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

Running title: pressure-bounded coronary flow reserve in STEMI

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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.

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 cardiovascular magnetic resonance imaging at 48-hours and 6-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 index of microcirculatory resistance (IMR) was significantly different across the pb-CFR subgroups. Similarly, significant differences were observed in microvascular obstruction (MVO), myocardium area-at-risk and 48-hours infarct-size (IS). A trend towards lower 6-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 and 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.

Keywords

STEMI; Fractional flow reserve; Non-invasive imaging; Other imaging modalities; MRI

Condensed abstract

Microvascular dysfunction is frequently observed in STEMI patients and is associated with suboptimal myocardial reperfusion. The value of pressure-bounded coronary flow reserve (pb-CFR) in assessing microvascular function in STEMI has not been determined.

Pb-CFR was measured in 148 STEMI patients undergoing PPCI and was found to be impaired (pb-CFR<2) in 70% of the cases. Pb-CFR was associated with the extent of microvascular impairment defined according to IMR or as the presence of MVO at CMR. pb-CFR was superior to thermodilution-derived CFR in predicting MVO but was inferior diagnostic performance to IMR in predicting the infarct size and MVO.

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 catheterization 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 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 6 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 Oxford Acute Myocardial Infarction (OxAMI) Study (REC number 10/H0408/24). The study protocol was approved by the local ethics committee and conducted in accordance with the Declaration of Helsinki.

Details of the OxAMI study have been previously described[1]. The diagnosis of STEMI required chest pain lasting at least 30 min, within 12 h from onset of symptoms, and ST-segment elevation of >2 mm (0.2 mV) in at least 2 contiguous leads on ECG. Symptom duration >12 hours, presence of severe hemodynamic 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 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 previously described[9].

Coronary angiography

Coronary flow was graded using the standard 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 hyperemia as previously described[1] using a coronary PressureWire (Abbott - St. Jude Medical, St. Paul, Minnesota). When measured before stent implantation, IMR value was corrected for collateral flow by coronary wedge pressure (Pw), measured during prolonged balloon inflation, as follows

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

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

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

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:

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

where ΔP is the pressure gradient across the lesion, Q is coronary flow, *f* is friction coefficient and *s* is 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 $\sqrt{\Delta P\ during\ hyperemia})/\sqrt{\Delta P\ at\ rest}$, 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 hyperemia 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:

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

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

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

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 image protocol and analysis

CMR was performed using a 3.0 Tesla magnetic resonance scanner (either MAGNETOM TIM Trio or MAGNETOM Verio; Siemens Healthcare, Erlangen, Germany) within 48 hours after PPCI and at 6-month follow-up. CMR protocol has been previously reported[12] and is described in detail in the supplementary material.

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 t test used for comparisons. Nonparametric distributions are reported as median (interquartile range), and the Mann-Whitney test used for unpaired data. Difference between groups were compared with one-way ANOVA or Kruskal-Wallis as appropriate. The Fisher exact chi-square test was used for binary variables. Correlation between variables was tested by Spearman-rho method.

Choen'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% (48h)≥38.1% and IS% (6months) ≥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 non-parametric Wilcoxon's test and variations in pb-CFR were assessed using McNemar's test. Patients were classified in good responders or partial/poor responders to stenting according to the final IMR value ≥40U, as previously described[1].

For regression and ROC curve analysis, Pb-CFR was used 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 (Mariakerke, Belgium). All tests were 2-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. 87 patients had both pre- and post-stenting pb-CFR data. was CMR available in all the cases (100%) at 48 hours and in 109 (74%) patients at 6 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 AAR% (Figure 1). Moreover, a trend towards smaller infarct size at 48 hours and 6 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 ($AUC_{IPB-CFR}$=0.53 [0.42-0.64] vs AUC_{IMR}=0.63 [0.52-0.73], p=0.12), the final infarct size at 6 month (AUC_{PB-CFR}=0.54 [0.42-0.67] vs AUC_{IMR}=0.64 [0.52-0.76]; p=0.17) and the presence of intramyocardial hemorrhage (AUC_{PB-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).

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 toward lower frequency of LAD as culprit vessel, higher TIMI flow post-stenting and lower peak troponin level.

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 material). 54/87 (62%) patients were classified as good responders to stenting according to final IMR value <40U. In this subgroup pb-CFR significantly improved at completion of PCI (p=0.007; Figure 2B; Supplementary material 8). Conversely no significant variations in pb-CFR were observed in patients categorized as partial or poor responders to stenting according to final IMR≥40U (Figure 2C). Notably, good responders to stenting presented smaller IS% at 48 hours and 6 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 6 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 and Supplementary Table 5-6).

No significant differences were observed in the LV ejection fraction across pb-CFR groups 6 months after STEMI (Figure 3).

