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Pressure-bounded coronary flow reserve to assess the extent of microvascular dysfunction in patients with ST-elevation acute myocardial infarction

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KEYWORDS

- fractional flow reserve
- non-invasive imaging
- MRI
- other imaging modalities
- STEMI

Abstract

Aims: Assessment of microvascular function in patients with ST-elevation acute myocardial infarction (STEMI) may be useful to determine treatment strategy. The possible role of pressure-bounded coronary flow reserve (pb-CFR) in this setting has not been determined. In this study we aimed to compare pb-CFR with thermodilution-derived physiology including the index of microcirculatory resistance (IMR) and CFR_{thermo} in a consecutive series of patients enrolled in the OxAMI study. Moreover, we aimed to assess the presence of microvascular obstruction (MVO) and myocardial injury on cardiovascular magnetic resonance (CMR) imaging performed at 48 hours and six months in STEMI patients stratified according to pb-CFR.

Methods and results: Thermodilution-pressure-wire assessment of the infarct-related artery was performed in 148 STEMI patients before stenting and/or at completion of primary percutaneous coronary intervention (PPCI). The extent of the myocardial injury was assessed with CMR imaging at 48 hours and six months after STEMI. Post-PPCI pb-CFR was impaired (<2) and normal (>2) in 69.9% and 9.0% of the cases, respectively. In the remaining 21.1% of the patients, pb-CFR was "indeterminate". In this cohort, pb-CFR correlated poorly with thermodilution-derived coronary flow reserve (k=0.03, p=0.39). The IMR was significantly different across the pb-CFR subgroups. Similarly, significant differences were observed in MVO, myocardium area at risk and 48-hour infarct size (IS). A trend towards lower six-month IS was observed in patients with high (>2) post-PPCI pb-CFR. Nevertheless, pb-CFR was inferior to IMR in predicting MVO and the extent of IS.

Conclusions: Pb-CFR can identify microvascular dysfunction in patients after STEMI. It provided superior diagnostic performance compared to thermodilution-derived CFR in predicting MVO. However, IMR was superior to both pb-CFR and thermodilution-derived CFR and, consequently, IMR was the most accurate in predicting all of the studied CMR endpoints of myocardial injury after PPCI.

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Abbreviations

CFR coronary flow reserve
CMR cardiac magnetic resonance
IMR index of microcirculatory resistance
IS infarct size
MVO microvascular obstruction
pb-CFR pressure-bounded coronary flow reserve
PPCI primary percutaneous coronary intervention
STEMI ST-elevation myocardial infarction

Introduction

Coronary physiology is a useful tool to assess the extent of coronary microvascular dysfunction in patients with ST-elevation acute myocardial infarction (STEMI) undergoing primary percutaneous coronary intervention (PPCI)[1].

The presence of microvascular obstruction (MVO) or high values of index of microcirculatory resistance (IMR) have been associated with poor myocardial reperfusion after PPCI, larger infarct size and worse long-term clinical outcome[1-3]. Moreover, STEMI patients with high IMR are at increased risk of post-procedural and in-hospital complications compared with patients with low post-PPCI IMR[4].

However, the use of coronary physiology to assess the extent of microvascular dysfunction in STEMI patients remains limited in routine clinical practice, partly because of the complexity of the available techniques to assess coronary flow and coronary resistance in the catheterisation laboratory[5].

Recently, pressure-bounded coronary flow reserve (pb-CFR) has been proposed to estimate CFR using standard pressure-wire technology, obviating the need for intracoronary thermodilution or Doppler-velocity measurements[6]. pb-CFR demonstrated a good correlation with Doppler and thermodilution-derived CFR (CFR_{thermo}) although its value to predict clinical outcomes remains uncertain[6-8].

The diagnostic accuracy of pb-CFR in detecting the extent of coronary microvascular dysfunction and predicting myocardial injury has not been assessed in patients with STEMI. In this study, we aimed to compare pb-CFR with thermodilution-derived physiology including IMR and CFR_{thermo} in a consecutive series of patients enrolled in the Oxford Acute Myocardial Infarction (OxAMI) study. Moreover, we aimed to assess the presence of MVO and myocardial injury on cardiovascular magnetic resonance imaging (CMR) performed at 48 hours and six months in STEMI patients stratified according to pb-CFR.

Methods

Patients with STEMI admitted to the Oxford Heart Centre for PPCI were prospectively considered for enrolment in the OxAMI study (REC number 10/H0408/24). The study protocol was approved by the local ethics committee and the study was conducted in accordance with the Declaration of Helsinki.

Details of the OxAMI study have been described previously[1]. The diagnosis of STEMI required chest pain lasting at least 30 minutes, within 12 hours from onset of symptoms, and ST-segment elevation of >2 mm (0.2 mV) in at least two contiguous leads on ECG. Symptom duration >12 hours, presence of severe haemodynamic instability, severe left main disease, contraindications to adenosine infusion, balloon angioplasty without stent implantation and general contraindications to CMR were all exclusion criteria for this analysis.

PPCI was performed in a standard fashion and decisions about direct stenting technique, thrombectomy and glycoprotein IIb/IIIa adoption were all left to the operator's discretion. All patients were loaded with dual antiplatelet therapy. Weight-adjusted unfractionated heparin or bivalirudin was adopted as antithrombotic regimen. Angiographic thrombus score was graded from 0 to 5 after the passage of the guidewire, as described previously[9].

CORONARY ANGIOGRAPHY

Coronary flow was graded using the standard Thrombolysis In Myocardial Infarction (TIMI) criteria[10]. Myocardial blush grade at the end of the procedure was evaluated according to van 't Hof[11]. Angiographic no-reflow was defined as TIMI flow grade <3 and/or TIMI flow grade 3 with myocardial blush grade <2 at completion of the procedure. Two interventional cardiologists blinded to clinical and outcome parameters performed the angiographic analyses, and differences were resolved by consensus.

INVASIVE CORONARY PHYSIOLOGY MEASUREMENTS

Indices of coronary physiology of the infarct-related artery were assessed after flow restoration (before stenting) and/or at completion of PPCI. IMR was defined as the mean distal pressure multiplied by the mean transit time (Tmn) at hyperaemia as previously described[1] using a coronary PressureWire™ (Abbott/St. Jude Medical, St. Paul, MN, USA). When measured before stent implantation, the IMR value was corrected for collateral flow by coronary wedge pressure (Pw), measured during prolonged balloon inflation, as follows:

$$Pa_{hyp} \times Tmn_{hyp}[(Pd_{hyp} - Pw)/(Pa_{hyp} - Pw)]$$

CFR_{thermo} was defined as the ratio of hyperaemic to resting coronary flow and was calculated using the equation:

$$Tmn_{base} / Tmn_{at\ hyperaemia}$$

PRESSURE-BOUNDED CORONARY FLOW RESERVE

The concept of pb-CFR has been proposed to estimate CFR applying a fundamental fluid dynamics equation that quantifies the pressure gradient induced across a lesion in an epicardial coronary vessel:

$$\Delta P = f \times Q + s \times Q^2$$

where ΔP is the pressure gradient across the lesion, Q is coronary flow, f is the friction coefficient and s is the separation coefficient. f and s are geometric and rheologic properties of the lesion and the vessel.

Pb-CFR assumes that, at one extreme, the lower bound of CFR is calculated as $\sqrt{\Delta P\ during\ hyperaemia} / \sqrt{\Delta P\ at\ rest}$, assuming

that all the energy losses across the stenosis may be explained by separation forces and, on the other extreme, the upper CFR bound is calculated as the ratio between ΔP at hyperaemia and ΔP at rest, assuming that the energy losses may be due to friction across the lesion[6]. In other words, pb-CFR defines the interval between the minimum and the maximum possible CFR values as follows:

$$\sqrt{\left[\frac{\Delta Phyp}{\Delta Prest}\right]} \leq \text{CFR} \leq \frac{\Delta Phyp}{\Delta Prest} \quad (1)$$

As reported by Ahn at al, the equation can also be rewritten as:

$$\sqrt{\frac{1-\frac{Pd}{Pa}hyp}{1-\frac{Pd}{Pa}rest}} \leq \text{CFR} \leq \frac{1-\frac{Pd}{Pa}hyp}{1-\frac{Pd}{Pa}rest} \quad (2)$$

Since Pd/Pa was available in 100% of the cases we adopted equation (2) to derive pb-CFR **(Supplementary Figure 1)**.

