

Original article

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.

Running title: Resistive reserve ratio in STEMI

Roberto Scarsini¹ MD*, Giovanni Luigi De Maria¹ MD*, Alessandra Borlotti^{1,3} PhD, Rafail A. Kotronias¹ MB ChB, Jeremy P. Langrish¹ MD PhD, Andrew J. Lucking¹ MD PhD, Robin P. Choudhury^{2,3} DM FRCP, Vanessa M. Ferreira MD DPhil^{1,4}, Keith M. Channon¹ MD FRCP, Rajesh K. Kharbanda¹ MD PhD, Adrian P. Banning¹ MBBS MD.

1. Oxford Heart Centre, NIHR Biomedical Research Centre, Oxford University Hospitals, Oxford, UK
2. Acute Vascular Imaging Centre, Radcliffe Department of Medicine, University of Oxford, Oxford, UK
3. Division of Cardiovascular Medicine, BHF Centre of Research Excellence, University of Oxford, Oxford UK.
4. Oxford Centre for Clinical Magnetic Resonance Research, Division of Cardiovascular Medicine, Radcliffe Department of Medicine, University of Oxford, Oxford UK.

*Joint first author: these authors equally contributed to the manuscript

Disclosures: None of the authors has conflicts of interest regarding this study.

Word count: 4932 (including Abstract, text, references, figure legends and tables)

Corresponding author:

Professor Adrian Banning
Oxford Heart Centre
Oxford University Hospitals
Headley Way, Oxford
OX3 9DU
United Kingdom
adrian.banning@ouh.nhs.uk

ABSTRACT

Aims. Resistive reserve ratio (RRR) is a novel index that expresses the ratio between basal and hyperemic microcirculatory resistance. We sought to compare the performance of RRR, coronary flow reserve (CFR) and index of microcirculatory resistance (IMR) in predicting the extent of infarct size (IS) after ST-elevation myocardial infarction.

Methods and Results. Thermodilution parameters were measured after primary percutaneous coronary intervention (PPCI) in 45 patients. In 30(67%) cases pre-stenting measurements were also performed to assess the effect of PPCI on myocardial reperfusion, defined by CFR. Cardiovascular magnetic resonance (CMR) was performed at 48-hours to assess area-at-risk (AAR), microvascular obstruction (MVO) and IS. CMR was repeated at 6 months in 39/45 patients.

RRR ($AUC_{RRR}=0.85, CI:0.71-0.99$) performed better compared to CFR ($AUC_{CFR}=0.67, CI:0.48-0.86$) and IMR ($AUC_{IMR}=0.70, CI:0.52-0.88$) in predicting IS% at 6-months.

Patients with impaired RRR showed larger acute-IS% ($27.4[14.5-42.5]$ vs $15.4[8.3-26]$, $p=0.018$), MVO% ($3.44[0-5.97]$ vs $0[0-0.89]$, $p=0.026$), AAR% ($43[35-52]$ vs $34[25-46]$, $p=0.03$) and 6-months-IS% ($22.7[10.2-35]$ vs $8.8[6.9-12.3]$, $p=0.006$), higher rate of adverse remodeling (22.2% vs 0% , $p=0.04$) and lower myocardial salvage index (34% [$22-8-59.2$ vs 53.2% [$37.7-71$], $p=0.032$) compared with other patients.

Furthermore, RRR but not IMR or CFR resulted independently associated with 6-months-IS%.

CFR (1.48 ± 0.87 vs 1.47 ± 0.61 , $p=0.94$) did not improve after PPCI in patients with impaired RRR, whereas it improved significantly in other patients (CFR: 1.37 ± 0.43 vs 1.93 ± 0.49 , $p=0.018$).

Conclusions. Patients with post-PPCI impaired RRR were more likely to have suboptimal myocardial reperfusion and larger IS at follow-up. RRR may offer incremental prognostic value compared with other thermodilution-derived indices.

Key words:

ST-elevation myocardial infarction; Index of microvascular resistance; Coronary flow reserve; Resistive reserve ratio; Cardiovascular magnetic resonance.

CONDENSED ABSTRACT

Patients with ST-myocardial infarction (STEMI) underwent intracoronary physiological assessment before and immediately after stenting. The presence of microvascular obstruction and the extent of myocardial injury was tested with cardiovascular magnetic resonance at 48 hours and 6 months. Resistive reserve ratio (RRR) resulted superior compared with index of microvascular resistance (IMR) and coronary flow reserve (CFR) in predicting the final infarct size at 6-months. Moreover, patients with post-stenting impaired RRR presented worse myocardial reperfusion compared with other patients, with lower CFR and higher IMR values after primary percutaneous coronary intervention.

1 INTRODUCTION

2 Prompt restoration of blood flow in the infarct-related artery by primary percutaneous coronary
3 intervention (PPCI) is the standard of care for patients presenting with ST-elevation myocardial
4 infarction (STEMI)(1).

5 However, coronary microvascular dysfunction and consequent suboptimal myocardial reperfusion is
6 still observed in STEMI patients despite apparent satisfactory post-procedural angiographic result in
7 the epicardial vessel. This is secondary to microvascular injury after PPCI and it has been associated
8 with larger infarct size (IS), adverse left ventricle remodeling and increased risk of heart failure and
9 cardiovascular mortality (2).

10 ~~To improve the clinical outcomes in STEMI,~~ Identification of STEMI patients who are likely to
11 experience suboptimal reperfusion ~~will enable appropriate-is required-to-allow~~ application of adjunctive
12 or alternative therapeutic strategies to further improve clinical outcomes (3, 4).

13 Thermodilution-derived parameters have been proposed for the assessment of the coronary
14 microcirculation in STEMI patients, ~~and they typically include namely~~ the index of microcirculatory
15 resistance (IMR), the coronary flow reserve (CFR), and the resistive reserve ratio (RRR)(5-7).

16 ~~However, it is not clear which parameter best describes coronary microvascular status after STEMI and~~
17 ~~can best predict the extent of myocardial injury at follow-up.~~

18 Compared to the well studied IMR and CFR, RRR is a novel index derived as the ratio between basal
19 and hyperemic microcirculatory resistance, and it describes the ability of the coronary microcirculation
20 to vary its resistance via vasodilation in response to adenosine.

21 The ability of RRR to acutely depict microvascular dysfunction in STEMI patients has already been
22 reported (5). Notably, the prognostic value of RRR and its performance in identifying of STEMI
23 patients at the highest risk of suboptimal myocardial reperfusion after PPCI has not been assessed.

1 In this retrospective analysis of the Oxford Acute Myocardial Infarction (OxAMI) study, we sought to
2 evaluate and compare the **different** performance of CFR, IMR and RRR, measured immediately after
3 PPCI, **in predicting the extent of infarct size (IS) at 6 months in STEMI patients.**
4

5 **METHODS**

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

9 Details of the OxAMI study have been previously described(3). The diagnosis of STEMI required chest
10 pain lasting longer than 30 min, within 12 h from onset of symptoms, and ST-segment elevation of
11 >2 mm (0.2 mV) in at least 2 contiguous leads on ECG. Symptom duration >12 hours, presence of
12 severe hemodynamic instability, severe left main disease, contraindications to adenosine infusion,
13 balloon angioplasty without stent implantation and general contraindications to cardiovascular
14 magnetic resonance (CMR) were all exclusion criteria for this analysis.