Post-PPCI pb-CFR was significantly associated with the presence of MVO (Table 1 and 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 hemorrhage and the extent of IS% at 48 hours and 6 months (Table 3 and Figure 3). Using alternate cutoffs 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 (please see 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 catheterization laboratory using IMR and with MVO measured using ~~cardiac MRI~~ CMR. In particular, pb-CFR was able to identify a subgroup of patients (~~lower~~ 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 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 apparent satisfactory angiographic result in the epicardial vessel[1]. This is mainly related to microvascular injury after PPCI and it has been associated with larger infarct size, adverse LV remodeling 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 catheterization laboratory. In particular IMR 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 and 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 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] and 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 "indeterminate" in 21.1% of the cases at completion of PPCI. Notably the proportion of cases categorized as "indeterminate" is lower than what 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 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 6 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 endpoint. 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 $\sqrt{\Delta P}$ 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 previously described. 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 hyperemic 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-CF 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 it 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.

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Appendix. Study collaborators

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2. Sam Dawkins, MD, PhD (Oxford Heart Centre, NIHR Biomedical Research Centre, Oxford University Hospitals, Oxford, UK)

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.

References

1. De Maria GL, Cuculi F, Patel N, Dawkins S, Fahrni G, Kassimis G, Choudhury RP, Forfar JC, Prendergast BD, Channon KM, Kharbanda RK and Banning AP. How does coronary stent implantation impact on the status of the microcirculation during primary percutaneous coronary intervention in patients with ST-elevation myocardial infarction? *Eur Heart J*. 2015;36:3165-77.

2. De Maria GL, Alkhalil M, Wolfrum M, Fahrni G, Borlotti A, Gaughran L, Dawkins S, Langrish JP, Lucking AJ, Choudhury RP, Porto I, Crea F, Dall'Armellina E, Channon KM, Kharbanda RK and Banning AP. Index of Microcirculatory Resistance as a Tool to Characterize Microvascular Obstruction and to Predict Infarct Size Regression in Patients With STEMI Undergoing Primary PCI. *JACC Cardiovasc Imaging*. 2019;12:837-848.

3. Carrick D, Haig C, Ahmed N, Carberry J, Yue May VT, McEntegart M, Petrie MC, Eteiba H, Lindsay M, Hood S, Watkins S, Davie A, Mahrous A, Mordi I, Ford I, Radjenovic A, Oldroyd KG and Berry C. Comparative Prognostic Utility of Indexes of Microvascular Function Alone or in Combination in Patients With an Acute ST-Segment-Elevation Myocardial Infarction. *Circulation*. 2016;134:1833-1847.

4. Fahrni G, Wolfrum M, De Maria GL, Cuculi F, Dawkins S, Alkhalil M, Patel N, Forfar JC, Prendergast BD, Choudhury RP, Channon KM, Banning AP and Kharbanda RK. Index of Microcirculatory Resistance at the Time of Primary Percutaneous Coronary Intervention Predicts Early Cardiac Complications: Insights From the OxAMI (Oxford Study in Acute Myocardial Infarction) Cohort. *J Am Heart Assoc*. 2017;6. pii: e005409. doi: 10.1161/JAHA.116.005409

5. Fearon WF, Farouque HM, Balsam LB, Caffarelli AD, Cooke DT, Robbins RC, Fitzgerald PJ, Yeung AC and Yock PG. Comparison of coronary thermodilution and Doppler velocity for assessing coronary flow reserve. *Circulation*. 2003;108:2198-200.

6. Zimmermann FM, Pijls NHJ, De Bruyne B, Bech GJ, van Schaardenburgh P, Kirkeeide RL, Gould KL and Johnson NP. What can intracoronary pressure measurements tell us about flow

reserve? Pressure-Bounded coronary flow reserve and example application to the randomized DEFER trial. *Catheter Cardiovasc Interv*. 2017;90:917-925.

7. Wijntjens GWM, van Lavieren MA, van de Hoef TP, Echavarria-Pinto M, Meuwissen M, Stegehuis VE, Murai T, Escaned J and Piek JJ. Pressure-derived estimations of coronary flow reserve are inferior to flow-derived coronary flow reserve as diagnostic and risk stratification tools. *Int J Cardiol*. 2019;279:6-11.

8. Ahn JM, Zimmermann FM, Johnson NP, Shin ES, Koo BK, Lee PH, Park DW, Kang SJ, Lee SW, Kim YH, Lee CW, Park SW, Pijls NHJ and Park SJ. Fractional flow reserve and pressure-bounded coronary flow reserve to predict outcomes in coronary artery disease. *Eur Heart J*. 2017;38:1980-1989.

9. Sianos G, Papafaklis MI and Serruys PW. Angiographic thrombus burden classification in patients with ST-segment elevation myocardial infarction treated with percutaneous coronary intervention. *J Invasive Cardiol*. 2010;22:6B-14B.

10. Group TS. The Thrombolysis in Myocardial Infarction (TIMI) trial. Phase I findings. *N Engl J Med*. 1985;312:932-6.

11. van 't Hof AW, Liem A, Suryapranata H, Hoorntje JC, de Boer MJ and Zijlstra F. Angiographic assessment of myocardial reperfusion in patients treated with primary angioplasty for acute myocardial infarction: myocardial blush grade. Zwolle Myocardial Infarction Study Group. *Circulation*. 1998;97:2302-6.

