal coronary pressure and hyperemic flow velocity⁶¹ and measured in mm Hg cm⁻¹ s • A guidewire with dual pressure and Doppler flow sensor is placed in the distal one third of the infarct-related artery. • At hyperemia, phasic coronary flow velocity are obtained from 3 consecutive cardiac cycles and used to calculate the average hyperemic flow velocity 	<ul style="list-style-type: none"> • The Doppler flow velocity tracings may not be consistent from beat to beat and could be a source of variability. • Requires the achievement of hyperemia. In the STEMI setting, using adenosine may be ineffective in those patients who may have consumed caffeinated products.
Pzf	<ul style="list-style-type: none"> • Pzf is defined as the distal coronary pressure when hypothetically there would be no flow in the coronary artery. • Does not require hyperemia. • Data from several cardiac cycles are used to plot Pd against the peak velocity. There are automated algorithms that can then sample the resultant pressure–velocity loop at the mid-diastolic period of the averaged cardiac cycle. A regression can then be drawn automatically from the diastolic data points, and Pzf is the 	<ul style="list-style-type: none"> • The Doppler flow velocity tracings may not be consistent from beat to beat and could be a source of variability. • Requires off-line post-processing.

	pressure at which this line crosses the x-axis. This is the extrapolated distal coronary pressure at which flow would cease in the infarct-related artery. ⁴⁰	
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CFVR: coronary flow reserve; IMR: index of microvascular resistance; STEMI: ST-segment elevation myocardial infarction; Pd: distal pressure; Tmn: mean transit time; Pw: wedge pressure; Pa: aortic pressure; HMR: hyperemic microvascular resistance; Pzf: zero

Figures legend

Figure 1: Relationship between reperfusion injury (RI) and MVO

The figure illustrates the different components of reperfusion injury (RI). Myocardial stunning and reperfusion arrhythmias are transient and self-limiting/ easily treated. However microvascular obstruction (MVO) and lethal myocardial reperfusion injury are currently irreversible and contribute up to 50% of the final myocardial infarct (MI) size.

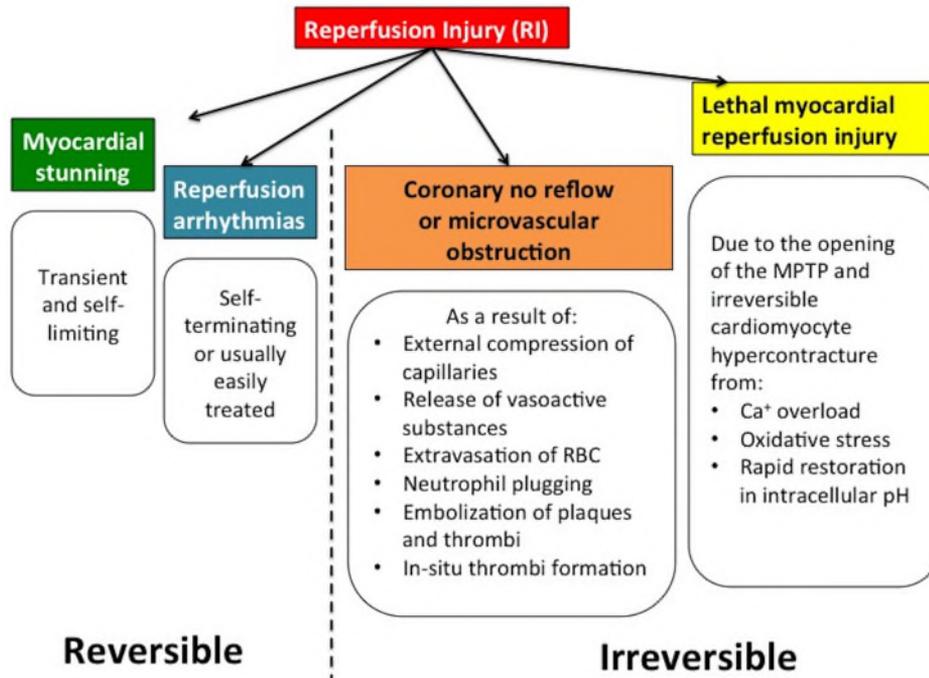


Figure 2: The coronary circulation and factors contributing to the development of MVO

This is an illustration of the coronary circulation. Coronary flow velocity reserve (CFVR) provides an indication of both the epicardial and microvascular circulation whereas index of microvascular resistance (IMR) / hyperemic microvascular resistance (HMR), diastolic deceleration time (DDT) and systolic flow reversal, and zero flow pressure (Pzf) interrogate the microvascular circulation in particular.

This figure also illustrates the some of the factors contributing to the development of microvascular obstruction (MVO), namely external compression of capillaries by interstitial and/or cellular edema, by swollen cardiomyocytes and endothelial cells, cellular plugging, capillary damage with extravasation of red blood cells, coronary micro-embolization of debris and in-situ thrombosis.

