

**The index of microcirculatory resistance as a tool to characterize microvascular obstruction and to predict infarct size regression in patients with ST elevation myocardial infarction undergoing primary percutaneous coronary intervention.**

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## ABSTRACT

**Objective:** We aimed to compare the value of the index of microvascular resistance (IMR) and microvascular obstruction (MVO) measured by cardiac magnetic resonance imaging (cMRI) in patients treated and recovering from ST elevation myocardial infarction (STEMI).

**Background:** IMR can identify patients with microvascular dysfunction acutely after primary percutaneous coronary intervention (pPCI) and a threshold of  $>40$  has been shown to be associated with an adverse clinical outcome. Similarly MVO is recognised as an adverse feature in STEMI patients. Even though both IMR and MVO reflect coronary microvascular status, the interaction between these two parameters is uncertain.

**Methods:** One hundred and ten patients treated with pPCI were included and IMR was measured immediately at completion of pPCI. Infarct size (IS) as a percentage of left ventricle mass was quantified at 48 hours ( $38.4 \pm 12.0$  hours) and 6 months ( $194.0 \pm 20.0$  days) using cMRI. MVO was identified and quantified at 48 hours by cMRI.

**Results:** Overall, a discordance between IMR and MVO was observed in 36.7% of cases, with 31 patients having MVO and  $IMR \leq 40$ . Compared with patients with MVO and  $IMR \leq 40$ , patients with both MVO and  $IMR > 40$  had a 1.9 fold risk of final  $IS > 25\%$  at six months ( $p = 0.001$ ). Accordingly, patients with MVO and  $IMR \leq 40$  had a significantly smaller IS at six months ( $p = 0.001$ ) with significant regression in IS over time ( $34.4\%$  ( $27.3 - 41.0$ ) vs  $22.3\%$  ( $16.0 - 30.0$ ),  $p = 0.001$ ).

**Conclusion:** Discordant prognostic information was obtained from IMR and MVO in nearly one third of cases. However, IMR can be helpful in grading the degree and severity of MVO.

**Keywords:** ST elevation myocardial infarction, primary percutaneous coronary intervention, index of microcirculatory resistance, microvascular obstruction

**CONDENSED ABSTRACT**

The index of microcirculatory resistance (IMR) is elevated in patients presenting microvascular obstruction (MVO). However the correlation between IMR and MVO extent is uncertain. We aimed to investigate the relationship between IMR and MVO in a cohort of 110 patients using a threshold of 40. Patients with MVO and  $IMR > 40$  had a significant larger infarct size (IS) at six months compared to patients with MVO and  $IMR < 40$ . Notably, in patients with MVO, an  $IMR > 40$  was associated to an 11.9 fold risk of final  $IS > 25\%$  at six months ( $p = 0.001$ ).

**ABBREVIATION LIST**

cMRI: cardiac magnetic resonance imaging

IMR: index of microcirculatory resistance

IQR: interquartile range

IS: infarct size

MVO: microvascular obstruction

Pa: aortic pressure

Pd: distal pressure

STEMI: ST elevation myocardial infarction

TIMI: thrombolysis in myocardial infarction

## INTRODUCTION

Immediate coronary revascularization by primary percutaneous coronary intervention (pPCI) is the gold standard treatment for patients with ST elevation myocardial infarction (STEMI)(1).

Unfortunately despite optimal interventional therapy some patients have a suboptimal result from pPCI with impaired myocardial perfusion. Immediate assessment of suboptimal myocardial reperfusion could allow prompt identification of high risk patients who could potentially benefit from additional therapy(2, 3).

Cardiac magnetic resonance imaging (cMRI) is regarded as the gold standard for detection and quantification of infarct size (IS) and evidence of microvascular obstruction (MVO) is recognised as a strong predictor of adverse clinical outcomes after STEMI(4). However, because of the inherent time-delay, cMRI is hampered by “logistic” difficulties in the very early stage after myocardial revascularization.