15 PPCI was performed according to international guidelines(1) and decisions about direct stenting
16 technique, thrombectomy and glycoprotein IIb/IIIa adoption were all left to operator discretion. All
17 patients were loaded with dual antiplatelet therapy. Weight-adjusted unfractionated heparin or
18 bivalirudin was adopted as antithrombotic regimen. Angiographic thrombus score was graded from 0 to
19 5 after the passage of the guidewire, as previously described(8).

20 **Coronary angiography**

21 Coronary flow was graded using the standard TIMI criteria(9). Myocardial blush grade at the end of the
22 procedure was evaluated according to van't Hof(10). 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. Quantitative coronary analysis (QCA) was performed off-line using angiographic imaging taken immediately before stenting, so after coronary flow restoration by means of thrombus-aspiration and/or balloon-angioplasty.

Invasive coronary physiology measurements

Indices of coronary physiology of the infarct-related artery were assessed at completion of PPCI.

Aortic pressure was recorded from the guiding catheter.

IMR was defined as the mean distal pressure multiplied by the mean transit time (Tmn) at hyperemia as previously described(3, 11) using a coronary PressureWire (Abbott - St. Jude Medical, St. Paul, Minnesota).

IMR 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 was defined as the ratio of hyperemic to resting coronary flow and was calculated using the equation:

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

Baseline resistance index, a measure of the resting tone in the coronary microcirculation, was calculated using the equation:

$$Baseline\ resistance\ index = Pa_{Base} \times Tmn_{Base} \times (Pd_{Base} - Pw) / (Pa_{Base} - Pw)$$

where Pa_{Base} is the resting aortic pressure, Pd_{Base} the resting distal pressure, Tmn_{Base} is the transit time under resting conditions ~~and Pw is coronary wedge pressure measured during prolonged balloon inflation.~~

RRR was calculated as previously described, using the equation(5):

$$RRR = \text{Baseline resistance index} / IMR$$

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 is described in details in Appendix 1.

Cvi42 image analysis software (Circle Cardiovascular Imaging Inc, Calgary, Canada) was used for image analysis. 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(12) 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(13). 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(13). 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 haemorrhage was assess on T2* and/or T2W imaging as a

hypointense area within the injured myocardium. Post-pPCI myocardial salvage index was measured as:

$$\text{myocardial salvage index} = [(AAR - \text{infarct size}) / AAR] * 100 \quad (12)$$

Percentage change in IS at six months was assessed as:

$$\text{IS shrinkage} = [(LGE_{48h} - LGE_{6mo}) / LGE_{48h}] * 100 \quad (15).$$

Variation of end-diastolic volume (EDV) between baseline and follow-up was assessed as:

$$\text{End-diastolic volume variation\%} = [(EDV_{48h} - EDV_{6months}) / EDV_{48h}] * 100.$$

A negative value of EDV variation% with a cut-off $\leq -20\%$ was considered diagnostic for adverse negative remodeling (16).

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. The Fisher exact chi-square test was used for binary variables. ~~Correlations between continuous variables were made using the Spearman rho correlation.~~

The performance of CFR, IMR and RRR in predicting the extent of ~~acute myocardial injury by LGE IS%~~ was assessed using receiver-operating characteristic (ROC) curve analysis. ~~The median value of IS% at 48h and 6 months was used as discriminatory cut-point for ROC curve analysis.~~ The area under the curve (AUC) was provided for each parameter. The Youden index (J) was used to identify the optimal cut-off values(17).

~~Regression analysis was performed to assess the correlation between CFR, IMR and RRR and CMR-derived endpoints. Multivariate models were employed to assess the independent prognostic value of RRR.~~

~~A t-test for paired samples~~ Wilcoxon signed-rank test was applied to assess change in CFR and IMR before and after coronary stenting in groups stratified according to the RRR.

Statistical analysis was performed using SPSS, Version 25.0 (IBM Corp., Armonk, NY, USA), and MedCalc 13.2.1.0 (Ostend, Belgium). All tests were 2-tailed and a p-value <0.05 was considered statistically significant.

RESULTS

Clinical and procedural characteristics

A total of 45 STEMI patients were included in this retrospective analysis of OxAMI study. ~~The study flowchart is shown in Figure 1.~~

The results of CMR at 48 hours were available for all patients (100%). Full CMR data at 6 months of follow up were available for 39 (87%) patients.

Post-PPCI invasive physiologic indices, including CFR, IMR and RRR, were available for all the patients, whereas repeated pre- and post-stenting measurements, were performed in 30 (66.7%) patients.

Overall clinical and angiographic characteristics of the study cohort are presented in Table 1 and stratified according to median value of RRR.

Coronary flow reserve

Clinical characteristics of patients stratified according to post-PPCI CFR values are shown in Supplementary Table 1 (Table S1).

The majority of the patients (33/45=73%) presented an impaired post-PPCI CFR (<2) value.

No significant differences were observed at the 48h or 6-months CMR assessment in terms of MVO% (0.0[0.0-6.1] vs 0.0[0.0-0.7], p=0.26), final IS% (12.7 [7.9-27.3] vs 8.1 [2.2-24.4], p=0.15), myocardial salvage index (41[31-59] vs 66[35-79], p=0.11) and LVEF% (53[44-59] vs 59[56-62], p=0.06) between patients with impaired (<2) or preserved (≥2) CFR.

Notably, patients with CFR<2 showed significantly higher post-PPCI FFR (0.97 [0.91-0.99] vs 0.90 [0.88-0.94], p=0.002), higher post-PPCI IMR (42.6 [20.2-64.6] vs 20 [12.6-32.6], p=0.006) and lower post-PPCI RRR (1.73 [1.39-2.29] vs 2.42 [1.87-2.93], p=0.038) compared with patients with post-PPCI CFR≥2.