Pb-CFR was considered abnormal when both the upper and the lower bounds of pb-CFR were <2 and normal when both the upper and the lower bounds were >2. In all other cases, pb-CFR was considered indeterminate, as previously described[6,8]. Patients with resting Pd/Pa >0.98 were excluded from the analysis.

CARDIOVASCULAR MAGNETIC RESONANCE IMAGING PROTOCOL AND ANALYSIS

CMR was performed using a 3.0 Tesla magnetic resonance scanner (either MAGNETOM Trio™ or MAGNETOM® Verio; Siemens Healthcare, Erlangen, Germany) within 48 hours after PPCI and at six-month follow-up. The CMR protocol has been reported previously[12] and is described in detail in **Supplementary Appendix 1**.

Cvi42 image analysis software (Circle Cardiovascular Imaging Inc., Calgary, Canada) was used for image analysis.

STATISTICAL ANALYSIS

Normally distributed variables are reported as mean±SD, and the Student's t-test used for comparisons. Non-parametric distributions are reported as median (interquartile range), and the Mann-Whitney test used for unpaired data. Differences between groups were compared with one-way ANOVA or the Kruskal-Wallis test as appropriate. Fisher's exact chi-square test was used for binary variables. Correlation between variables was tested by the Spearman-rho method.

Cohen's kappa coefficient method and % agreement were used to assess the agreement between pb-CFR and CFR_{thermo}. Receiver operating characteristic (ROC) curve analysis was used to test the diagnostic performance of physiological variables to predict the extent of microvascular dysfunction and myocardial injury after STEMI. In calculating ROC curves for IS, the cut-off value for the highest quartile was used to define the endpoint (IS% [48 hrs] ≥38.1% and IS% [6 months] ≥30.0%). Areas under the ROC curve were compared using the DeLong method.

In cases with repeated pre- and post-stent physiological assessment, the variations of IMR were measured using a non-parametric Wilcoxon test and variations in pb-CFR were assessed using McNemar's test. Patients were classified as good responders or partial/poor responders to stenting according to the final IMR value ≥40 U, as described previously[1].

For regression and ROC curve analysis, pb-CFR was used as a binary categorical variable in the analysis, excluding patients with indeterminate results.

Statistical analysis was performed using SPSS, Version 25.0 (IBM Corp., Armonk, NY, USA) and MedCalc statistical software, version 15.8 (MedCalc, Mariakerke, Belgium). All tests were two-tailed and a p-value <0.05 was considered statistically significant.

Results

One hundred and sixty-five patients presenting with STEMI underwent coronary physiological assessment of the infarct-related artery during PPCI as part of the OxAMI study. Pb-CFR was available in 148 patients (before and/or after PPCI) and was measured before stenting in 112 patients and at completion of PPCI in 123 patients. Eighty-seven (87) patients had both pre- and post-stenting pb-CFR data. CMR was available in all the cases (100%) at 48 hours and in 109 (74%) patients at six months of follow-up.

PB-CFR IN THE INFARCT-RELATED ARTERY BEFORE STENTING (IMMEDIATELY AFTER FLOW RESTORATION)

After flow restoration, pb-CFR was <2 in 89/112 (79.5%) patients, >2 in 5/112 (4.5%) patients and indeterminate in 18/112 (16.0%) patients **(Supplementary Table 1)**.

No significant difference in CFR_{thermo} was observed in patients stratified according to pb-CFR **(Supplementary Table 2)**.

Notably, significant differences in pre-stenting IMR were observed stratifying the patients according to pb-CFR **(Supplementary Table 2)**.

CORRELATION BETWEEN PRE-STENTING PB-CFR AND THE EXTENT OF MYOCARDIAL INJURY AFTER STEMI

Pre-stenting pb-CFR >2 was associated with smaller myocardial area at risk percentage (AAR%) **(Figure 1)**. Moreover, a trend towards smaller infarct size at 48 hours and six months was observed in patients with pre-stenting pb-CFR >2 **(Figure 1, Supplementary Table 1)**.

At ROC curve analysis, pre-stenting pb-CFR demonstrated inferior but not statistically different diagnostic value compared to pre-stenting IMR in predicting the infarct size at 48 hours ($AUC_{pb\text{-}CFR}$=0.53 [0.42-0.64] vs AUC_{IMR}=0.63 [0.52-0.73], p=0.12), the final infarct size at six months ($AUC_{pb\text{-}CFR}$=0.54 [0.42-0.67] vs AUC_{IMR}=0.64 [0.52-0.76]; p=0.17) and the presence of intramyocardial haemorrhage ($AUC_{pb\text{-}CFR}$=0.50 [0.32-0.68] vs AUC_{IMR}=0.60 [0.41-0.77]; p=0.35). Moreover, the performance of pb-CFR in predicting the presence of MVO was inferior but marginally non-statistically different compared with IMR ($AUC_{pb\text{-}CFR}$=0.52 [0.41-0.63] vs AUC_{IMR}=0.64 [0.53-0.74], p for AUC comparison=0.052).

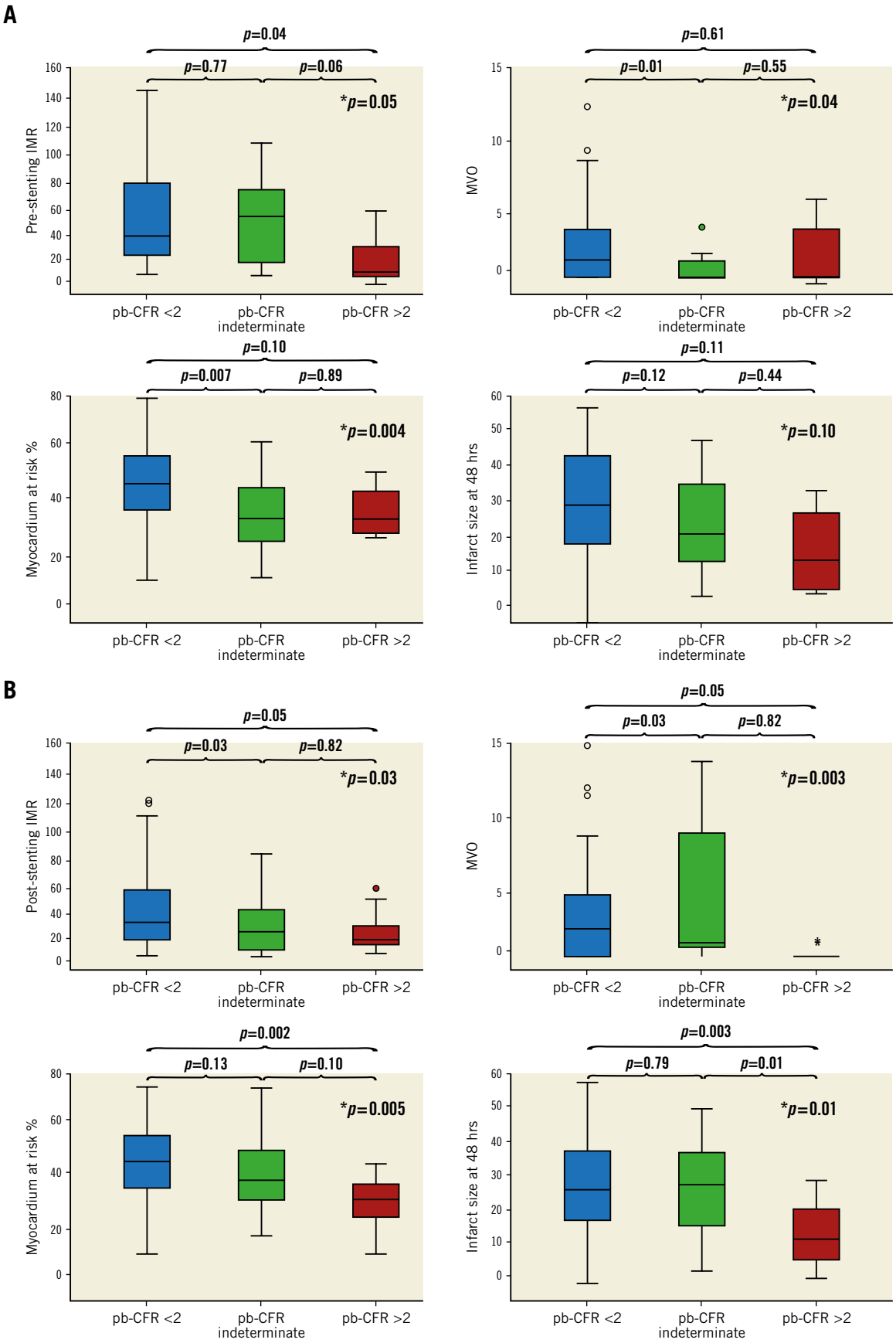

Figure 1. *Differences in IMR, MVO, myocardial AAR% and 48-hour IS% in patients stratified according to pre-stenting or post-stenting pb-CFR. A) Pre-stenting. B) Post-stenting, measured at completion of PPCI. *indicates overall p-value*