For this reason, invasive indices of coronary physiology have been reconsidered(5). These parameters provide an early and “in-the-cathlab” assessment of post pPCI microvascular function. Among these parameters, the index of microcirculatory resistance (IMR) has considerable appeal as it is readily performed (6)providing assessment of coronary microvascular status early post pPCI(7). This index has been validated against cMRI(8) with higher IMR values reported in STEMI patients with MVO on cMRI(8). Moreover, IMR has previously been identified as a predictor of change in left ventricular ejection fraction and IS at six months following STEMI(9). Higher values indicate greater degrees of microvascular dysfunction and an  $IMR < 25$  is accepted as reflection of normal microvascular function(10). In STEMI, a post-stenting  $IMR > 40$  reflects severe microvascular impairment and is associated with worse clinical outcomes in terms of death, myocardial infarction and readmission for heart failure(11, 12).

Even though validated against cMRI, the actual reported relationship between IMR and MVO extension is unclear and it appears that there are cases in whom cMRI findings and IMR values could be surprisingly discordant(13). The meaning of this discordance between presence of MVO on cMRI and post-procedural IMR have never been specifically investigated.

In the current study, we aimed to understand coronary microvasculature injury post-pPCI by measuring how often IMR and MVO provide concordant or discordant assessment of the microvasculature and define the clinical implications of these measures at follow up.

## **METHODS**

Patients with STEMI admitted to the Oxford Heart Centre for pPCI were prospectively considered for enrolment in the OxAMI (Oxford Acute Myocardial Infarction) study (REC number 10/H0408/24) from January 2011 until December 2016. Details about OxAMI study have been previously described(14). The current study represents a retrospective analysis of patients prospectively enrolled. The study protocol was approved by the local ethics committee and conducted in accordance with the Declaration of Helsinki.

STEMI was defined as the occurrence of ongoing chest pain for at least 30 minutes associated with ST-segment elevation  $>2$  mm in at least two contiguous leads. PPCI was performed according to international guidelines(1, 15). All patients were loaded with double antiplatelet therapy (aspirin 300 mg and clopidogrel 600 mg or ticagrelor 180 mg). Periprocedural anticoagulation was achieved by weight-adjusted unfractionated heparin or bivalirudin. Decisions about stenting technique (direct versus non direct), thrombectomy and glycoprotein IIb/IIIa inhibitors adoption were left to the operator's discretion.

### **Index of microcirculatory resistance measurement**

At the end of pPCI, IMR was measured using thermodilution technique as previously described (16). Briefly, a standard pressure wire (Certus, St. Jude Medical, St. Paul, Minnesota) was calibrated, equalized and advanced towards the distal third of the infarcted related artery. After intracoronary injection of 250 µg isosorbide dinitrate, the following parameters were measured both at baseline and then after inducing hyperaemia with intravenous infusion of adenosine at a rate of 140 µg/kg/min: 1) mean aortic pressure (Pa), 2) mean distal pressure (Pd) and 3) mean transit time. Mean transit time was calculated as the average of three transit time measurements during three separate injections of 3ml of room temperature 0.9% saline solution. IMR was then calculated as Pd at hyperaemia multiplied by mean transit time at hyperaemia.

### **Cardiac magnetic resonance**

CMR scans were performed at 48 hours ( $38.4 \pm 12.0$  hours) after PPCI and at 6 months ( $194.0 \pm 20.0$  days) using a 3.0 Tesla scanner (either MAGNETOM TIMTrio or MAGNETOM Verio, Siemens Healthcare, Germany). The protocol included: SPSS cine imaging, T2-weighted (T2W) imaging, native Shortened Modified Look-Locker Inversion recovery (ShMOLLI) T1 mapping, T2\* mapping and late gadolinium enhancement (LGE). Sequences acquisition was performed as previously described (17) (Supplementary Material).

Matching short axis slices covering the left ventricle were analysed using cvi42 software (Circle Cardiovascular Imaging Inc., Canada) by two expert and independent operators) blind to clinical, procedural and coronary physiology data. Disagreement was resolved by consensus. Left ventricular end diastolic volume, end systolic volume and ejection fraction were assessed on cine images. Area at risk and infarct size (IS) were quantified as percentage of left ventricle mass on T2W (on native T1 if T2W not available) and LGE, respectively, by placing a reference region of interest in remote myocardium and setting the signal intensity threshold at 2 and 5 standard deviations above the mean intensity of the reference region of interest, respectively (18-20).