~~The median value of post-PPCI CFR was 1.57 [1.07-2.05]. Patients with CFR<1.57 showed higher angiographic lesion severity at quantitative coronary analysis (%DS: 59.9[51.6-66.3] vs 48.9[43-57.8], p=0.017) and less frequently showed resolution of ST segment elevation after the PPCI (48% vs 91%, p=0.003).~~

~~Notably, no significant difference was observed in the angiographic thrombus score (p=0.98), post-procedural TIMI flow (p=0.53) and myocardial blush grade (p=0.7). No further significant differences were observed in the baseline clinical characteristics of patients stratified by CFR (Appendix 2).~~

~~At 48 hours CMR, patients with CFR<1.57 had higher MVO% (1.1[0-7.1] vs 0[0-1.1], p=0.03) but no significant difference in the IS% (21.6[9.5-42.8] vs 19.4[8.2-27.9], p=0.23), in the area at risk% (35.9[25.6-50.4] vs 37.6[33-45.7], p=0.67) and LV EDV (162[122-181] vs 162.5[137-200], p=0.71) or function (LVEF%: 46[41-56] vs 49[43-52], p=0.89).~~

~~At 6 months CMR, patients post-PPCI CFR<1.57 presented no significant differences in terms of IS% (18.9 [7.9-32.2] vs 10.5 [6.6-21.6], p=0.11), left ventricle end diastolic volume (165.5[124-204] vs 163[145-189], p=0.76) and ejection fraction (56[42-65] vs 56.5[52-61], p=0.7), myocardial salvage index (40.6[26.3-65.3] vs 47.1[34.7-71.2], p=0.19) compared with other patients.~~

Index of microvascular resistance

Clinical characteristics of patients stratified according to post-PPCI IMR are shown in Supplementary Table 2 (Table S2). Eighteen out of 45 patients (40%) presented an IMR value above 40 Units.

At 48 hours, ~~this high-risk subgroup of patients~~ patients with IMR>40 U showed significantly larger MVO (3.75[0-7.1] vs 0[0-0.94], p=0.03) and IS% (27.1[20.5-42.8] vs 14.3[8.7-26.5], p=0.02) compared with other STEMI patients. Notably, at 6 months of follow-up, patients with IMR ≥40 demonstrated larger IS% (21.3[10.9-35.6] vs 8.8[5.8-19.1], p=0.014), lower myocardial salvage index (31.6[23.4-48.7] vs 53.2[38.5-70.3], p=0.006) and lower LVEF% (45[37.2-56.7] vs 58.5[53.2-64], p=0.002) compared with those with a post-PPCI <40 U.

Patients with IMR>40 presented significantly higher post-PPCI FFR (0.99 [0.97-1] vs 0.92 [0.89-0.97] p<0.001), lower CFR (1.24 [1.01-1.58] vs 1.82 [1.33-2.35], p=0.007) and lower RRR (1.47 [1.35-2.02] vs 2.38 [1.78-3.03], p=0.001) compared with other patients.

~~The median value of post PPCI IMR was 31 U [18.2-51.3]. Patients with IMR>31 U were more frequently female (32% vs 4%, p=0.022), presented less frequently post-procedural ST-resolution (50% vs 87%, p=0.01), final TIMI flow 3 (73% vs 96%, p=0.047) and myocardial blush grade≥2 (64% vs 100%, p=0.001). Other baseline and procedural characteristics are shown in Appendix 3.~~

~~At 48 hours CMR, no significant differences were observed in patients with IMR>31 U in terms of IS% (24.1[10.8-39.4] vs 16.3[9-26.5], p=0.11), area at risk% (38.8[27.9-52] vs 39.1[32.4-46.4], p=0.98) MVO% (1.81[0-6.3] vs 0[0-0.94], p=0.08), left ventricle end-diastolic volume (160[117-192.5] vs 162[142-200], p=0.4) or ejection fraction% (49[40.5-54] vs 49[42-54], p=0.95).~~

~~At 6 months patients with post-PPCI IMR>31 U demonstrated lower left ventricle ejection fraction% (54[38-58] vs 58.5[53-61], p=0.03) and lower myocardial salvage index (32.5[23.4-63] vs 53.2[38.5-~~

~~70], $p=0.017$). However, no significant difference was observed in the final IS at 6 months between patients with impaired (>31 U) or preserved (≤ 31 U) post-PPCI IMR (20[7.7-30.4] vs 9.5[7-19.2], $p=0.11$).~~

Resistance reserve ratio

The median value of RRR was 1.98 [1.43-2.52]. Patients with RRR <1.98 were more frequently male (95% vs 74%, $p=0.047$) and presented higher rate of thrombus score ≥ 4 (95% vs 70%, $p=0.04$) and higher myocardial blush grade ≥ 2 (73% vs 95%, $p=0.045$; Table 1).

~~No significant difference was observed in terms of post-procedural TIMI flow 3 (77.3% vs 91.3%, $p=0.24$) and ST-resolution (59% vs 78%, $p=0.59$), even though a trend towards worse post-procedural result was observed in patients with post-PPCI RRR <1.98 . No significant correlation with the pain-to-balloon time was observed ($\rho=0.22$, $p=0.14$).~~

~~RRR was significantly correlated with the extent of infarct size at 48 hours ($\rho=0.36$, $p=0.019$) and at 6 months of follow up ($\rho=-0.51$, $p=0.002$), with the area at risk ($\rho=-0.41$, $p=0.008$) and with the IS shrinkage at 6 months ($\rho=-0.47$, $p=0.033$).~~

Patients with RRR <1.98 showed larger IS% (27.4 [14.5-42.5] vs 15.4 [8.3-26], $p=0.018$), higher MVO% (3.5 [0-5.97] vs 0 [0-0.89], $p=0.026$) at 48h from PPCI compared with patients with RRR ≥ 1.98 .

At 6 months CMR assessment, patients with RRR <1.98 showed larger IS% (22.7[10.2-35] vs 8.8 [6.9-12.3], $p=0.006$), larger end-diastolic volume (183 [155-202] vs 146 [106.5-173], $p=0.02$) and lower myocardial salvage index (34 [22-8-59.2 vs 53.2 [37.7-71], $p=0.032$) compared with other patients.

Furthermore, the rate of late adverse left ventricle remodeling was higher among patients with $RRR < 1.98$ (22.2% vs 0%, $p=0.04$).

$RRR < 1.49$ was identified by ROC curve analysis as the best cut-point in predicting the extent of final infarct size (Figure 2 and supplementary material, Supplementary Table S6).

ROC Curve Analysis

~~At 48 hours CMR, the median value of IS% was 20.7 [9.1-30.6].~~ At ROC curve analysis the performance of RRR was similar compared with CFR and IMR in predicting the median extent of IS% at 48 h (Figure 1A).

~~At 6 months of follow up, the median value of IS% was 15 [7-29]. Clinical, angiographic and physiological characteristics of patients stratified by the 6 months IS% are presented in Table 1.~~

At ROC curve analysis, RRR ($AUC_{RRR}=0.85$, $CI:0.71-0.99$) outperformed IMR ($AUC_{IMR}=0.71$, $CI:0.54-0.88$) and CFR ($AUC_{CFR}=0.69$, $CI:0.52-0.87$) in predicting the extent of IS at 6 months (Figure



Predictors of 6 months infarct size

Univariate regression analysis for angiographic and physiological predictors of the 6 months IS% is presented in Table 2.

CFR was not significantly associated with the extent of IS% at 6 months ($r=-0.31$, $p=0.06$). Conversely, IMR ($r=0.35$, $p=0.027$) and RRR ($r=-0.46$, $p=0.003$) resulted significantly associated with the 6 months IS%.