PB-CFR IN THE INFARCT-RELATED ARTERY AT COMPLETION OF PRIMARY PCI

At completion of PPCI, 86/123 (69.9%) patients presented a pb-CFR <2 and 11/123 (9.0%) patients had a pb-CFR >2. In the remaining 26/123 (21.1%) patients pb-CFR was indeterminate. Clinical, angiographic and imaging characteristics of patients stratified according to the post-PPCI pb-CFR are presented in **Table 1** and **Supplementary Table 3**. Patients with pb-CFR >2 at completion of PPCI presented a trend towards a lower frequency of the left anterior descending (LAD) artery as the culprit vessel, higher TIMI flow post stenting and lower peak troponin levels.

No significant difference was observed in CFR_{thermo} across the pb-CFR groups **(Table 2)**. Moreover, a poor agreement was observed between pb-CFR and CFR_{thermo} (k=0.031, p=0.39; % agreement=65%) **(Supplementary Figure 2)**.

At completion of PPCI, IMR was significantly different across the pb-CFR groups, with pb-CFR >2 associated with lower IMR values **(Table 2)**.

We found no interaction between binary pb-CFR and culprit vessel (p for interaction=0.601).

Significant variations were observed in IMR values before and after stenting (44.0 [28.4-80.0] to 28.7 [16.7-50.6], p<0.001). Notably, an overall improvement was observed in pb-CFR values at completion of PPCI (p<0.001) **(Figure 2A, Supplementary Appendix 2)**. According to final IMR value <40 U, 54/87 (62%) patients were classified as good responders to stenting. In this subgroup, pb-CFR significantly improved at completion of PCI (p=0.007) **(Figure 2B, Supplementary Appendix 2)**. Conversely, no significant variations in pb-CFR were observed in patients categorised as partial or poor responders to stenting according to final IMR ≥40 U **(Figure 2C)**. Notably, good responders to stenting presented smaller IS% at 48 hours and six months, less MVO% and greater myocardial salvage compared with partial/poor responders to stenting **(Supplementary Table 4, Supplementary Figure 3)**.

CORRELATION BETWEEN PB-CFR AT COMPLETION OF PPCI AND THE EXTENT OF MYOCARDIAL INJURY AFTER STEMI

Post-PCI pb-CFR was significantly associated with the myocardial AAR% and the extent of myocardial injury at 48 hours after STEMI **(Figure 1)**. A trend towards smaller infarct size at six months was observed in patients with pb-CFR >2. Notably, IMR and CFR_{thermo} outperformed pb-CFR in predicting the extent of final IS **(Table 3, Supplementary Table 5, Supplementary Table 6)**.

Table 1. Clinical and procedural characteristic of patients with STEMI stratified according to post-procedural pb-CFR.

Clinical data	pb-CFR <2 n=86	pb-CFR indeterminate n=26	pb-CFR >2 n=11	*p*-value
Age, years	61 (54-67)	65 (55-71)	54 (48-68)	0.34
Sex, male	75 (87)	21 (81)	11 (100)	0.28
Hypertension	46 (53)	10 (38)	8 (72)	0.14
Dyslipidaemia	32 (37)	17 (65)	2 (18)	0.10
Diabetes	36 (42)	6 (23)	3 (27)	0.17
Smoking	39 (45)	13 (50)	5 (45)	0.91
eGFR, ml/min/1.73 m^2	94.2 (78.9-106.8)	89.2 (77.0-99.0)	83.0 (75.0-121.1)	0.41
Pain-to-balloon time, min	193 (125-379)	146 (118-234)	195 (167-380)	0.14
Peak troponin	32.1 (8.3-67.8)	32.1 (0.5-60.0)	2.5 (1.99-2.5)	0.07
CMR imaging at 48 hours				
EDV, ml	168.5 (142.0-199.0)	148.0 (125.5-180.5)	132.0 (109.0-162.0)	0.005
ESV, ml	92.0 (73.2-114.7)	76.0 (58.0-95.0)	67.0 (56.0-87.0)	0.005
LVEF%	46.5 (40.0-50.7)	49.0 (39.5-55.0)	48.0 (46.0-55.0)	0.26
SV, ml	77.0 (66.0-89.0)	66.0 (55.0-84.5)	59.0 (52.0-78.0)	0.044
AAR%	46.1 (37.0-55.6)	39.7 (31.5-53.0)	33.3 (27.1-40.2)	0.005
IS% at 48 hours	28.7 (20.4-39.3)	30.0 (18.0-41.0)	15.5 (8.3-25.0)	0.010
MVO, %	2.0 (0.0-4.43)	1.0 (0.0-10.0)	0.0 (0.0-2.2)	0.003
CMR imaging at 6 months				
EDV, ml	172.5 (147.5-197.5)	147.5 (119.0-184.5)	159.0 (120.5-165.0)	0.052
ESV, ml	78.5 (57.7-103.0)	66.0 (55.2-86.5)	69.0 (44.0-72.0)	0.13
LVEF%	52.5 (43.0-60.0)	55.5 (48.0-59.0)	57.0 (55.5-65.0)	0.21
SV, ml	88.5 (73.5-99.0)	81.5 (59.0-93.5)	88.0 (76.5-94.0)	0.37
IS at 6 months, %	21.8 (13.3-30.3)	20.0 (8.0-30.4)	12.9 (5.5-21.8)	0.18
Salvage, %	34.5 (23.5-48.8)	37.1 (14.8-60.6)	42.9 (32.7-64.4)	0.39

Table 2. Intracoronary physiology of patients with STEMI stratified according pb-CFR.

Post-stenting	pb-CFR <2	pb-CFR indeterminate	pb-CFR >2	*p*-value
Baseline Pd/Pa	0.93 (0.91-0.95)	0.97 (0.94-0.98)	0.98 (0.97-0.98)	<0.001
FFR	0.91 (0.89-0.94)	0.93 (0.89-0.97)	0.91 (0.88-0.93)	0.43
Delta PdPa-FFR	0.01 (0.0-0.03)	0.02 (0.01-0.07)	0.07 (0.04-0.10)	<0.001
Pd (Hyp), mmHg	75 (68-88)	75 (64-84)	76 (67-85)	0.55
Tmn (Rest)	0.75 (0.44-1.14)	0.64 (0.39-1.01)	0.50 (0.35-0.98)	0.23
Tmn (Hyp)	0.41 (0.27-0.86)	0.39 (0.20-0.55)	0.28 (0.22-0.44)	0.10
CFR	1.50 (1.10-2.18)	1.81 (1.34-2.59)	1.96 (1.35-2.46)	0.17
IMR	32.5 (20.3-55.4)	26.0 (13.3-41.0)	20.2 (16.5-37.0)	0.03
RA pressure, mmHg	8 (6-10)	8 (2-12)	5 (3-8)	0.42
Lower pb	1.10 (1.00-1.22)	1.53 (1.41-1.67)	2.45 (2.01-2.83)	<0.001
Upper pb	1.22 (1.00-1.45)	2.33 (2.00-2.87)	6.00 (4.00-8.00)	<0.001

No significant differences were observed in the left ventricular ejection fraction (LVEF) across pb-CFR groups six months after STEMI **(Figure 3)**.

Post-PPCI pb-CFR was significantly associated with the presence of MVO **(Table 1, Figure 1)**. Using regression analysis, pb-CFR outperformed CFR_{thermo} in predicting the presence of MVO (OR=0.08; 95% CI: 0.02-0.42, p=0.003) **(Table 3)** but presented only modest diagnostic accuracy at ROC curve analysis (AUC=0.63 [0.52-0.73], p=0.003). Nonetheless, a pb-CFR >2 demonstrated high sensitivity (96.7% [88.5%-99.6%]) and fair negative predictive value (81.8% [48.2%-97.7%]) in excluding the presence of MVO.