Myocardial salvage index was calculated as previously described as  $[(\text{Area at risk} - \text{Infarct Size})/\text{Area at risk}] \times 100$ (19). Microvascular obstruction was defined as hypointense area within the hyperenhancement region on late gadolinium enhancement and manually contoured(18). Presence of haemorrhage was assessed firstly visually on T2\* maps and/or T2W imaging by identifying a hypointense core inside the hyperenhanced region(12, 13) and then quantified on T2W imaging setting the signal intensity threshold at 2 standard deviations below the average intensity of the reference region of interest in periphery of the area at risk(13).

### **Groups Definition**

Patients were identified according to final IMR and presence of MVO. A cut off of 40 was adopted for IMR based on previous literature (11, 12) and a pre-specified sensitivity analysis to predict six months IS (Supplementary Figure 1). We anticipated four groups: 1) patients with  $\text{IMR} \leq 40$  and no MVO; 2) patients with  $\text{IMR} > 40$  and no MVO; 3) patients with  $\text{IMR} \leq 40$  and MVO; 4) patients with  $\text{IMR} > 40$  and MVO.

### **Statistical analysis**

After verifying normal distribution by Shapiro-Wilk's test, variables were expressed as mean and ( $\pm$ ) standard deviation (SD) or as median accompanied by interquartile range (IQR), as appropriate. Frequencies were compared using Chi square test or Fisher's exact test, as appropriate. Continuous variables were compared using T test or analysis of variance (ANOVA) with Scheffe's post-hoc comparisons, as appropriate. T test or Wilcoxon test were used as appropriate for paired samples. Non-normally distributed continuous variables were compared using Mann-Whitney's test or Kruskal Wallis' test, as appropriate. Correlations between variables were expressed using Pearson r or Spearman rho coefficients as appropriate.

In the subgroup of patients with evidence of MVO on cardiac MRI, a binary logistic regression model was used to calculate odds ratio for post-stenting IMR>40 to predict 6 months IS%>25% (21). In the same subgroup of patients a linear regression model was also considered to predict extent of IS% at six months using the same covariates, after verifying that the assumptions for collinearity, independence of residuals, homoscedasticity and normality of residuals distribution were all met. In both binary logistic and linear regression models, covariates with p values less than 0.05 at the univariate model were included in the multivariate model.

Statistical analysis was performed using SPSS 22.0 (SPSS, Inc Chicago, Illinois) and a p value <0.05 was considered statistically significant.

## **RESULTS**

### **Clinical and procedural characteristics**

110 patients were included in the current analysis, as they had complete data for post-procedural IMR, 48 hours and 6 months cMRI (Figure 1). Clinical and procedural characteristics are reported in Table 1 and 2.

### **Correlation of IMR with Infarct Size and Microvascular Obstruction**

A significant correlation was observed between post-procedural IMR and IS at 48 hours ( $\rho=0.21$ ,  $p=0.03$ , Panel A Figure 2), IS at 6 months ( $\rho=0.43$ ,  $p=0.001$ , Panel B Figure 2) and MVO extent ( $\rho=0.29$ ,  $p=0.002$ , Panel C Figure 2). Moreover, a significant higher IMR value was confirmed in patients with evidence of MVO compared to those without (35.6 (24.5 -56.5) versus 26.6 (19.0 – 37.0),  $p=0.001$ , Panel D Figure 2).

### **IMR and MVO discordance**

Discordance between IMR and presence of MVO was observed in 40 patients out of 110, accounting for 36.4% of the whole cohort (Figure 3). 42 patients (38.2%) had  $IMR \leq 40$  and no MVO and 28 (25.4%) had  $IMR > 40$  and MVO on cMRI. Conversely, in the context of a discordant pattern between IMR and MVO, most of patients (31 out of 40, 77.5%) presented  $IMR \leq 40$  and evidence of MVO, whilst a minority of cases (9 out of 40) had  $IMR > 40$  without evidence of MVO (Figure 3).