When inserted into multivariate model with other thermodilution indices only RRR resulted associated with the extent of the final myocardial injury at 6 months ($r=-0.36$, $p=0.03$; Table S4). Furthermore, RRR ($r=-0.34$, $p=0.02$), but not IMR ($p=0.26$, $p=0.08$), remained significantly associated with the 6 months IS% when tested in multivariate fashion with other angiographic and procedural variables (Table 3).

Figure 2 shows the relationship between RRR and IMR in the study cohort. Notably, patients with impaired RRR (<1.98) demonstrated larger IS% irrespectively to the IMR classification, suggesting the possible superior prognostic value of RRR. Nonetheless, the subgroup of lesions with a combination of impaired RRR and impaired IMR demonstrated the worse outcome at the 6 months CMR assessment.

Repeated coronary pressure/flow measurements before and after IRA stenting

In a subgroup of patients ($n=30$, 67%), coronary pressure and flow measurements were performed in the infarct-related artery both immediately after flow restoration and at PPCI completion. Variations in physiological indices, stratified by post-PPCI RRR, are shown in Table 4.

In patients with preserved RRR, CFR (1.37 ± 0.43 vs 1.93 ± 0.49 , $p=0.016$) and IMR (56.8 ± 31.2 vs 35.9 ± 26.5 , $p=0.008$) improved significantly after PPCI. On the contrary, in patients with $RRR<1.98$, both CFR (1.48 ± 0.87 vs 1.47 ± 0.61 , $p=0.81$) and IMR (58.04 ± 37.7 vs 55.01 ± 49 , $p=0.44$) remained impaired at PPCI completion (Figure 3).

~~Overall, CFR (1.44 ± 0.7 vs 1.64 ± 0.6 , $p=0.19$) IMR (57.6 ± 34.9 vs 48.1 ± 43 , $p=0.1$) showed no significant variations before and after stenting.~~

~~However, when stratified according to the RRR, Patients with preserved final RRR (≥ 1.98) where those experining significant increase in CFR (1.37 ± 0.43 vs 1.93 ± 0.49 , $p=0.018$ 0.016) and IMR decreased significantly after PPCI (56.8 ± 31.2 vs 35.9 ± 26.5 , $p=0.003$ 0.08) (Figure 3).~~

On the contrary, patients with final RRR <1.98 were those with no improvement in myocardial reperfusion assessed by CFR showed significant variation in the CFR (1.48 ± 0.87 vs 1.47 ± 0.61 , $p=0.94$ 0.81) and IMR values (58.04 ± 37.7 vs 55.01 ± 49 , $p=0.72$ 0.44) before and after stenting (Figure 3).

DISCUSSION

These analyses demonstrate that intracoronary thermodilution-derived parameters, namely IMR, CFR and RRR, measured after PPCI, all predict the extent of myocardial injury at 48 hours from PPCI. However, RRR, a novel index that expresses the microcirculation vasodilatory capacity, significantly outperformed IMR and CFR in predicting the extent of IS at 6 months of follow-up after STEMI. Furthermore, RRR was effective in identifying those patients likely to experience a significant improvement in myocardial reperfusion at PPCI completion.

Complete restoration of coronary blood flow is the main aim in the treatment of STEMI patients(1). However, the response of the microvasculature to stenting is heterogeneous and the consequent improvement in the myocardial perfusion after PPCI is not universal(3). We have previously demonstrated that a consistent proportion of STEMI patients undergoing PPCI have evidence of impaired microvascular function at completion of the revascularization procedure with an impaired IMR (>40 units) after stent implantation(3). Notably, although stent implantation was associated with an overall improvement in IMR, there is still a variable proportion of patients with a post-procedural IMR that is suboptimal, either because of incomplete IMR normalization or because IMR increases after stent implantation. Persistent impairment of IMR was observed more commonly in patients presenting with long time delays, whereas worsening IMR post-stent implantation was more likely in patients with large thrombotic burden and/or larger volume of implanted stent (3).

1 In this retrospective analysis, post-PPCI RRR appears to accurately identify that subset of patients with
2 a suboptimal response of the microvasculature to stenting. In fact, in patients with impaired RRR, CFR
3 and IMR did not improve after PPCI, whereas in patients with $RRR \geq 1.98$, coronary flow and
4 microvascular resistances improved significantly after stenting. Therefore, if confirmed in larger
5 clinical studies, measurement of RRR could emerge as a useful marker of successful myocardial
6 reperfusion after PPCI in STEMI patients.

7 Interestingly, in this study the performance of CFR, IMR and RRR in predicting the extent of
8 myocardial injury acutely after STEMI was similar. However, RRR had significant incremental
9 prognostic value compared with other thermodilution-derived indices in predicting the final extent of
10 myocardial injury after STEMI (Figure 2). Furthermore, being significantly correlated with the area at
11 risk and the myocardial salvage index, RRR proved to be a marker of salvage after infarction. Notably,
12 IMR showed a worse performance at ROC curve analysis in predicting the final myocardial injury after
13 STEMI compared to RRR. Nonetheless, when stratifying patients according to the clinically validated
14 cut-point of ≥ 40 U, IMR was still able to accurately identify a high-risk subgroup of patients with
15 larger injury and worse myocardial recovery after STEMI.

16 The higher prognostic value of RRR compared with the other thermodilution indices, and specifically
17 compared with IMR, can be related to its dynamic characteristics. RRR expresses the ratio between
18 myocardial resistance during resting conditions and during maximal hyperemia, and describes how the
19 coronary microcirculation can functionally adapt to a hyperemic stimulus(5,18). On the contrary, IMR
20 only describes the status of the microvasculature's response to maximal achievable hyperemia. This
21 dynamic nature of RRR may therefore be a marker of the ability of microcirculation to recover after the
22 acute injury of myocardial infarction.

IMR is a readily available thermodilution-derived parameter which reflects the status of the coronary microvasculature and showed high accuracy in predicting adverse outcome after STEMI alone or combined with other clinical and angiographic characteristics(6, 12, 19).

Layland et al. have demonstrated that RRR was significantly impaired in STEMI patients compared with patients with non-ST elevation myocardial infarction and stable patients. This suggests that the ability of the coronary microcirculation to vasodilate is related to the severity of the initial injury and the extent of microvascular dysfunction(5). It has been observed that impaired microvascular vasodilatory function occurs in the presence of prolonged ischemia and MVO(4) and consistently, in this study, patients with lower RRR had significantly more MVO. However, no association between RRR and ischemic time was observed in our cohort.

Notably, Layland et al, also showed in a subgroup of patients with acute STEMI a similar RRR as the non-culprit non-ST elevation myocardial infarction control group(5). These findings suggest that RRR can identify STEMI patients with smaller extent of microvascular injury. Indeed, in our series, patients with preserved RRR (≥ 1.98) showed favorable outcome in terms of smaller final myocardial injury, lower MVO, greater myocardial salvage and less evidence of adverse LV remodeling at 6 months after PPCI.