Pb-CFR was inferior compared to IMR in predicting the presence of haemorrhage and the extent of IS% at 48 hours and six months **(Table 3, Figure 3)**. Using alternative cut-offs other than 2 for pb-CFR (1.5 or 2.5) to define microvascular dysfunction did not improve the prognostic role of the index regarding CMR endpoints **(Supplementary Table 7)**.

Discussion

Pb-CFR measured before and after stent placement has poor correlation with CFR_{thermo} in this cohort of patients with STEMI undergoing PPCI. However, pb-CFR was associated with the extent of microvascular dysfunction assessed both in the catheterisation laboratory using IMR and with MVO measured using CMR. In particular, pb-CFR was able to identify a subgroup of patients (pb-CFR >2) who experienced better reperfusion after PPCI with lower IMR, MVO and smaller acute myocardial injury after STEMI.

Unfortunately, despite the advantage of being an easy technique based on a standard pressure wire without additional measurements of transit time or other coronary flow surrogates, pb-CFR is a suboptimal index of microvascular dysfunction in the STEMI population, with inferior diagnostic metrics compared with IMR.

Prompt restoration of coronary flow in the infarct-related artery by PPCI is the standard of care in patients presenting with STEMI. Nevertheless, a significant number of patients do not achieve complete myocardial reperfusion despite an apparently satisfactory angiographic result in the epicardial vessel[1]. This is mainly related to microvascular injury after PPCI and has been associated with larger infarct size, adverse LV remodelling and increased risk of heart failure and cardiovascular mortality[3,12-14].

The identification of patients who are less likely to experience optimal reperfusion post PPCI and may be candidates to adjunctive or alternative therapeutic strategies is a field of ongoing research[13]. Coronary physiological indices, and specifically CFR and IMR, have been extensively investigated as potential tools to identify high-risk patients in the catheterisation laboratory. In particular, IMR has emerged as an accurate index of microvascular function with good predictive value for adverse outcome after STEMI[15-17], as confirmed by this analysis **(Figure 2, Supplementary Table 4)**.

However, the use of physiological assessment in STEMI is still limited because of the additional technical complexity, the additional procedural time and requirement for dedicated equipment to measure coronary flow using either Doppler or thermodilution techniques[5].

Pb-CFR offers the advantage of avoiding thermodilution or Doppler velocity measurements and has been demonstrated to provide important information on the relationship between fractional flow reserve (FFR) and CFR[6,8]. However, Ahn et al showed that pb-CFR was not associated with clinical outcome in a large cohort of patients with stable coronary artery disease[8]. This result was recently confirmed by Wijntjens et al at long-term follow-up[7].

The applicability of pb-CFR is also limited by the fact that it produces an indeterminate result (lower limit <2 and upper limit >2) in those cases that cannot be classified as normal (both limits >2) or abnormal (both limits <2)[6,8]. In our study, pb-CFR resulted in being "indeterminate" in 21.1% of the cases at completion of PPCI. Notably, the proportion of cases categorised as "indeterminate" is lower than that which has been observed by previous investigators[6-8]. It is of interest that this subgroup of patients presented intermediate-risk characteristics compared with the low and high CFR groups, with lower IMR values and smaller

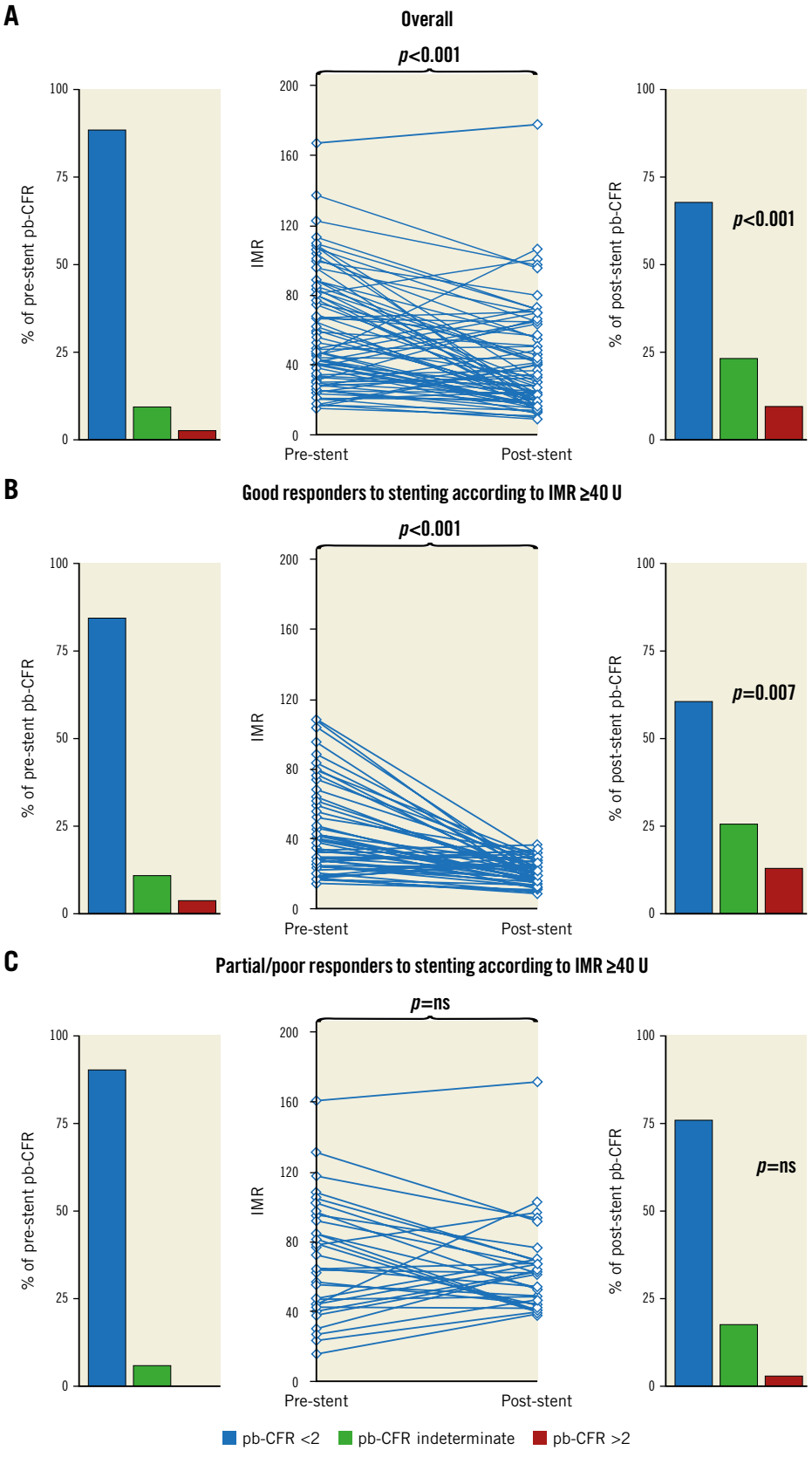

Figure 2. *IMR and pb-CFR variations before and after stenting. Overall IMR and pb-CFR variations before and after stenting (panel A). Patients with both pre- and post-stenting physiological measurements were classified, according to the final IMR, as good responders to stenting (post-PPCI IMR <40 U) (panel B) or partial/poor responders (post-PPCI IMR ≥40 U) (panel C). Pb-CFR improved significantly in good responders but not in partial/poor responders to stenting.*