### **IMR-MVO discordance and final Infarct Size**

Table 3 reports coronary physiology and cMRI features for the whole cohort and after stratification in the four groups according to IMR and MVO. At 6 months follow up, patients with both MVO and higher values of IMR had a significantly larger IS compared to all other groups. Similarly, patients with both low IMR and no MVO had a significantly smaller IS compared to all other groups (Figure 4, Panel A). Notably, among patients with MVO, those with concordant  $IMR > 40$  had a significant larger IS compared to those with  $IMR \leq 40$  ( $p < 0.001$ ) (Figure 4 – Panel A).

When change in IS over time was analysed, presence of a lower IMR was associated with a regression in IS at six months. Indeed, among patients without MVO, significant regression in IS was observed only in those patients with  $IMR \leq 40$  (16.1% (9.0 – 25.3) vs 9.3% (4.1 – 14.3),  $p = 0.001$ ) but not in those with  $IMR > 40$  (28.6% (9.4 – 40.8) vs 28.2% (9.2 – 29.7),  $p = 0.26$ ) (Table 4 – Panel C).

Similarly, amongst patients with MVO, IS was unchanged in patients with concordant  $IMR > 40$  (34.7% (23.0 – 44.4) vs 31.2 (25.0 – 39.5),  $p = 0.19$ ) whilst significant regression was evident in the group with  $IMR \leq 40$  (34.4% (27.3 – 41.0) vs 22.3% (16.0 – 30.0),  $p = 0.001$ ) (Table 4 – Panel C). These data are supplemented by the lack of difference in terms of MVO extent (4.6% (2.0 – 6.4) vs 2.8% (1.6 – 5.4),  $p = 0.26$ ) (Figure 4 – Panel C) or presence of intramyocardial haemorrhage (75.0% vs 51.6%,  $p = 0.10$ ) (Table 3) when comparing patients with MVO and high IMR and patients

with MVO and low IMR. However a significant larger extent of intramyocardial haemorrhage was observed in patients with MVO and increased IMR (3.0% (1.0 – 6.0) vs 1.0% (0.0 – 3.2),  $p=0.004$ ) (Figure 4 – Panel D).

In the multivariable model, in patients with MVO and an  $\text{IMR} > 40$ , there was an 11.9 fold increased chance of final IS at six months greater than 25% (OR 11.9, CI95% (2.8 – 51.3),  $p=0.001$ , model  $R^2=0.30$ ) (Table 4) with an increase of a single unit of IMR resulting into a 0.28% increase in final IS (beta coefficient= 0.28,  $p=0.003$ ) (Table 4).

## DISCUSSION

In the current study the correlation between IMR and MVO has been explored in patients following STEMI. We observed that:

1. IMR and MVO are related but when a threshold of 40 is adopted for IMR, then there is a discordance in the information obtained between IMR and MVO in one third of cases.
2. In patients with MVO and higher IMR, a larger IS is observed, compared to those in whom MVO is associated with  $\text{IMR} \leq 40$ ;
3. Patients with MVO but  $\text{IMR} \leq 40$  have evidence of significant regression of IS at six months, while no significant change in IS extent is observed in patients with MVO and higher IMR.

Cardiac magnetic resonance imaging is considered to be the gold standard for accurate assessment of the status of the coronary microvasculature post pPCI. However, invasive indices of coronary physiology have been recently proposed to facilitate early and in-the-cathlab diagnosis of post-procedural coronary microvascular injury(22). In this context, IMR is the most investigated invasive index of coronary physiology in STEMI, because of its ease of use(6). IMR has been showed to be significantly related to long term clinical outcomes and to predict IS and MVO on cMRI(8, 12), with most of the studies reporting higher occurrence of MVO when IMR is above a

predefined threshold(8, 12, 23). However, when the actual correlation between IMR and extent of MVO is assessed, results across studies have been less consistent. Indeed, Patel et al failed to show a strong correlation between MVO extent and IMR in a small cohort of 34 STEMI patients(24), while Payne et al reported a significant, but modest correlation of 0.38 between IMR and MVO extent in a larger cohort of 108 patients(13). Consequently, we investigated in depth the relationship between IMR and MVO.