Limitations

Our study has several limitations. First of all, the sample size is small. Second, the prognostic value of RRR has been tested against the evidence of myocardial damage at CMR and not against clinical endpoints. Moreover, the study cohort includes a limited number of patients with diabetes patients and, thus, our results may not be generalisable to the diabetic population.

Furthermore, six months CMR follow up data were available only in 39/45 (87%) patients and complete coronary physiology assessment, including pre- and post-stenting pressure and thermodilution parameters were available for 30/45(67%) cases.

~~Furthermore, coronary wedge pressure requires to record pressure traces during coronary balloon inflation and obtaining adequate trace recording can be technically demanding in the setting of acute STEMI.~~

Notwithstanding the limitations of a small sample size, single-center study, this is the first study to directly compare the performance of RRR with CFR and IMR in predicting the extent of IS at early and mid-term follow up after STEMI.

Lastly, no clinical cut-off for RRR has been previously validated, and our study was not powered for optimal RRR threshold identification. Therefore, our results should be interpreted as hypothesis generating only and need to be validated in larger prospective series.

CONCLUSION

IMR, CFR and RRR similarly predicted the extent of myocardial injury at 48 hours from PPCI. RRR demonstrated incremental prognostic value compared to other thermodilution-derived indices in predicting the extent of myocardial infarction at 6 months of follow up. Patients with impaired RRR showed lower myocardial reperfusion after PPCI, more MVO, larger acute (48 hours) and late (6 months) myocardial injury and lower myocardial salvage index. Further studies, designed to assess clinical outcomes, are warranted to confirm our initial results.

FUNDING

This study was supported by the British Heart Foundation (BHF; grant CH/16/1/32013), the BHF Centre of Research Excellence, Oxford (RG/13/1/30181), and the National Institute for Health Research (NIHR) Oxford Biomedical Research Centre.

DISCLOSURES

Prof Banning received institutional funding for an interventional fellowship from Bosoton Scientific.

Prof Banning is partially funded by the NHS NIHR Biomedical Research Centre, Oxford

IMPACT ON DAILY PRACTICE

Coronary physiology may have an important role in discriminating STEMI patients with sub-optimal results after PPCI. However, the best physiological index to predict the extent of myocardial injury acutely and at long-term after STEMI is still undetermined. In this study, RRR, a novel index that expresses the microcirculation vasodilatory capacity, demonstrated to be superior to IMR and CFR in predicting the 6-months infarct size. Furthermore, RRR was effective in discriminating between patients who achieved a significant improvement in CFR and IMR after stenting and those with only partial myocardial reperfusion after PPCI. RRR could be used in future trials to prospectively identify STEMI patients ~~who achieved~~ with suboptimal reperfusion after PPCI and who are candidates to further therapeutic options.

REFERENCES

1. Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, Caforio ALP, Crea F, Goudevenos JA, Halvorsen S, Hindricks G, Kastrati A, Lenzen MJ, Prescott E, Roffi M, Valgimigli M, Varenhorst C, Vranckx P, Widmisky P. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J. 2018;39:119-77.
2. 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, 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.
3. De Maria GL, Cuculi F, Patel N, Dawkins S, Fahrni G, Kassimis G, Chouldhury RP, Forfar JC, Prendergast BD, Channon KM, Kharbanda RK, 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.

- 1 4. Bulluck H, Foin N, Tan JW, Low AF, Sezer M, Hausenloy DJ. Invasive Assessment of the
2 Coronary Microcirculation in Reperfused ST-Segment-Elevation Myocardial Infarction Patients:
3 Where Do We Stand? *Circ Cardiovasc Interv.* 2017;10:e004373.
- 4 5. Layland J, Carrick D, McEntegart M, Ahmed N, Payne A, McClure J, Sood A, McGeoch R,
5 MacIsaac A, Whitbourn R, Wilson A, Oldroyd K, Berry C. Vasodilatory capacity of the coronary
6 microcirculation is preserved in selected patients with non-ST-segment-elevation myocardial
7 infarction. *Circ Cardiovasc Interv.* 2013;6:231-6.
- 8 6. Fearon WF, Low AF, Yong AS, McGeoch R, Berry C, Shah MG, Ho MY, Kim HS, Loh JP,
9 Oldroyd KG. Prognostic value of the Index of Microcirculatory Resistance measured after primary
10 percutaneous coronary intervention. *Circulation.* 2013;127:2436-41.
- 11 7. Carrick D, Haig C, Carberry J, May VT, McCartney P, Welsh P, Ahmed N, McEntegart M,
12 Petrie MC, Eteiba H, Lindsay M, Hood S, Watkins S, Mahrous A, Rauhalammi SM, Mordi I, Ford I,
13 Radjenovic A, Sattar N, Oldroyd KG, Berry C. Microvascular resistance of the culprit coronary artery
14 in acute ST-elevation myocardial infarction. *JCI Insight.* 2016;1:e85768.
- 15 8. Sianos G, Papafaklis MI, Serruys PW. Angiographic thrombus burden classification in patients
16 with ST-segment elevation myocardial infarction treated with percutaneous coronary intervention. *J*
17 *Invasive Cardiol.* 2010;22(10 Suppl B):6B-14B.
- 18 9. Group TS. The Thrombolysis in Myocardial Infarction (TIMI) trial. Phase I findings. *N Engl J*
19 *Med.* 1985;312:932-6.
- 20 10. van 't Hof AW, Liem A, Suryapranata H, Hoorntje JC, de Boer MJ, Zijlstra F. Angiographic
21 assessment of myocardial reperfusion in patients treated with primary angioplasty for acute myocardial
22 infarction: myocardial blush grade. Zwolle Myocardial Infarction Study Group. *Circulation.*
23 1998;97:2302-6.

- 1 11. De Maria GL, Alkhalil M, Wolfrum M, Fahrni G, Borlotti A, Gaughran L, Dawkins S, Langrish
2 AJ, Lucking Aj, Choudhury RP, Porto I, Crea F, Dall'Armellina E, Channon KM, Kharbanda RK,
3 Banning AP. The ATI score (age-thrombus burden-index of microcirculatory resistance) determined
4 during primary percutaneous coronary intervention predicts final infarct size in patients with ST-
5 elevation myocardial infarction: a cardiac magnetic resonance validation study. *EuroIntervention*.
6 2017;13:935-43.
- 7 12. Piechnik SK, Ferreira VM, Dall'Armellina E, Cochlin LE, Greiser A, Neubauer S, Robson MD.
8 Shortened Modified Look-Locker Inversion recovery (ShMOLLI) for clinical myocardial T1-mapping
9 at 1.5 and 3 T within a 9 heartbeat breathhold. *J Cardiovasc Magn Reson*. 2010;19:12-69.
- 10 13. Ugander M, Bagi PS, Oki AJ et al. Myocardial edema as detected by pre-contrast T1 and T2 CMR
11 delineates area at risk associated with acute myocardial infarction. *JACC Cardiovasc Imaging*.
12 2012;5:596-603.
- 13 14. Eitel I, Desch S, Fuernau G, Hildebrand L, Gutberlet M, Schuler G, Thiele H. Prognostic
14 significance and determinants of myocardial salvage assessed by cardiovascular magnetic resonance in
15 acute reperfused myocardial infarction. *J Am Coll Cardiol*. 2010;55:2470-9.
- 16 15. Baks T, van Geuns RJ, Biagini E, Biagini E, Wielopolski P, Mollet NR, Cademartiri F, van der
17 Giessen WJ, Krestin GP, Serruys PW, Duncker DJ, de Feyter PJ. Effects of primary angioplasty for
18 acute myocardial infarction on early and late infarct size and left ventricular wall characteristics. *J Am*
19 *Coll Cardiol*. 2006;47:40-4.
- 20 16. Tarantini G, Razzolini R, Cacciavillani L, Bilato C, Sarais C, Corbetti F, Marra MP, Napodano M,
21 Ramondo A, Iliceto S. Influence of transmural, infarct size, and severe microvascular obstruction on
22 left ventricular remodeling and function after primary coronary angioplasty. *Am J Cardiol*.
23 2006;98:1033-40.