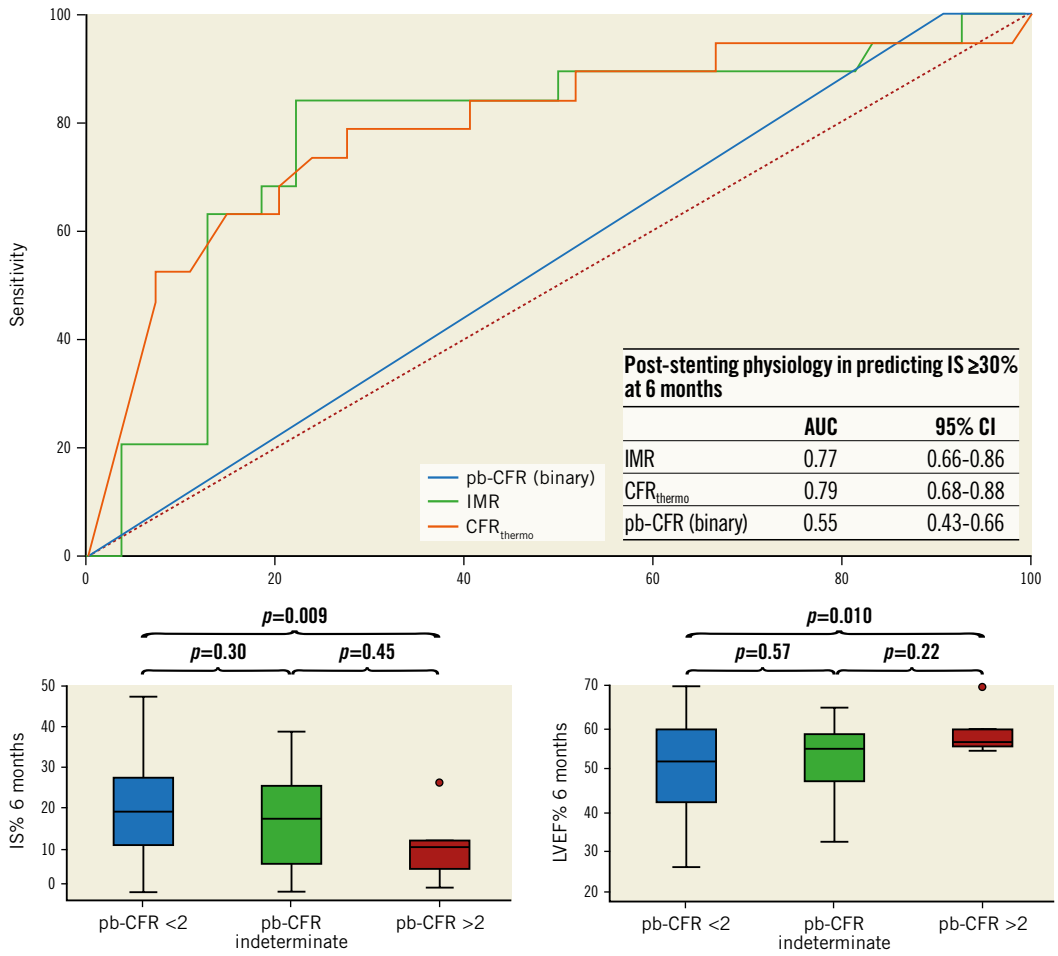

Figure 3. *Diagnostic accuracy of physiological indices in predicting the final infarct size at six months after STEMI. IMR and CFR_{thermo} presented a significantly higher AUC at ROC curve analysis compared with pb-CFR in predicting an IS ≥30.0% at CMR. In the lower panel, a trend towards smaller IS% at six months was observed for patients with post-PPCI pb-CFR >2. Conversely, no difference in left ventricular ejection fraction (LVEF%) was observed between the groups.*

Table 3. Regression analysis for pb-CFR, CFR and IMR in predicting physiological and CMR endpoints.

	pb-CFR		CFR		IMR	
	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
IS% (48 hrs)*	0.93 (0.32-2.66)	0.89	0.75 (0.45-1.27)	0.29	1.01 (1.00-1.02)	0.022
MVO**	0.08 (0.02-0.42)	0.003	0.71 (0.48-1.05)	0.09	1.02 (1.01-1.03)	0.008
Haemorrhage%	0.42 (0.04-4.32)	0.46	0.75 (0.43-1.31)	0.31	1.02 (1.01-1.04)	0.019
IS% (6 months)*	0.92 (0.29-2.91)	0.89	0.54 (0.27-1.06)	0.07	1.02 (1.01-1.03)	0.017

*For infarct size (IS) at 48 hours and 6 months the cut-off value for the highest quartile was used to define the endpoint: IS% (48 hrs) ≥38.1% and IS% (6 months) ≥30.0%. **The presence versus absence of MVO at 48 hours. CMR has been used to define the endpoint MVO. IS: infarct size; MVO: microvascular obstruction

AAR% compared with patients with pb-CFR <2, but larger IS% compared with patients with pb-CFR >2.

In this study, pb-CFR measured in the infarct-related artery was impaired when measured post stenting in the majority of the cases (86/123=69.9%) and, consequently, the value of pb-CFR <2 in identifying cases with high IMR (>40 U) or MVO is limited. However, a lower limit pb-CFR >2 (normal pb-CFR) was significantly associated with lower IMR, smaller MVO and IS% at 48 hours and six months after STEMI.

Limitations

Our study has several limitations. This is a retrospective analysis of the OxAMI study and pb-CFR has been calculated using pre-existing recorded physiological data.

Another limitation of our study is the relatively small sample size and the fact that the prognostic value of pb-CFR has been tested against thermodilution-derived indices and CMR parameters and not against clinical endpoints. Nevertheless, this is the first study to explore the value of pb-CFR in predicting the extent of microvascular dysfunction and myocardial damage in the setting of STEMI patients.

An additional inherent limitation of pressure-derived CFR is the required minimum resting pressure gradient. In fact, in cases with small ΔP at rest, the measurement of pb-CFR might become inaccurate, as the value of √ΔP at rest is in the range of the error of the pressure measurement itself[18,19]. To overcome this limitation, we excluded those patients with a final resting Pd/Pa >0.98, as described previously. In our series, the overall mean Pd/Pa and FFR were 0.94±0.04 and 0.92±0.05, respectively, and, even in the subgroup of patients with post-PPCI pb-CFR >2, the resting and hyperaemic gradient across the lesion allowed a reliable measurement of pb-CFR **(Table 2)**. Nonetheless, we cannot exclude some degree of inaccuracy in the measurement of post-PCI pb-CFR, especially in those cases with high FFR.

Conclusions

Pb-CFR is a pressure-only derived index of coronary flow reserve. In our study, pb-CFR was impaired (upper limit <2) in 70% of the cases at completion of PPCI and was modestly associated with the extent of microvascular dysfunction and myocardial injury after STEMI. Pb-CFR provided superior diagnostic performance compared to thermodilution-derived CFR in predicting MVO after STEMI. However, IMR was superior to both pb-CFR and thermodilution-derived CFR and, consequently, IMR was the most accurate in predicting all of the studied CMR endpoints of myocardial injury after PPCI.

Impact on daily practice

Pressure-bounded coronary flow reserve (pb-CFR) is a simple tool to estimate CFR and is calculated using standard pressure-wire technology without the need for thermodilution or Doppler-velocity measurement. Pb-CFR is associated with the extent of microvascular dysfunction and myocardial injury in STEMI. In particular, patients with impaired pb-CFR have significantly higher IMR, MVO, area at risk and infarct size compared with patients with normal pb-CFR. However, pb-CFR is a suboptimal index of microvascular dysfunction in the STEMI population with inferior diagnostic metrics compared with IMR.

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Appendix. Study collaborators

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Conflict of interest statement

R. Scarsini has received an education and training grant from EAPCI and served on an advisory board for Abbott. A. Banning has received institutional funding for an interventional fellowship from Boston Scientific. R. Kharbanda is a proctor for Boston Scientific and has received speaker fees from Abbott. The other authors have no conflicts of interest to declare.

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Supplementary Table 6. Comparison of areas under the curve (AUC) for pb-CFR (binary) and CFR in predicting CMR endpoints.

Supplementary Table 7. Comparison between different cut-offs for pb-CFR in discriminating major cardiac MRI endpoints.

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Supplementary data

Supplementary Appendix 1. Cardiovascular magnetic resonance (CMR) protocol

CMR was performed using a 3.0 Tesla magnetic resonance scanner (either MAGNETOM Trio [a Tim system] or MAGNETOM Verio; Siemens Healthcare, Erlangen, Germany) within 48 hours after PPCI and at six-month follow-up.

Left ventricle (LV) volumes and ejection fraction (EF%) were assessed from steady-state free precession (SSFP) images. The myocardial area at risk (AAR), defined as the myocardial tissue within the perfusion bed distal to the culprit lesion, was assessed using the Shortened Modified Look-Locker Inversion recovery T1-mapping technique identified using a signal intensity threshold of 2SD above the mean T1 of remote reference region of interest placed 180 degrees opposite to the injured myocardium with no visible regional wall abnormalities or infarction as previously described. AAR was then measured as a percentage of the LV mass.