12. Scarsini R, De Maria GL, Borlotti A, Kotronias RA, Langrish JP, Lucking AJ, Choudhury RP, Ferreira VM, Ribichini F, Channon KM, Kharbanda RK and Banning AP. Incremental value of coronary microcirculation resistive reserve ratio in predicting the extent of myocardial infarction in patients with STEMI. Insights from the Oxford Acute Myocardial Infarction (OxAMI) study. *Cardiovasc Revasc Med*. 2019. doi: 10.1016/j.carrev.2019.01.022.

13. De Maria GL, Alkhalil M, Borlotti A, Wolfrum M, Gaughran L, Dall'Armellina E, Langrish JP, Lucking AJ, Choudhury RP, Kharbanda RK, Channon KM and Banning AP. Index of microcirculatory resistance-guided therapy with pressure-controlled intermittent coronary sinus occlusion improves coronary microvascular function and reduces infarct size in patients with ST-elevation myocardial infarction: the Oxford Acute Myocardial Infarction - Pressure-controlled Intermittent Coronary Sinus Occlusion study (OxAMI-PICSO study). *EuroIntervention*. 2018;14:e352-e359.

14. van Kranenburg M, Magro M, Thiele H, de Waha S, Eitel I, Cochet A, Cottin Y, Atar D, Buser P, Wu E, Lee D, Bodi V, Klug G, Metzler B, Delewi R, Bernhardt P, Rottbauer W, Boersma E, Zijlstra F and van Geuns RJ. Prognostic value of microvascular obstruction and infarct size, as measured by CMR in STEMI patients. *JACC Cardiovasc Imaging*. 2014;7:930-9.

15. Fearon WF, Low AF, Yong AS, McGeoch R, Berry C, Shah MG, Ho MY, Kim HS, Loh JP and Oldroyd KG. Prognostic value of the Index of Microcirculatory Resistance measured after primary percutaneous coronary intervention. *Circulation*. 2013;127:2436-41.

16. Fearon WF, Shah M, Ng M, Brinton T, Wilson A, Tremmel JA, Schnittger I, Lee DP, Vagelos RH, Fitzgerald PJ, Yock PG and Yeung AC. Predictive value of the index of microcirculatory resistance in patients with ST-segment elevation myocardial infarction. *J Am Coll Cardiol*. 2008;51:560-5.

17. De Maria GL, Alkhalil M, Wolfrum M, Fahrni G, Borlotti A, Gaughran L, Dawkins S, Langrish JP, Lucking AJ, Choudhury RP, Porto I, Crea F, Dall'Armellina E, Channon KM, Kharbanda RK and Banning AP. The ATI score (age-thrombus burden-index of microcirculatory resistance) determined during primary percutaneous coronary intervention predicts final infarct size in patients with ST-elevation myocardial infarction: a cardiac magnetic resonance validation study. *EuroIntervention*. 2017;13:935-943.

18. Akasaka T, Yamamuro A, Kamiyama N, Koyama Y, Akiyama M, Watanabe N, Neishi Y, Takagi T, Shalman E, Barak C and Yoshida K. Assessment of coronary flow reserve by coronary pressure measurement: comparison with flow- or velocity-derived coronary flow reserve. *J Am Coll Cardiol*. 2003;41:1554-60.

19. Shalman E, Barak C, Dgany E, Noskowitcz H, Einav S and Rosenfeld M. Pressure-based simultaneous CFR and FFR measurements: understanding the physiology of a stenosed vessel. *Comput Biol Med*. 2001;31:353-63.

Figure legends

Figure 1. Upper panel: differences in IMR, MVO, myocardial AAR% and 48 hours IS% in patients stratified according to pre-stenting pb-CFR. *indicates overall p-value

Lower panel: differences in IMR, MVO, myocardial AAR% and 48 hours IS% in patients stratified according to pb-CFR measured at completion of PPCI. *indicates overall p-value

Figure 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 <40U) or partial/poor responders (post-PPCI IMR ≥40U). Pb-CFR improved significantly good responders but not in partial/poor responders to stenting.

Figure 3. Diagnostic accuracy of physiological indices in predicting the final infarct size at 6 months after STEMI. IMR and CFRthermo 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 6 months was observed for patients with post-PPCI pb-CFR>2. Conversely, no difference in LV ejection fraction (LVEF%) was observed between the groups.