1 17. Youden WJ. Index for rating diagnostic tests. *Cancer*.1950;3:32–35.

2 18. Corcoran D, Young R, Adlam D, McConnachie A, Mangion K, Ripley D, Cairns D, Brown J,
3 Bucciarelli-Ducci C, Baumbach A, Kharbanda R, Oldroyd KG, McCann GP, Greenwood JP, Berry C.
4 Coronary microvascular dysfunction in patients with stable coronary artery disease: The CE-MARC 2
5 coronary physiology sub-study. *Int J Cardiol*. 2018;1:266-7.

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

FIGURE LEGENDS

Figure 1. ROC curve analysis

ROC curve analysis comparing the performance of CFR, IMR and RRR in predicting the infarct size at 48 hours (A) and 6 months of follow up after STEMI (B). ~~The thermodilution indices performed comparably in detecting the myocardial injury acutely after PPCI. However, RRR outperformed IMR and CFR in predicting the final extent of myocardial injury at 6 months.~~

Figure 2. Scatter plot of post-PPCI RRR and IMR

Scatter plot of RRR and IMR value. Patients with $RRR < 1.98$ and $IMR > 40$ U showed worse outcome at the CMR assessment

Figure 3. Figure 3. Pre- and post-PPCI coronary physiology

Coronary physiology assessment was repeated before and after PPCI in a subgroup of 30 STEMI patients. Patients with preserved RRR (≥ 1.98) presented good reperfusion outcome after stenting, with significant improvement in the CFR and IMR values. Conversely, those with impaired RRR (< 1.98) did not showed a significant improvement in coronary physiology after PPCI.

1
2
3
4
5

Table 1. Clinical angiographic, physiological and imaging parameters of the study cohort				
Variable	Overall	RRR<1.98	RRR>=1.98	p-value
patient number	45(100)	22(49)	23(51)	
Age, yr	63(58-68)	63(61-67)	66(55-70)	0.85
Sex male, n(%)	38(84)	21(95)	17(74)	0.047
BSA, m2	2.07(1.88-2.24)	2.11(1.92-2.26)	2.07(1.81-2.24)	0.39
Smoker, n(%)	9(19)	4(18)	5(22)	0.53
Hypertension, n(%)	21(46)	11(50)	10(40)	0.55
Diabetes, n(%)	3(7)	3(14)	0(0)	0.11
Hypercholesterolemia, n(%)	11(24)	6(27)	5(22)	0.81
ST-resolution	31(68)	13(59)	18(78)	0.16
Pain-to-balloon time, min	177(119-364)	182.5(95.7-313)	177(138-522)	0.35
Troponin peak, ng/L	54.3(20.7-135.6)	75.2(19.5-186.3)	41.8(20.7-109.5)	0.35
Angiographic and procedural data				
Culprit LAD, n(%)	17(38)	10(45)	7(31)	0.55
Thrombus score>=4	38(84)	21(95)	17(74)	0.047
Thrombus aspiration, n(%)	39(86)	19(86)	20(86)	0.69
Stent lenght, mm	26(20-32)	30.13±13.6	27.7±13.3	0.55
Vessel diameter, mm	3.53±0.5	3.67±0.5	3.45±0.49	0.15
DS%	53.2(45.7-63.6)	55.4±12.6	54.4±12.4	0.8
Post-PCI TIMI flow 3	39(86)	17(77)	22(95)	0.06
MBG>= 2	38(84)	16(73)	22(95)	0.045
Intracoronary physiology				
Tmn	0.45(0.26-0.71)	0.51(0.32-0.86)	0.4(0.25-0.63)	0.22
Pdhyp	73(67-82)	75(67-88)	71(61-79)	0.35
CFR	1.57(1.07-2.05)	1.24(1.01-1.79)	1.82(1.34-2.25)	0.02
IMR	31(18-51)	43.3(19.2-69.7)	28(17.7-39)	0.1
FFR	0.96(0.90-1)	0.97(0.91-1)	0.93(0.9-1)	0.24
RRR	1.98(1.44-2.51)	1.43(1.26-1.72)	2.51(1.23-3.04)	<0.0001
RAP	9(6-11)	9(6.75-11)	9(5-13)	0.56
Pwedge	22(18-30)	22(18.7-29.3)	22(17-32)	0.67
CMR - 48h				
EDV	162(134-195)	167(147-201)	154(122-189)	0.15
LVEF%	49(42-53.5)	45(40-54)	50(44-53)	0.77
AAR%	38.8(30.3-46.9)	43(35-52)	34(25-46)	0.028
T1 AAR*	1361(1325-1398)	1346(1330-1408)	1366(1330-1408)	0.21
T1 Remote	1182(1161-1209)	1189(1156-1209)	1180(1168-1211)	0.84
IS%	20.7(9-30.6)	27.4(14.5-42.5)	15.4(8.3-26.1)	0.018
MVO%	0.8(0-2.1)	3.5(0-5.9)	0.0(0.0-0.9)	0.026
CMR - 6 months				

EDV	163(130-192)	183(155-202)	146(106.5-173)	0.020
LVEF%	56(48-61)	52(41-61)	57(53-63)	0.14
IS%	14.3(6.8-29.4)	22.7(10.2-35.1)	8.76(6.9-12.3)	0.006
Myocardial salvage index	43.9(31.8-67.8)	34(22.8-59.2)	53.2(37.7-71)	0.032
IS shirkage	25.4(3.4-50.7)	13.5(3.74-32.5)	36.1(1.3-54.1)	0.21

AAR, area at risk; LVEDV, left ventricle end-diastolic volume; IS, infarct size; LAD, left anterior descending artery; LGE, late gadolinium enhancement; LVEF, left ventricle ejection fraction; MBG, myocardial blush grade; Pd, diastolic pressure; TIMI, Thrombolysis in Myocardial infarction; Tmn, mean transit time.