To quantify acute infarct size, as depicted by late gadolinium enhancement (LGE), signal intensity threshold was set at five standard deviations above the remote reference myocardium. When present, T1 core and MVO were included in the measurements of AAR and LGE, respectively. The MVO percentage fraction was quantified by manual delineation of the hypointense areas within the LGE region. Presence of intramyocardial haemorrhage was assessed on T2* (T2 star) and/or T2W imaging as a hypointense area within the injured myocardium. Post-PPCI myocardial salvage index was measured as:

$$\text{myocardial salvage index} = [(\text{AAR} - \text{infarct size})/\text{AAR}] * 100$$

The scan protocol comprised SSFP for functional images, native Shortened Modified Look-Locker Inversion recovery (ShMOLLI) T1 mapping for AAR characterisation, T2* mapping and T2-weighted (T2-prepared SSFP) for intramyocardial haemorrhage assessment, and LGE for infarct size and MVO quantification.

Typical acquisition parameters for SSFP retrospectively gated cine images were TE/TR = 1.4/3.2 ms; flip angle 50°; voxel size: 2.4 x 1.8 x 8.0 mm.

T2W was performed using a T2-prep-SSFP single shot sequence with surface coil correction (TE/TR = 1/4.1 msec; effective TE = 60 msec; flip angle 90°; voxel size: 2.1 x 1.6 x 8.0 mm).

ShMOLLI T1 maps were generated from 5-7 SSFP images with variable inversion preparation S2 time as described previously. Typical acquisition parameters were: TE/TR = 1.07/2.14 msec, flip angle=35°, FOV=340×255 mm, matrix size=192×144, 107 phase encoding steps, actual experimental voxel size = 1.8 × 1.8 × 8 mm, interpolated reconstructed voxel size = 0.9 x 0.9 x 8 mm, GRAPPA = 2, 24 reference lines, cardiac delay time TD = 500 msec and 206 msec acquisition time for single image, phase partial Fourier 6/8.

T2* maps were obtained using a gradient echo sequence. Typical imaging parameters were: flip angle 20°; voxel size 1.8 x 1.8 x 8 mm.

LGE was performed with a T1-weighted segmented inversion recovery gradient echo-phase sensitive-inversion recovery (GRE_PSIR) sequence (TE/TR = 2.5 msec/5 msec, voxel size =1.8 x 1.4 x 8.0 mm, flip angle 20°). LGE images were collected 10-15 min after the administration of 0.1 mmol/kg contrast agent (Dotarem®; Guerbet, Villepinte, France). The inversion time was adjusted for optimal nulling of remote normal myocardium.

Supplementary Appendix 2. IMR and pb-CFR variations before and after stenting

Patients with both pre- and post-stenting physiological measurements were classified, according to the final IMR, as good responders to stenting (post-PPCI IMR <40 U) or partial/poor responders (post-PPCI IMR ≥40 U).

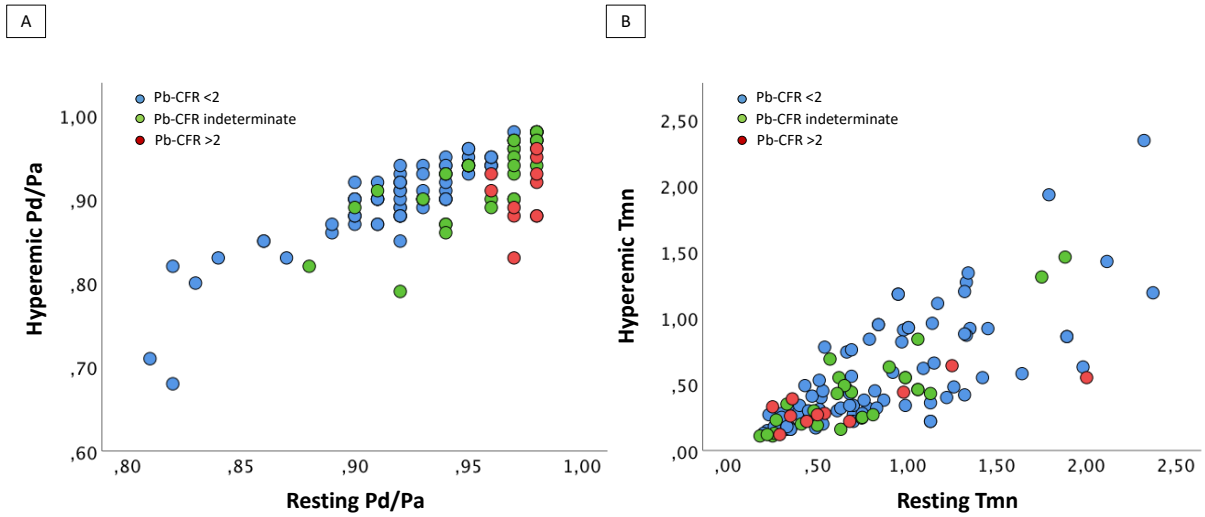
Repeat measurements of IMR and pb-CFR before and after stenting were available in 87 (58.8%) patients. Overall, IMR decreased significantly after stenting (from 44.0 [28.4-80.0] to 28.7 [16.7-50.6], p<0.001) **(Figure 2)**.

Similarly, a significant overall variation was observed in pb-CFR after stenting of the infarct-related artery. In particular, pre-stent pb-CFR was <2 in 88.5% of the cases, indeterminate in 9.2% and >2 in 2.3%. After stenting, pb-CFR was <2 in 67.8%, indeterminate in 23% and >2 in 9.2% of the cases (p<0.0001).

Fifty-four out of 87 (62%) patients were classified as good responders to stenting based on post-PPCI IMR <40 U **(Figure 2B)**. In this subgroup, IMR significantly decreased after stenting (36.5 [25.5-59.9] vs 19.1 [15.4-26.4], p<0.001). Consistently, pb-CFR improved significantly after stenting (pre-stent pb-CFR was <2 in 85.2%, indeterminate in 11.1% and >2 in 3.7% of the patients; post-stent pb-CFR was <2 in 61.1%, indeterminate in 25.9% and >2 in 13.0% of the cases [p=0.007]).

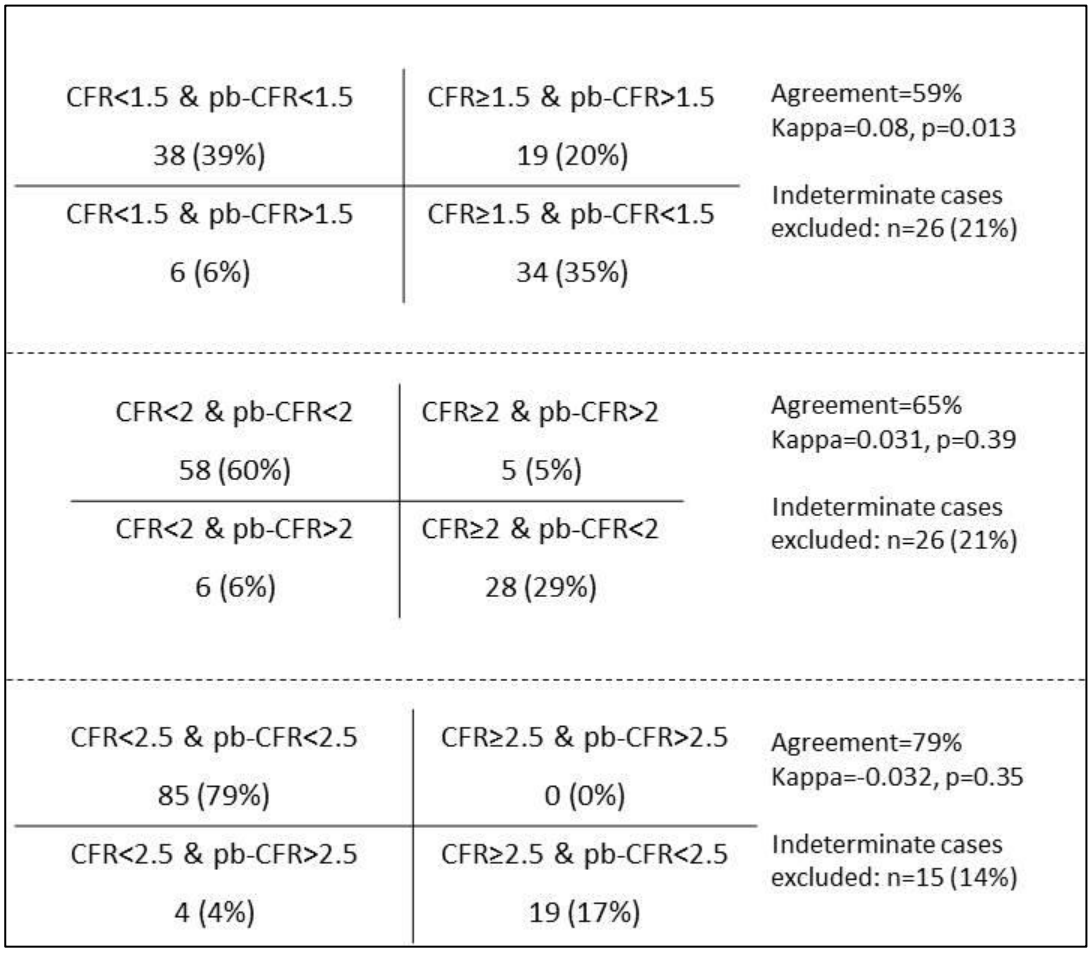
Thirty-three out of 87 (38%) patients were classified as partial or poor responders to stenting based on post-PPCI IMR ≥40 U **(Figure 2C)**. In this subgroup, IMR did not vary significantly after stenting (67.7 [44.5-97.5] vs 64.4 [45.9-71.9], p=ns). Similarly, pb-CFR did not improve significantly after stenting (pre-stent pb-CFR was <2 in 94.0%, indeterminate in 6.0% and >2 in 0% of the patients; post-stent pb-CFR was <2 in 78.8%, indeterminate in 18.2% and >2 in 3% of the cases [p=ns]).