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

	PB-CFR <2	PB-CFR indeterminate	PB-CFR >2	p-value
Clinical data	*n=86*	*n=26*	*n=11*	
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
Dyslipedemia	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/1.73m^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 h				
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 48h	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 m, %	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

	PB-CFR <2	PB-CFR indeterminate	PB-CFR >2	p-value
Post-Stenting				
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
LowerPB	1.10(1.00-1.22)	1.53(1.41-1.67)	2.45(2.01-2.83)	<0.001
UpperPB	1.22(1.00-1.45)	2.33(2.00-2.87)	6.00(4.00-8.00)	<0.001

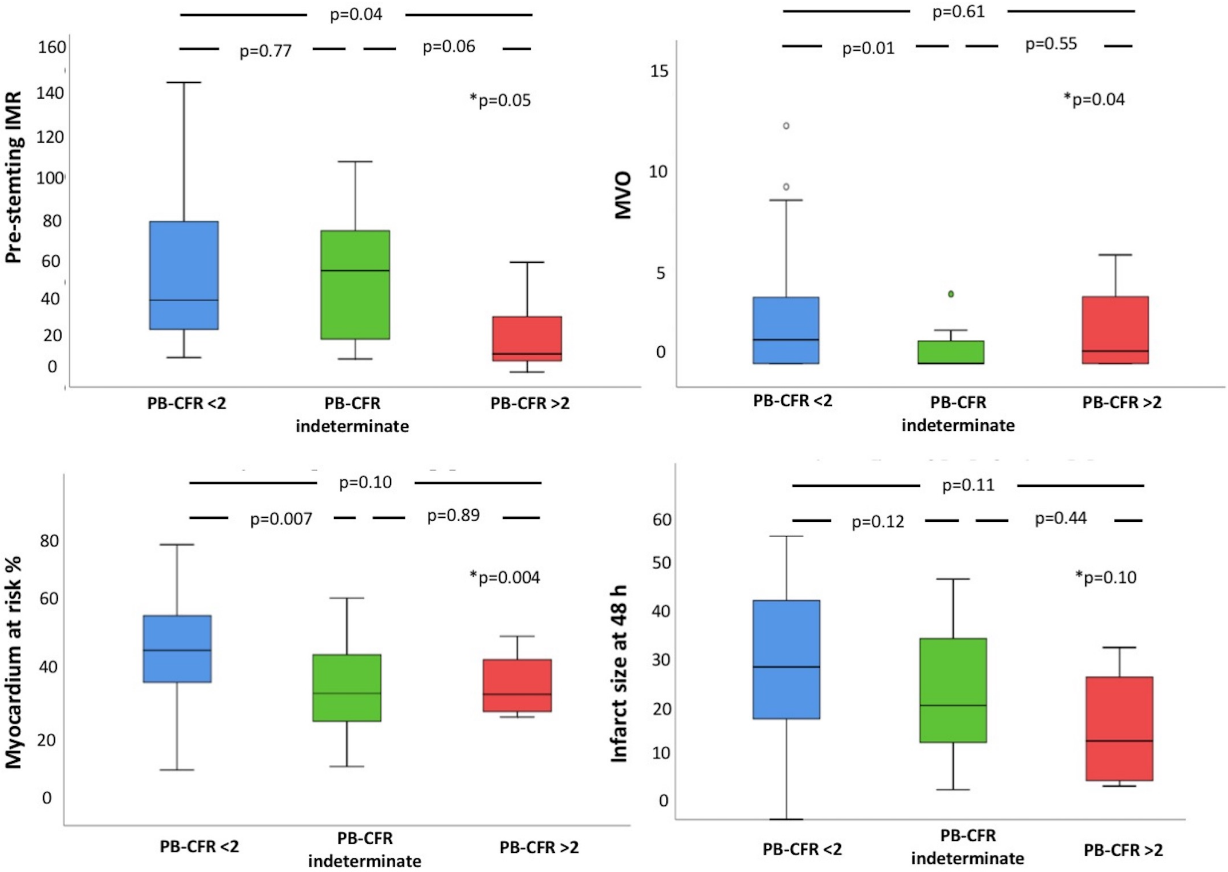
Table 3. Regression analysis for pb-CFR, CFR and IMR in predicting physiological and CMR endpoints						
	Pb-CFR		**CFR**		**IMR**	
	OR (95%CI)	**p-value**	**OR (95%CI)**	**p-value**	**OR (95%CI)**	**p-value**
IS% (48h)*	0.93 (0.32-2.66)	0.89	0.75 (0.45-1.27)	0.29	1.01 (1.00-1.02)	0.022
MVO**	0.08 (0.02-0.42)	0.003	0.71 (0.48-1.05)	0.09	1.02 (1.01-1.03)	0.008
Hemorrhage%	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% (6months)*	0.92 (0.29-2.91)	0.89	0.54 (0.27-1.06)	0.07	1.02 (1.01-1.03)	0.017

IS, infarct size; MVO, microvascular obstruction.