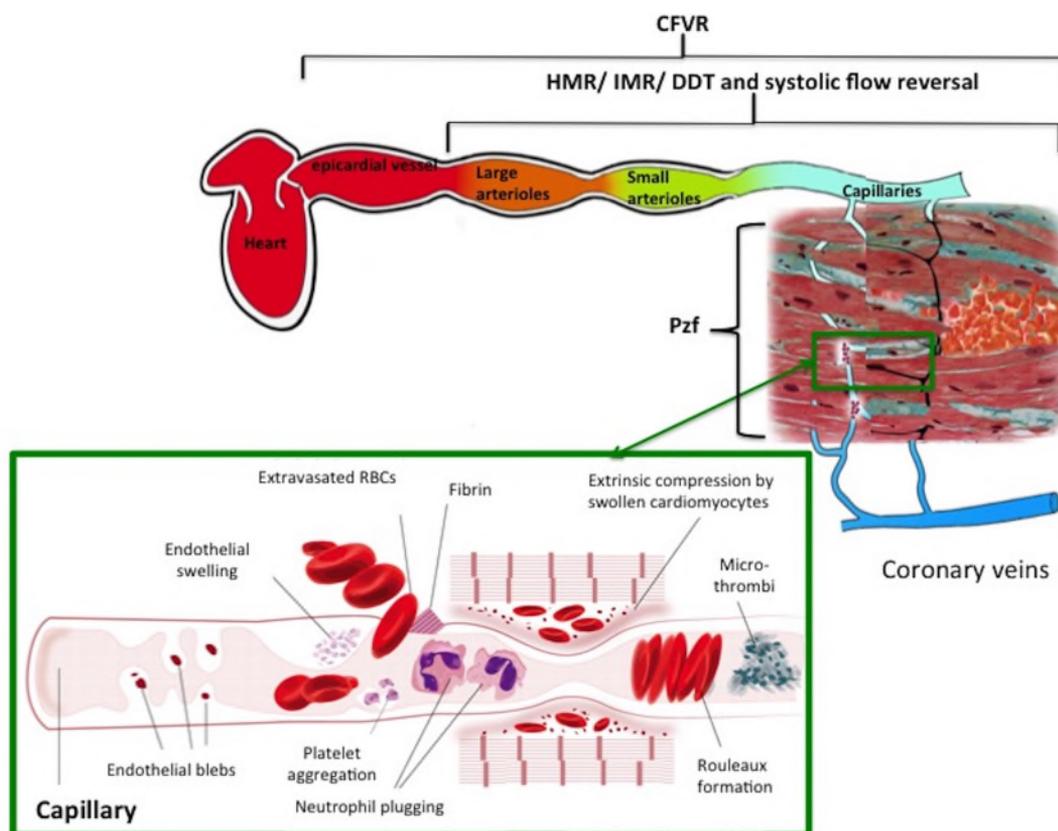


Figure 3: Microvascular obstruction by cardiovascular magnetic resonance

This is an example of a patient with an anterior STEMI with extensive areas of microvascular obstruction (MVO) (red arrows) on the late gadolinium enhancement images (a: mid ventricular short axis; b: 3-chamber; c: 4-chamber; d: 2-chamber views) of a cardiovascular magnetic resonance performed within a week of reperfusion by primary percutaneous coronary intervention (PPCI). Despite having a patent epicardial coronary at the end of the PPCI procedure with thrombolysis in myocardial flow 3 (normal flow), this patient suffered an extensive myocardial infarction with a large burden of MVO (red arrows).

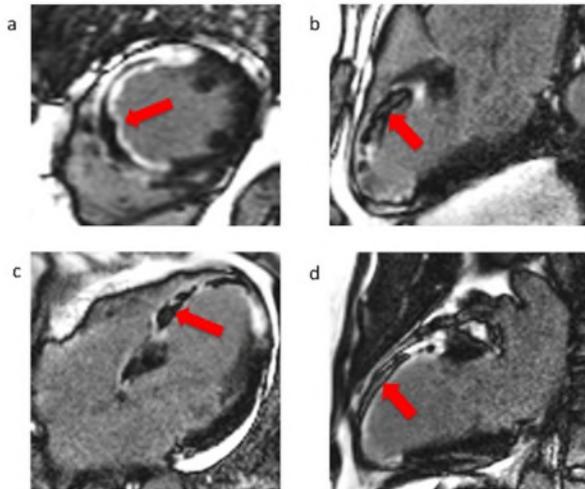


Figure 4: A hypothetical approach to identify the patients at high-risk of developing MVO using IMR

This algorithm shows that index of microvascular resistance (IMR) could be used in those with thrombolysis in myocardial infarction (TIMI) flow 3 grade at the end of the primary percutaneous coronary intervention (PPCI) to further identify those who would benefit from further adjuvant intracoronary therapies.