Supplementary Table 4 summarises the cardiac MRI endpoints stratified according to microcirculatory response to stenting categorised according to post-stenting IMR < or ≥40 U.



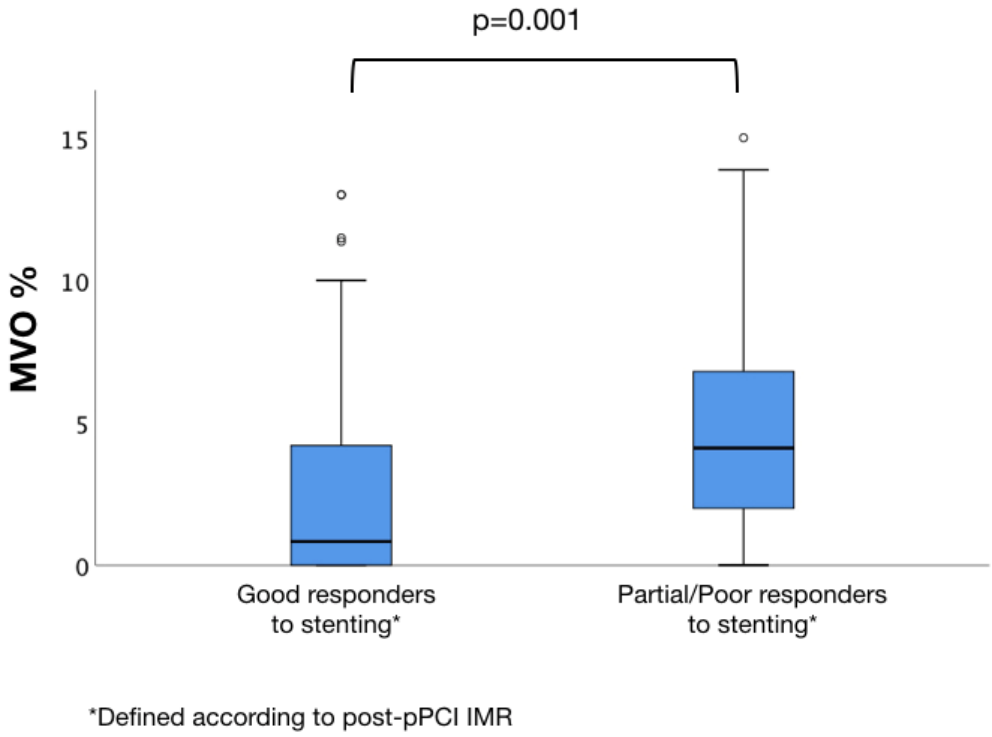
Supplementary Figure 1. Regression between resting and hyperaemic Pd/Pa and transit time.

A) Pd/Pa at rest is plotted versus Pd/Pa measured at maximal hyperaemia.
B) Transit time (Tmn) at rest is plotted versus Tmn at hyperaemia.



Supplementary Figure 2. Agreement between pb-CFR and CFR_{thermo}.

The agreement between pb-CFR and CFR_{thermo} has been tested using Cohen's kappa coefficient and % agreement.



Supplementary Figure 3. Difference in microvascular obstruction between good responders and partial/poor responders to stenting.

Patients categorised as good responders to stenting (post-PPCI IMR <40 U) presented significantly less microvascular obstruction (MVO) at 48-hour cardiac MRI compared with partial/poor responders (post-PPCI IMR ≥40 U).

Supplementary Table 1. Clinical and procedural characteristics of patients with STEMI stratified according to pre-stenting pb-CFR.

	pb-CFR <2	pb-CFR indeterminate	pb-CFR >2	*p*-value
Clinical data	**n=89**	**n=18**	**n=5**	
Age, years	61 (54-67)	61 (46-68)	68 (61-74)	0.26
Sex, male	83 (93)	12 (67)	5 (100)	0.003
Hypertension	46 (52)	12 (67)	5 (100)	0.06
Dyslipidaemia	40 (45)	8 (44)	1 (20)	0.55
Diabetes	36 (40)	8 (44)	2 (40)	0.95
Smoking	43 (48)	10 (56)	0 (0)	0.08
eGFR	95.7 (82.0-106-8)	87.2 (77.7-101.0)	77.7 (65.7-89.2)	0.03
Pain-to-balloon time, min	190 (129-360)	130 (91-171)	231 (157-478)	0.006
Procedural data				
LAD (culprit)	57 (64)	3 (17)	0 (0)	<0.001
Baseline TIMI flow 3	7 (7.9)	2 (11)	1 (20)	0.45
Thrombus score (4&5)	52 (58)	9 (50)	4 (80)	0.48
Thrombus aspiration	59 (66)	13 (72)	3 (60)	0.84
Predilatation	87 (98)	17 (94)	5 (100)	0.68
Total stent length, mm	28 (20-38)	28 (20-42)	18 (13-30)	0.19
Total stent diameter, mm	3.5 (3.0-3.7)	4.0 (3.0-4.0)	3.5 (3.5-4.25)	0.14
Post-dilatation	66 (74)	14 (78)	4 (80)	0.92
Final TIMI flow 3	79 (89)	15 (83)	5 (100)	0.21
ST-resolution	62 (70)	12 (67)	4 (80)	0.85
Final MBG >2	69 (77)	12 (67)	5 (100)	0.28
CMR imaging at 48 hrs				
EDV, ml	170.5 (142.0-193.7)	136.0 (104.0-165.2)	200.0 (138.0-220.5)	0.007
ESV, ml	90.0 (65.7-114.0)	58.0 (53.5-74.5)	104.0 (63.0-129.5)	0.003
LVEF%	49 (40-52)	54 (46-61)	48 (41-55)	0.078
SV, ml	78 (63-93)	70 (52-94)	78 (75-100)	0.36
AAR%	44 (36-53)	33 (26-44)	33 (28-45)	0.009
IS% at 48 hrs	28.6 (18.6-41)	21.3 (13.6-34.1)	14.7 (6.8-29.4)	0.10
MVO	2.0 (0.0-6.0)	0.0 (0.0-1.9)	1.0 (0.0-7.4)	0.04
CMR imaging at 6 months				
EDV, ml	171.5 (145.0-189.5)	140.0 (116.5-157.5)	156.0 (140.5-200.7)	0.03
ESV, ml	75.0 (57.0-100.0)	59.0 (39.5-79.0)	73.5 (52.7-101.0)	0.11
LVEF%	52 (43-61)	56 (49-63)	52 (46-66)	0.48
SV, ml	88 (72-100)	71 (61-90)	96 (72-101)	0.17
IS at 6 mo, %	22.3 (12.3-34.5)	16.8 (9.6-29.2)	14.3 (3.6-24.2)	0.28
Salvage, %	32.8 (18.2-50.0)	41.9 (24.2-56.9)	44.6 (16.4-80.2)	0.47

Supplementary Table 2. Intracoronary physiology of patients with STEMI stratified according to pre-stenting pb-CFR.