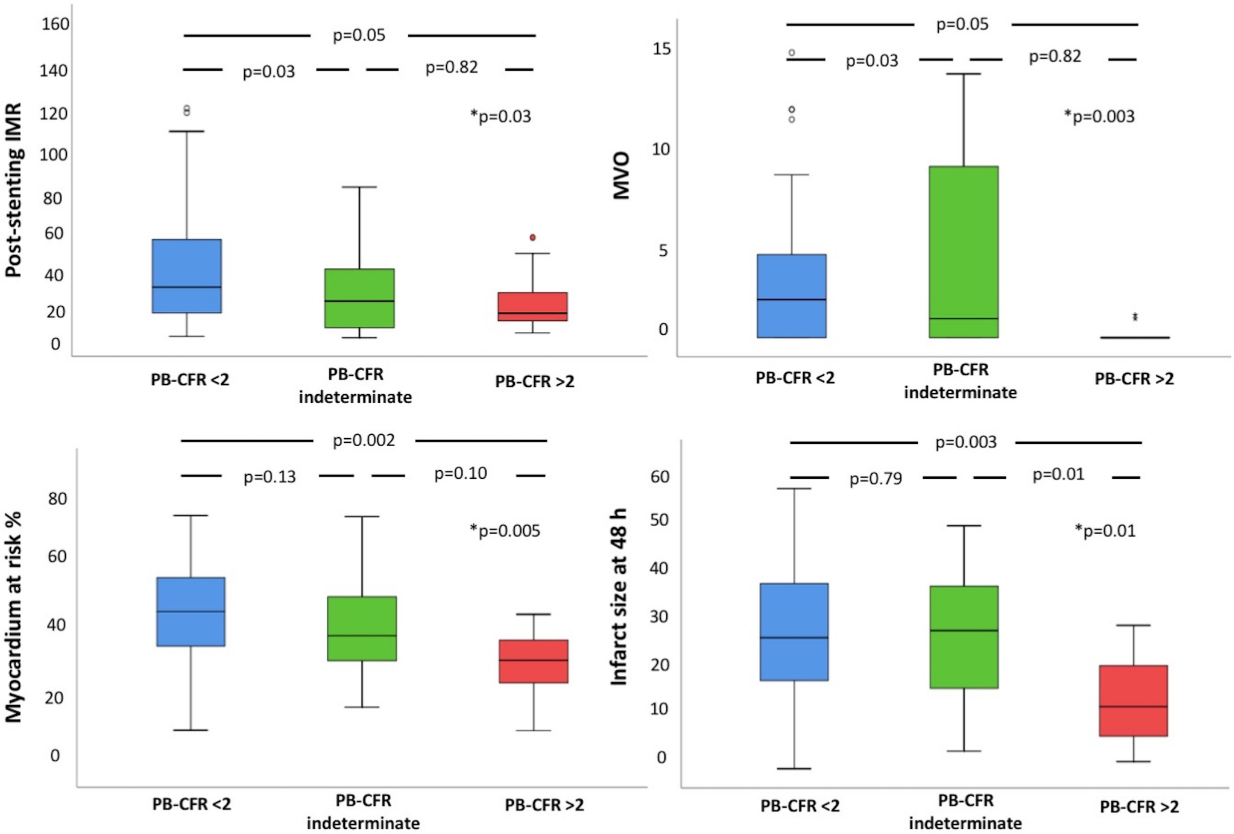
*For infarct size (IS) at 48 hours and 6 months the cut-off value for the highest quartile was used to define the endpoint: IS% (48h)≥38.1% and IS% (6months) ≥30.0%