*this includes area of MVO which can lower T1 values

Table 2. Univariate regression analysis bewteen the extent of 6 months infarct size and procedural and physiological indices

Variable	rho	p-value
Thrombus score	0.42	0.008
MBG	0.15	0.35
Post-PPCI TIMI flow	0.34	0.032
ST-resolution	0.42	0.008
CFI	0.06	0.74
CFR	0.31	0.054
IMR	0.35	0.027
RRR	0.46	0.003

MBG, myocardial blush grade; CFI, collateral flow index; CFR, coronary flow reserve; IMR, index of microcirculatory resistance; RRR, resistive reserve ratio.

1
2
3
4
5
6

Table 3. Multivariate regression analysis between the extent of 6 months infarct size and procedural and physiological indices

Model 1. Variables: CFR, Post-PPCI TIMI flow, Thrombus score		
Variable	rho	p-value
CFR	0.27	0.07
Post-PPCI TIMI flow	0.33	0.03
Thrombus score	0.32	0.03
Model 2. Variables: IMR, Post-PPCI TIMI flow, Thrombus score		
Variable	rho	p-value
IMR	0.26	0.08
Post-PPCI TIMI flow	0.23	0.11
Thrombus score	0.36	0.01
Model 3. Variables: RRR, Post-PPCI TIMI flow, Thrombus score		
Variable	rho	p-value
RRR	0.34	0.02
Post-PPCI TIMI flow	0.25	0.08
Thrombus score	0.03	0.04
Model 4. Variables: CFR, Post-PPCI TIMI flow, Thrombus score, ST-resolution		
Variable	rho	p-value
CFR	0.17	0.27
Post-PPCI TIMI flow	0.28	0.06
Thrombus score	0.30	0.04
ST-resolution	0.23	0.15
Model 5. Variables: IMR, Post-PPCI TIMI flow, Thrombus score, ST-resolution		
Variable	rho	p-value
IMR	0.22	0.13
Post-PPCI TIMI flow	0.21	0.15
Thrombus score	0.31	0.03
ST-resolution	0.27	0.06

Model 6. Variables: RRR, Post-PPCI TIMI flow, Thrombus score, ST-resolution		
Variable	rho	p-value
RRR	0.28	0.05
Post-PPCI TIMI flow	0.22	0.11
Thrombus score	0.26	0.06
ST-resolution	0.23	0.12

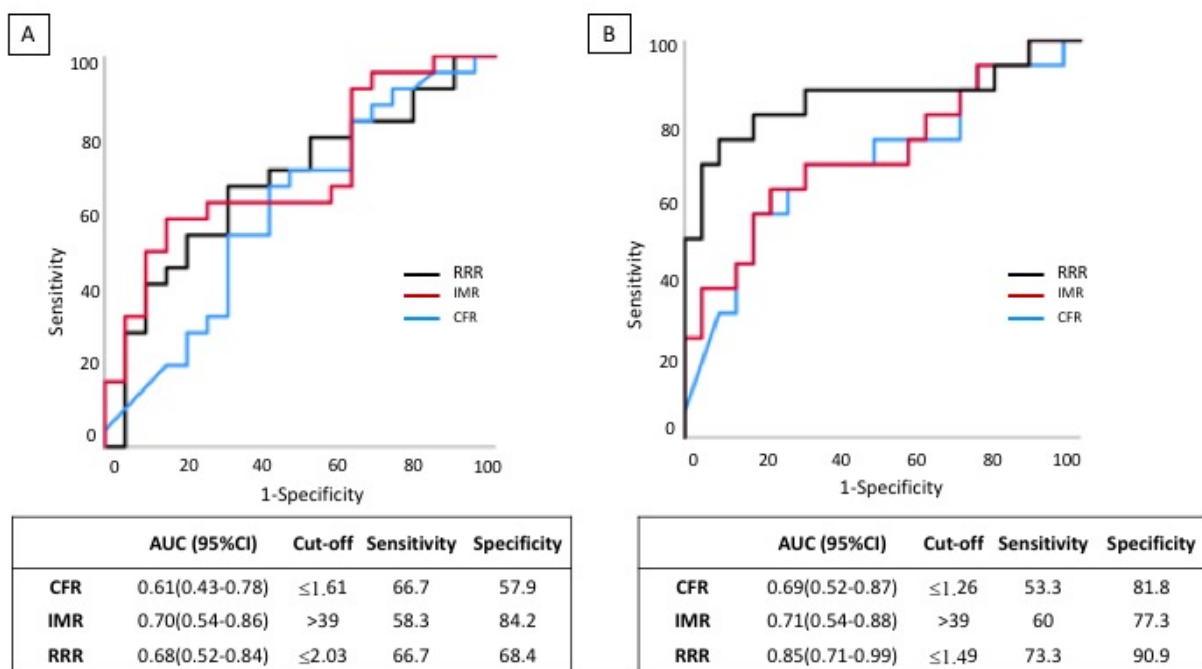
CFR, coronary flow reserve; IMR, index of microcirculatory resistance; RRR, resistive reserve ratio.

Table 4. Repeated coronary pressure/flow measurements before and after IRA stenting

	RER <1.98			RER ≥1.98		
Variable	Pre-Stent	Post-Stent	p-value	Pre-Stent	Post-Stent	p-value
Pd(hyp)	64.3±18.1	76.4±14.2	0.001	58.7±11.8	71±10.9	0.008
Tmn(hyp)	0.91±0.63	0.67±0.52	0.049	1.02±0.61	0.52±0.38	0.007
Pd/Pa	0.85±0.12	0.97±0.03	<0.0001	0.8±0.17	0.96±0.05	0.003
FFR	0.79±0.16	0.95±0.05	<0.0001	0.73±0.18	0.94±0.07	0.003
CFR	1.48±0.87	1.47±0.61	0.81	1.37±0.43	1.93±0.49	0.016
IMR	58.04±37.7	55.01±49	0.44	56.8±31.2	35.9±26.5	0.008

Pd(hyp), hyperemic distal pressure; Tmn, mean transit time; FFR, fractional flow reserve; CFR, coronary flow reserve; IMR, microvascular resistance index.