	pb-CFR <2	pb-CFR indeterminate	pb-CFR >2	*p*-value
Baseline Pd/Pa	0.82 (0.72-0.88)	0.93 (0.87-0.97)	0.93 (0.83-0.96)	<0.001
FFR	0.74 (0.62-0.83)	0.82 (0.66-0.92)	0.78 (0.64-0.91)	0.17
Delta PdPa-FFR	0.06 (0.02-0.11)	0.08 (0.04-0.18)	0.08 (0.03-0.25)	0.15
Pd (Hyp)	62 (52-73)	66 (46-70)	55 (48-70)	0.69
Tmn (Rest)	0.94 (0.64-1.39)	1.26 (0.88-1.59)	0.77 (0.21-1.10)	0.054
Tmn (Hyp)	0.78 (0.47-1.24)	0.99 (0.31-1.45)	0.37 (0.26-0.82)	0.44
CFR	1.20 (1.00-1.43)	1.31 (1.18-2.35)	1.00 (1.00-3.10)	0.055
IMR	45.9 (31.9-82.9)	54.7 (22.2-82.4)	17.9 (13.7-51.2)	0.05
IMR corrected	41.0 (27.0-78.9)	54.9 (22.5-79.7)	15.6 (9.7-46.1)	0.09
P wedge, mmHg	20 (16-27)	17 (13-19)	22 (18-25)	0.12
Lower pb	1.14 (1.04-1.22)	1.58 (1.49-1.71)	2.24 (2.02-2.61)	<0.001
Upper pb	1.30 (1.08-1.50)	2.50 (2.23-2.93)	5.00 (4.08-6.91)	<0.001

Supplementary Table 3. Procedural data of patients with STEMI stratified according to post-procedural pb-CFR.

	pb-CFR <2	pb-CFR indeterminate	pb-CFR >2	*p*-value
LAD (culprit)	67 (78)	14 (54)	3 (27)	0.001
Baseline TIMI flow 3	3 (4)	3 (11)	3 (27)	0.16
Thrombus score (4&5)	55 (64)	17 (65)	5 (45)	0.46
Thrombus aspiration	67 (78)	15 (58)	6 (54)	0.06
Predilatation	80 (93)	25 (95)	10 (91)	0.79
Total stent length, mm	24 (20-32)	24 (20-38)	24 (18-38)	0.99
Total stent diameter, mm	3.5 (3.0-3.5)	3.5 (3.0-4.0)	3.5 (3.0-4.0)	0.27
Post-dilatation	59 (69)	21 (81)	9 (82)	0.36
Final TIMI flow 3	74 (86)	23 (88)	10 (91)	0.87
ST-resolution	60 (70)	18 (69)	8 (73)	0.98
MBG	67 (78)	23 (88)	9 (82)	0.49

Supplementary Table 4. CMR endpoints according to microcirculatory response to stenting defined according to post-PPCI IMR ≥40 U.

	Good responders	**Partial/poor responders**	***p*-value**
AAR%	44.3 (34.1-52.0)	44.7 (36.9-55.0)	0.37
LVEF%	49.0 (43.0-54.0)	46.0 (39.0-51.0)	0.36
IS% 48 hrs	25.2 (15.6-34.2)	32.0 (21.4-43.2)	0.041
MVO, %	0.8 (0.0-4.6)	4.1 (1.8-7.0)	0.001
Haemorrhage, %	0.0 (0.0-4.5)	4.0 (0.0-12.0)	0.046
Salvage, %	40.7 (23.7-55.5)	21.8 (14.5-38.8)	0.011
IS% 6 mo	17.5 (9.5-25.9)	30.4 (24.3-41.4)	<0.0001

Supplementary Table 5. Comparison between post-PPCI pb-CFR, thermodilution-derived CFR and IMR in predicting CMR endpoints at 48 hours and 6 months after STEMI.

	pb-CFR <2	**pb-CFR >2**	***p*-value**	**CFR <2**	**CFR ≥2**	***p*-value**	**IMR ≥40**	**IMR <40**	***p*-value**
LVEF% (48 hrs)	46.5 (40.0-50.7)	48.0 (46.0-55.0)	0.13	46.5 (39.0-51.0)	47.0 (42.5-52.0)	0.67	45.0 (39.0-50.7)	47.0 (41.0-51.0)	0.67
AAR%	46.1 (37.0-55.6)	33.3 (27.1-40.2)	0.002	45.2 (34.5-53.8)	45.6 (37.0-56.1)	0.74	46.4 (38.0-56.1)	45.1 (34.0-52.0)	0.21
IS% (48 hrs)	28.7 (20.4-39.3)	15.5 (8.3-25.0)	0.003	28.8 (18.3-40.9)	25.2 (17.1-33.7)	0.22	32.4 (23.0-44.0)	25.0 (12.6-33.6)	0.002
MVO, %	2.0 (0.0-4.4)	0.0 (0.0-0.0)	0.001	1.8 (0.0-4.2)	0.9 (0.0-4.2)	0.37	3.7 (1.3-6.0)	0.5 (0.0-2.1)	<0.001
Haemorrhage, %	0.0 (0.0-3.5)	0.0 (0.0-2.2)	0.49	0.0 (0.0-3.0)	0.0 (0.0-4.0)	0.81	1.0 (0.0-1.0)	0.0 (0.0-1.0)	0.018
Salvage, %	34.5 (23.5-48.8)	42.9 (32.7-64.4)	0.16	32.6 (20.4-47.9)	38.8 (28.9-57.3)	0.06	27.8 (17.5-37.8)	42.0 (29.2-55.5)	<0.001
LVEF% (6 mo)	52.5 (43.0-60.0)	57.0 (55.5-65.0)	0.09	52.0 (42.0-59.0)	55.5 (50.5-61.0)	0.09	47.0 (37.7-57.5)	55.0 (49.0-60.5)	0.024
IS% (6 mo)	21.8 (13.3-30.3)	12.9 (5.5-21.8)	0.09	20.5 (12.6-35.2)	19.0 (16.0-26.7)	0.66	30.0 (21.4-37.7)	16.2 (8.9-22.8)	<0.001

AAR: myocardial area at risk; IS: infarct size; LVEF: left ventricle ejection fraction; MVO: microvascular obstruction

Supplementary Table 6. Comparison of areas under the curve (AUC) for pb-CFR (binary) and CFR in predicting CMR endpoints.

	Pre-stent			Post-stent		
	AUC (95% CI) pb-CFR	vs CFR	*p*-value	AUC (95% CI) pb-CFR	vs CFR	*p*-value
IS% (48 hrs)*	0.53 (0.42-0.64)	0.53 (0.42-0.63)	0.94	0.58 (0.47-0.68)	0.69 (0.58-0.78)	0.29
MVO, %**	0.52 (0.41-0.63)	0.53 (0.42-0.64)	0.87	0.63 (0.52-0.73)	0.62 (0.51-0.72)	0.87
Haemorrhage, %	0.50 (0.32-0.68)	0.58 (0.39-0.75)	0.46	0.53 (0.38-0.67)	0.55 (0.41-0.70)	0.80
IS% (6 mo)*	0.54 (0.42-0.67)	0.52 (0.39-0.64)	0.74	0.55 (0.43-0.66)	0.79 (0.68-0.88)	0.004

*For infarct size (IS) at 48 hours and 6 months the cut-off value for the highest quartile was used to define the endpoint: IS% (48 hrs) ≥38.1% and IS% (6 months) ≥30.0%.
IS: infarct size; MVO: microvascular obstruction

Supplementary Table 7. Comparison between different cut-offs for pb-CFR in discriminating major cardiac MRI endpoints.

	pb-CFR (cut-off=2)		pb-CFR (cut-off=1.5)		pb-CFR (cut-off=2.5)	
	AUC (95% CI)	*p*-value	AUC (95% CI)	*p*-value	AUC (95% CI)	*p*-value
MVO, %**	0.37 (0.24-0.50)	0.045	0.37 (0.25-0.498)	0.047	0.46 (0.33-0.59)	0.50
IS% (6 months)*	0.45 (0.31-0.60)	0.55	0.41 (0.27-0.55)	0.23	0.48 (0.35-0.62)	0.81

*For infarct size (IS) at 6 months the cut-off value for the highest quartile was used to define the endpoint: IS% (6 months) ≥30.0%.
**The presence versus absence of MVO at 48 hours cardiac MRI has been used to define the endpoint MVO.
IS: infarct size; MVO: microvascular obstruction