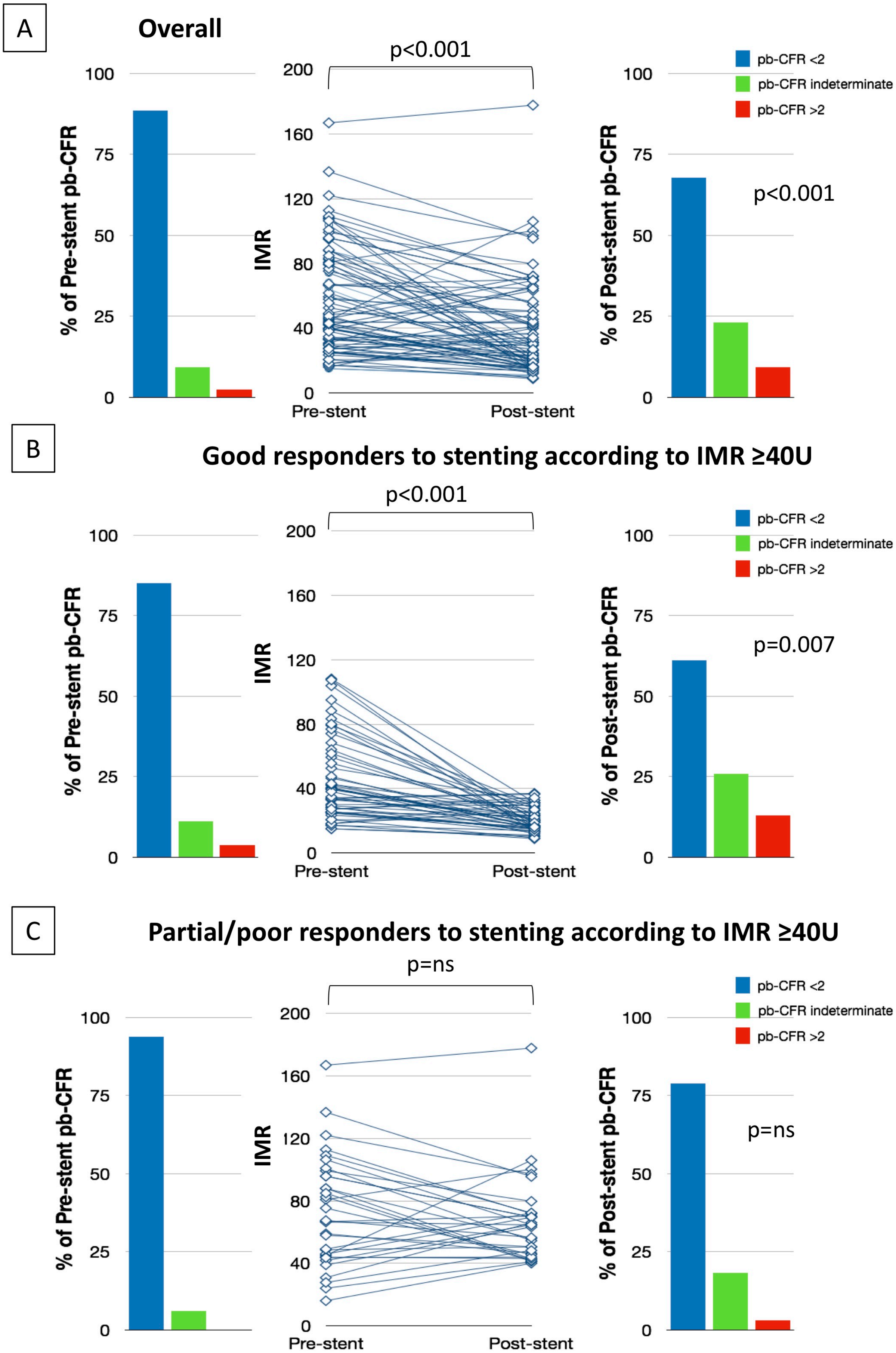
**The presence vs. absence of MVO at 48 hours CMRhas been used to define the endpoint MVO.