We reported a correlation between post-procedural IMR and IS at 48 hours and six months follow up. Although higher IMR was observed more frequently in patients with MVO, the correlation between IMR and MVO was relatively weak ( $\rho = 0.29$ ). However, by applying a clinically relevant threshold of 40 for IMR(11), we observed a concordance between IMR and MVO in 73.6% of cases, with discordance in the remaining 36.4%. In this regard, previous studies have suggested that Doppler-derived hyperaemic microvascular resistance may show a better concordance with MVO(25), even though greater technical complexity and lower reproducibility making its application more challenging in clinical practice.

Patients with MVO and abnormal IMR had a significantly larger IS and patients with no MVO and  $\text{IMR} \leq 40$  had the best outcome with a significantly lower IS at six months follow up. Importantly, patients with MVO but  $\text{IMR} \leq 40$  had a significantly smaller final IS compared to patients with both MVO and  $\text{IMR} > 40$ . This observation was further corroborated by reporting a significant regression in IS at six months only in patients with MVO and  $\text{IMR} \leq 40$ , but not in those with evidence of MVO and higher IMR.

These data illustrate an additive insight from measuring IMR in assessing infarct healing and prognosis. MVO on cMRI is essentially an anatomical observation with no direct insight into the function of coronary microvasculature. Together with the presence of intramyocardial haemorrhage,

it could be considered to be evidence of severe and potentially irreversible myocardial injury in that particular area. Conversely, IMR is a functional measure of the status and viability of coronary microvasculature within the whole distribution of the culprit vessel. Our data confirm the overlap between the “anatomical microvascular impairment” observed on cMRI and the “functional microvascular impairment” depicted by IMR. However, these data also show that in nearly one third of cases there is a lack of concordance of these two parameters. When these circumstances occur, it is possible to assume that patients with MVO but  $\text{IMR} \leq 40$  are those in whom the ischemic and/or ischemic/reperfusion injury has been relatively small and/or partially contained allowing for continued functional integrity of most of the coronary microvasculature. Additionally, by reflecting the status of the whole microvascular bed in the territory supplied by the culprit artery, IMR could be considered as a marker of integrity and viability of the watershed zones adjacent to the infarct core. Previous cMRI and histopathology studies have showed how the integrity of the peri-infarct zone is ultimately responsible for the final extent of IS(26, 27), and similarly we have observed here how an  $\text{IMR} \leq 40$  is associated with a regression of IS at long term follow up even in the presence of MVO.

These data translate into the observation that when the microvascular bed is damaged irreversibly, IMR is likely to be high whereas a lower IMR reflects the potential for recovery. This concept that IMR can aid understanding and exploring MVO phenomenon, is in line with previous reports in which indices of coronary physiology provide insights in the process of microvascular healing post-STEMI(14, 28). Notably, when both functional (high IMR) and anatomical (MVO on cMRI) impairment is evident, the long term prognosis is significantly worse. Conversely, a margin of improvement and recovery can be expected when MVO is associated with some preservation of microvascular function defined by  $\text{IMR} \leq 40$ .

After correcting for baseline IS and MVO extent, we observed that in the presence of MVO,  $\text{IMR} > 40$  increased more than 10 fold the risk of having  $\text{IS} > 25\%$  at six months. This observation

could provide some pathophysiological explanation to the results recently reported by De Waha et al(4). These authors reported in a pooled analysis of 7 trials that not only the occurrence of MVO but also its severity was prognostically relevant with an MVO extent  $>1.55\%$  significantly associated to worse 1 year clinical outcome(4). In our study, the ability of IMR in defining a more severe degree of MVO is also suggested by the observation that patients with MVO and IMR  $>40$  presented a larger extent of intramyocardial haemorrhage, thus extending the results of previous studies also showing an association of IMR  $>40$  and occurrence of intramyocardial haemorrhage(12, 29).