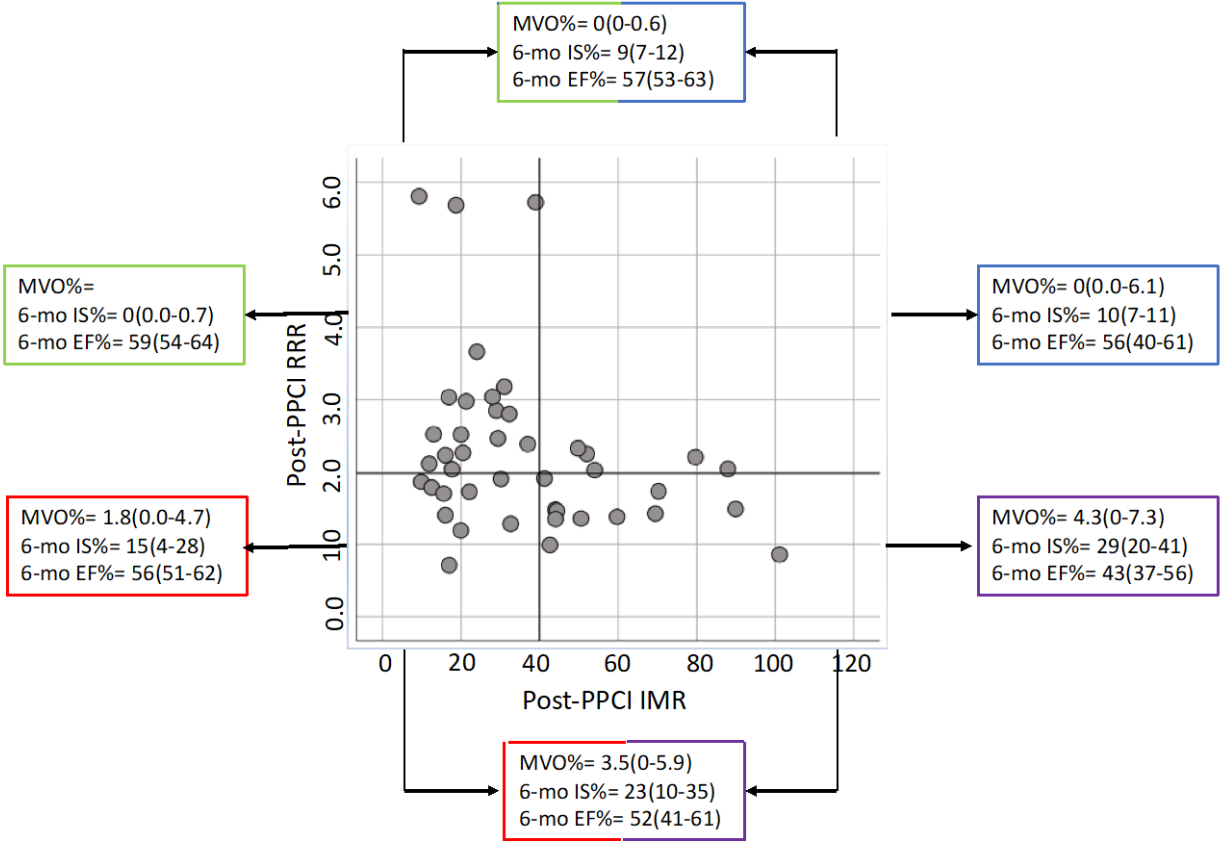
Figure 1.



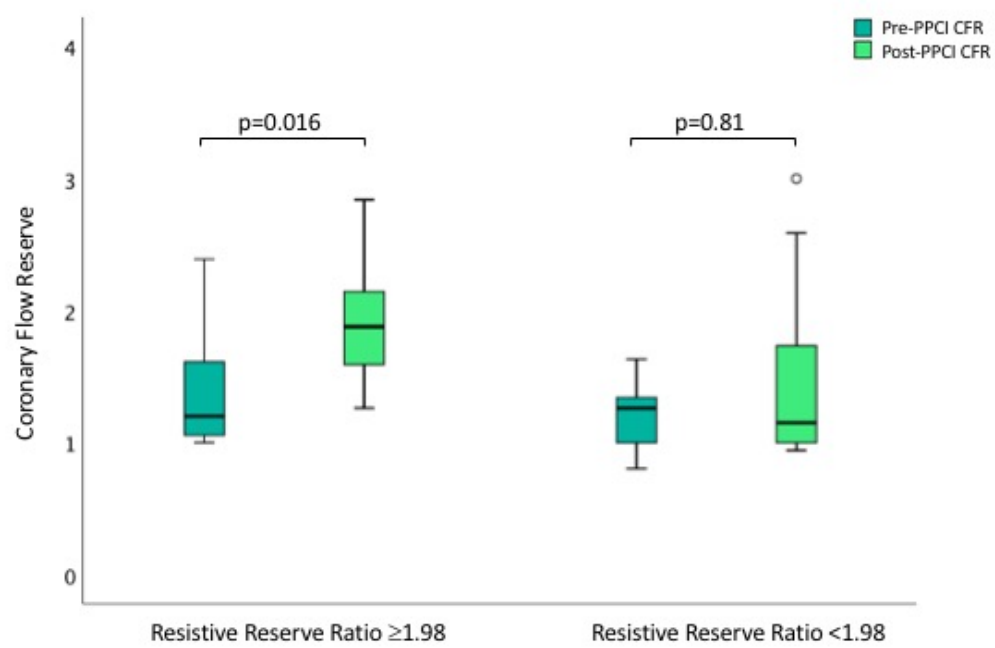
1
2
3
4
5
6
7
8

9
10
11
12

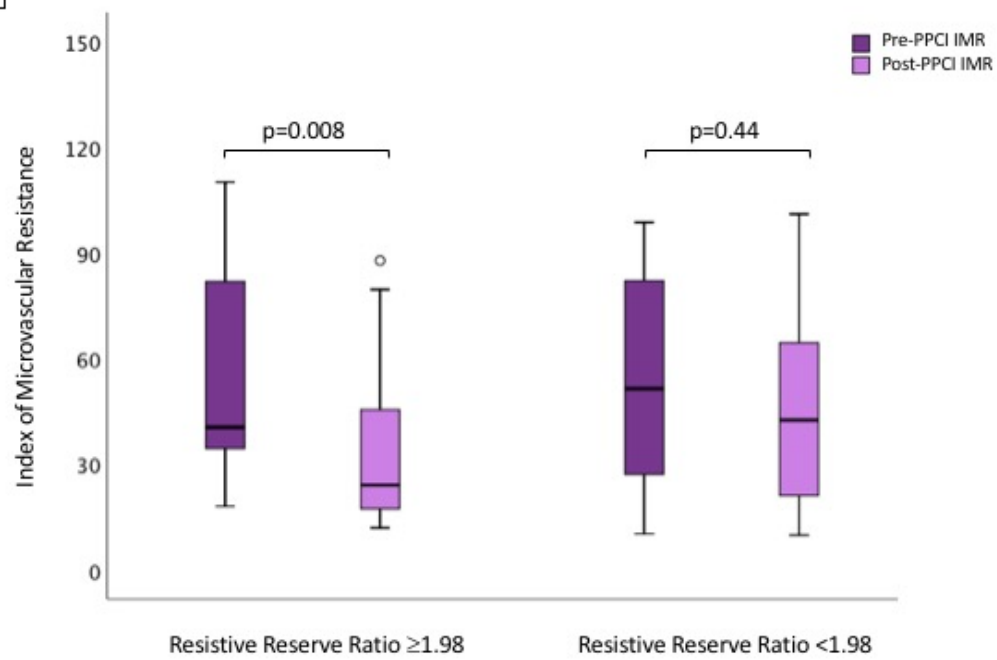
Figure 2.



A



B



1

2