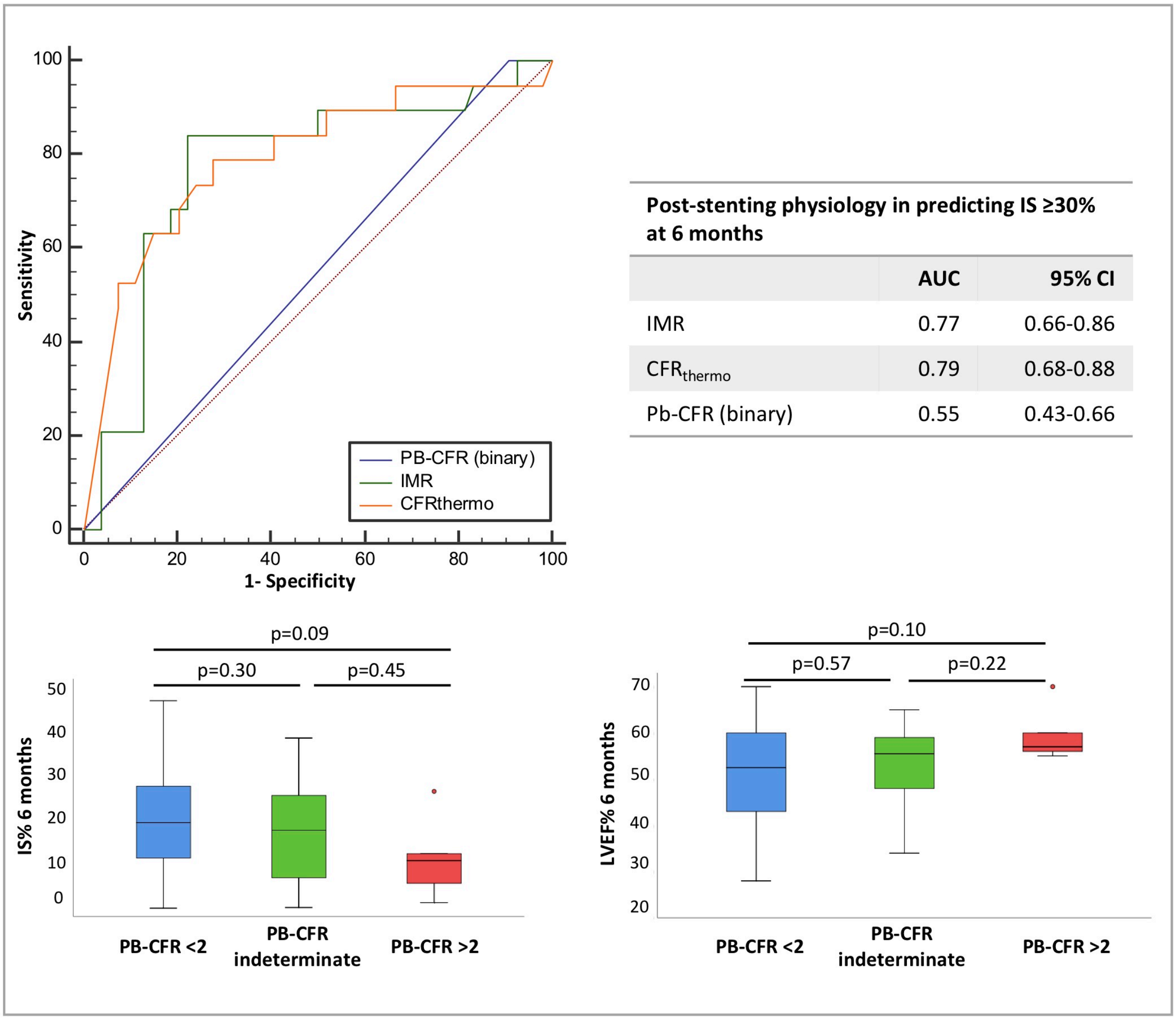
Pre-stenting



Post-stenting




A
Overall
100
75
50
25
0
% of Pre-stent pb-CFR
p<0.001
200
160
120
80
40
0
IMR
Pre-stent
Post-stent
% of Post-stent pb-CFR
p<0.001
pb-CFR <2
pb-CFR indeterminate
pb-CFR >2
B
Good responders to stenting according to IMR ≥40U
p<0.001
p=0.007
C
Partial/poor responders to stenting according to IMR ≥40U
p=ns
p=ns



Post-stenting physiology in predicting IS ≥30% at 6 months

	AUC	95% CI
IMR	0.77	0.66-0.86
CFR_{thermo}	0.79	0.68-0.88
Pb-CFR (binary)	0.55	0.43-0.66

Supplementary material

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

1. Cardiovascular magnetic resonance (CMR) protocol

CMR was performed using a 3.0 Tesla magnetic resonance scanner (either MAGNETOM TIM Trio or MAGNETOM Verio; Siemens Healthcare, Erlangen, Germany) within 48 hours after PPCI and at 6-month follow-up.

Left ventricle (LV) volumes and ejection fraction (EF%) were assessed from steady state free precession images. The myocardial area at risk (AAR), defined as the myocardial tissue within the perfusion bed distally 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 degree 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 5 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 intra-myocardial hemorrhage was assessed on T2* 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 Steady State Free Precession (SSFP) for functional images, native Shortened Modified Look-Locker Inversion recovery (ShMOLLI) T1 mapping for area at risk characterization (1), T2* mapping and T2-weighted (T2-prepared SSFP) for intramyocardial hemorrhage assessment, and late gadolinium enhancement (LGE) for infarct size and MVO quantification.

Typical acquisition parameters for steady state free precession (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).

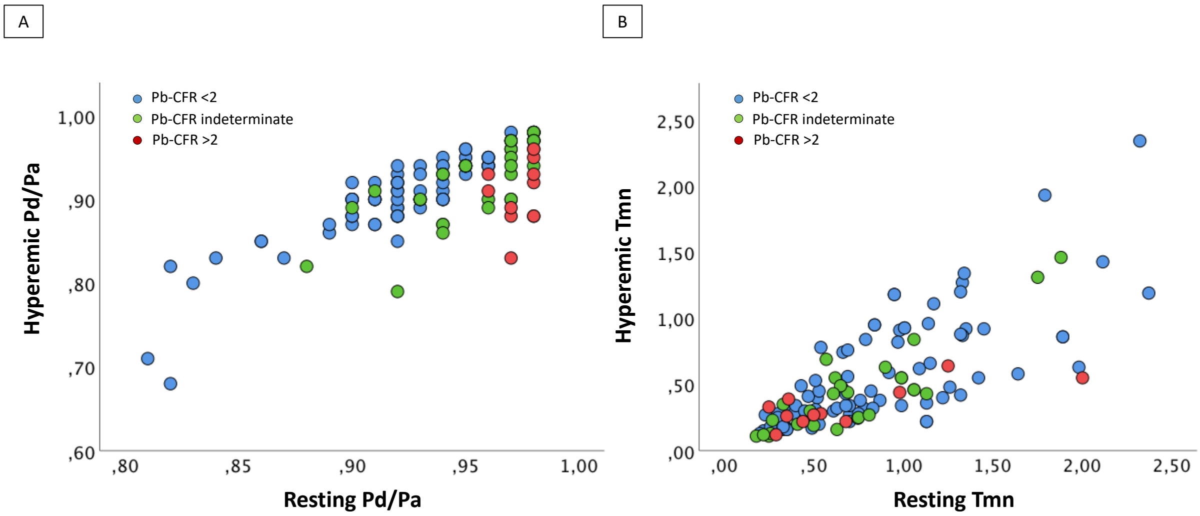
ShMOLLI T1 maps were generated from 5-7 SSFP images with variable inversion preparation S2 time as described previously. Typical acquisition parameters were: TE/TR = 1.07/2.14 msec, flip angle=35°, FOV=340×255mm, matrix size=192×144, 107 phase encoding steps, actual experimental voxel size = 1.8 × 1.8 × 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.