In our study we also observed a small group of patients with higher IMR without evidence of MVO. Because of the low number of cases in this group ( $n=9$ ), definitive evidence is not possible but it is interesting to observe that these patients with impaired IMR and no MVO had no significant IS regression at six months. This observation gives further emphasis to the value of IMR which presumably reflects extensive “microvascular stunning” or severe and long lasting functional microcirculatory impairment in these cases without anatomical microvascular injury (MVO) at 48 hours(30).

In conclusion, our study explored for the first time the relationship between IMR and the acute evidence of MVO on cMRI reporting a discordance between these two parameters in nearly one third of cases. IMR assesses the status of the coronary microvasculature with significant implications for both the clinical/imaging cardiologist and the interventional cardiologist. Indeed, when combined with cMRI findings, IMR can be used to grade the severity of MVO and to identify those patients at highest risk who might require more aggressive therapeutic strategies at follow up. Our data further confirm previous literature(11, 12, 31), that a final IMR  $\leq 40$  could represent a reasonable criterion for the interventional cardiologist to judge the efficacy of pPCI in STEMI

allowing ad-hoc myocardial treatment options for those patients with  $IMR > 40$  whilst still in the catheterization laboratory.

## **LIMITATIONS**

This study is a retrospective analysis of patients prospectively enrolled within the OxAMI study and selection bias is possible although the four groups of patients were well balanced in terms of both clinical and procedural variables. Patients were enrolled over a long time period and only patients presenting full dataset for post-procedural IMR and 48 hours and six months cMRI were included in the analysis. We observed only a 19.9% drop off rate at six months follow up, with 190 patients out of 237 completing the protocol with 6 months cMRI.

Our study reported for the first time the potential of IMR in depicting two main typologies of MVO (functional vs anatomical), however it should be acknowledged that our results provide only minimal insights into the actual mechanisms accounting for the discordance between IMR and MVO occurrence on cMRI. Additional, potentially interesting insights into the role of IIBIIA inhibitors in the pathogenesis of MVO in STEMI were not possible because of the non randomised nature of the study and drug administration.

## **PERSPECTIVE**

### **Competency in Medical Knowledge**

A mismatch between “anatomical” and “functional” microvascular indices can appear in nearly one third of STEMI patients. Even in the presence of MVO, an  $IMR \leq 40$  is significantly associated to a higher chance of IS regression at six months follow up.

### **Competency in Patients' Care**



Whilst MVO remains the current gold standard to assess microvascular injury, IMR can be applied as a marker of “functional severity” of microvascular injury and as a possible marker of viability of the peri-infarct zone. If applied in combination with cMRI, IMR can be helpful in grading the severity of MVO on top of MVO extent or haemorrhage occurrence, allowing to identify those patients requiring more aggressive follow up and medical management. At the same time, in line with previous literature,  $IMR \leq 40$  is confirmed as a reasonable criterion to assess the success and efficacy of pPCI, allowing early identification, in the catheterization laboratory, of high risk patients who could benefit from ad-hoc additional or alternative therapeutic strategies.

### **Translational Outlook**

Additional studies are required to explore the efficacy of an IMR guided approach for selecting high risk STEMI patients requiring more aggressive therapeutic strategies. Similarly, additional studies are needed to assess if a combined approach integrating IMR and MVO for risk stratification in STEMI is plausible and cost-effective.

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## FIGURES LEGEND

**Figure 1. Study flow chart.**

**Figure 2. Correlations between IMR, IS and MVO.** Panel A. Scatter plot reproducing correlation between IMR and 48 hours IS. Panel B. Scatter plot reporting correlation between IMR and 6 months IS. Panel C. Scatter plot reporting correlation of IMR with MVO at 48 hours. Panel D. Box plots report median IMR values in patients with and without of MVO on cMRI.

**Figure 3. IMR and MVO discordance.**

**Figure 4.** Panel A. Difference in IS at six months between four groups derived after stratifying according to MVO and IMR. Panel B. Time trend in IS in the four groups. Panel C. MVO extent in patients with  $IMR \leq 40$  and  $>40$ . Panel D. Comparison on intramyocardial haemorrhage extent in patients with  $IMR \leq 40$  and  $>40$ .