2. Supplementary Figure 1

In panel A, Pd/Pa at rest is plotted vs Pd/Pa measured at maximal hyperemia. In panel B, transit time (Tmn) at rest is plotted vs Tmn at hyperemia.



3. Supplementary Table 1

Table S1. Clinical and procedural characteristic 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
Dyslipidemia	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
Pre-dilatation	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 h				
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 48h	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 m, %	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

4. Supplementary Table 2

Supplementary Table 2. Intracoronary physiology of patients with STEMI stratified according 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
LowerPB	1.14(1.04-1.22)	1.58(1.49-1.71)	2.24(2.02-2.61)	<0.001
UpperPB	1.30(1.08-1.50)	2.50(2.23-2.93)	5.00(4.08-6.91)	<0.001

5. Supplementary Table 3

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
Pre-dilatation	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

6. 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.

CFR<1.5 & pb-CFR<1.5 38 (39%)	CFR≥1.5 & pb-CFR>1.5 19 (20%)	Agreement=59% Kappa=0.08, p=0.013
CFR<1.5 & pb-CFR>1.5 6 (6%)	CFR≥1.5 & pb-CFR<1.5 34 (35%)	Indeterminate cases excluded: n=26 (21%)

CFR<2 & pb-CFR<2 58 (60%)	CFR≥2 & pb-CFR>2 5 (5%)	Agreement=65% Kappa=0.031, p=0.39
CFR<2 & pb-CFR>2 6 (6%)	CFR≥2 & pb-CFR<2 28 (29%)	Indeterminate cases excluded: n=26 (21%)

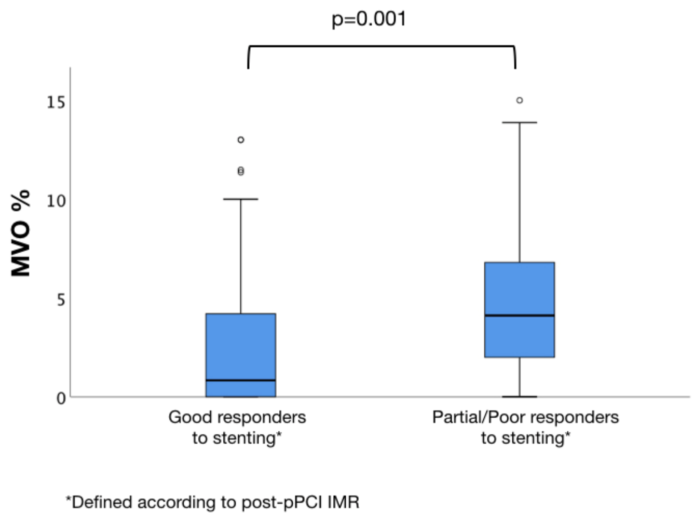
CFR<2.5 & pb-CFR<2.5 85 (79%)	CFR≥2.5 & pb-CFR>2.5 0 (0%)	Agreement=79% Kappa=-0.032, p=0.35
CFR<2.5 & pb-CFR>2.5 4 (4%)	CFR≥2.5 & pb-CFR<2.5 19 (17%)	Indeterminate cases excluded: n=15 (14%)

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

Table S4. 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% 48h	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
Hemorrhage%	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% 6mo	17.5(9.5-25.9)	30.4(24.3-41.4)	<0.0001

8. Supplementary Figure 3

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



9. Supplementary Table 5.

Table S5. 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% (48h)	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% (48h)	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
Hemorrhage%	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% (6mo)	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% (6mo)	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

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

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

Table S6. 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% (48h)*	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
Hemorrhage%	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% (6m)*	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

IS, infarct size; MVO, microvascular obstruction.

*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% (48h)≥38.1% and IS% (6months) ≥30.0%

11. Supplementary Table 7.

Supplemental Table S7. Comparison between different cutoffs 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% (6months)*	0.45 (0.31-0.60)	0.55	0.41 (0.27-0.55)	0.23	0.48 (0.35-0.62)	0.81

IS, infarct size; MVO, microvascular obstruction.

*For infarct size (IS) at 6 months the cut-off value for the highest quartile was used to define the endpoint: IS% (6months) ≥30.0%

**The presence vs. absence of MVO at 48 hours cardiac MRI has been used to define the endpoint MVO.

12. 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 <40U) or partial/poor responders (post-PPCI IMR ≥40U).

Repeated measurements of IMR and pb-CFR before and after stenting were available in 87 (58.8%). 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).

54 out of 87 (62%) of the patients were classified as good responders to stenting based on post-pPCI IMR <40U (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 significantly improved 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]).

33 out of 87 (38%) of the patients were classified as partial or poor responders to stenting based on post-pPCI IMR ≥40U (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 significantly improve 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]).

Table S4 summarizes the cardiac MRI endpoints stratified according to microcirculatory response to stenting categorized according to post-stenting IMR < or ≥40 U.