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ORIGINAL PAPER

Angiography-derived index of microcirculatory resistance (IMR_{angio}) as a novel pressure-wire-free tool to assess coronary microvascular dysfunction in acute coronary syndromes and stable coronary artery disease

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Abstract

To investigate the diagnostic accuracy of (1) hyperaemic angiography-derived index of microcirculatory resistance (IMR_{angio}) in defining coronary microvascular dysfunction (CMD) across patients with acute coronary syndromes (ST-elevation myocardial infarction [STEMI]; non-ST elevation acute coronary syndrome [NSTE-ACS]) and stable chronic coronary syndrome [CCS]) and (2) the accuracy of non-hyperaemic IMR_{angio} (NH-IMR_{angio}) to detect CMD in STEMI. 145 patients (STEMI = 66; NSTEMI = 43; CCS = 36) were enrolled. 246 pressure-wire IMR measurements were made in 189 coronary vessels. IMR_{angio} and NH-IMR_{angio} was derived using quantitative flow ratio. In patients with STEMI, cardiac magnetic resonance was performed to quantify microvascular obstruction (MVO). IMR_{angio} was correlated with IMR (overall rho = 0.78, $p < 0.0001$; STEMI, rho = 0.85 $p < 0.0001$; NSTE-ACS and rho = 0.72, $p < 0.0001$; CCS, rho = 0.70, $p < 0.0001$) and demonstrated good diagnostic performance in predicting high IMR (STEMI $AUC_{ROC} = 0.93$ [0.88–0.98]; NSTE-ACS $AUC_{ROC} = 0.77$ [0.63–0.92]; CCS $AUC_{ROC} = 0.88$ [0.79–0.97]). Agreement between the two indices was evident on Bland Altman analysis. In STEMI, NH-IMR_{angio} was also well correlated with IMR (rho = 0.64, $p < 0.0001$), with good diagnostic accuracy in predicting high invasive IMR ($AUC_{ROC} = 0.82$ [0.74–0.90]). Both IMR_{angio} ($AUC_{ROC} = 0.74$ [0.59–0.89]) and NH-IMR_{angio} ($AUC_{ROC} = 0.76$ [0.54–0.87]) were significantly associated with MVO in STEMI. In conclusions, IMR_{angio} is a valid alternative to invasive IMR to detect CMD in patients with acute and stable coronary syndromes, whilst NH-IMR_{angio} has a good diagnostic accuracy in STEMI where it could become a user-friendly diagnostic tool as it is adenosine-free.

Keywords STEMI · NSTE-ACS · Stable chronic coronary syndrome · Coronary microvascular dysfunction · Index of microcirculatory resistance · QFR · IMR_{angio}

Introduction

Coronary microvascular dysfunction (CMD) often remains under-diagnosed in patients with coronary artery disease, despite its well reported clinical and prognostic implications [1]. Various methods have been proposed to aid the diagnosis of CMD in the catheterization laboratory [2]. Among them, the index of microcirculatory resistance (IMR) has gained particular attention [3]. It has been validated in patients with ST-elevation myocardial infarction (STEMI), in whom an elevated IMR (> 40U) has been associated with adverse clinical outcome and more extensive myocardial

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injury [4, 5]. IMR has also been adopted to define the degree of CMD in patients with stable chronic coronary syndrome (CCS) with or without obstructive coronary disease [6, 7].

However, the application of invasive coronary physiology to assess the extent of CMD remains very limited in routine clinical practice. This is partly due to the required additional procedural time, costs and technical complexity mainly related with pressure-wire manipulation and the need of adenosine infusion to achieve maximal hyperaemia.

We have recently presented a novel pressure-wire-free and angiography-based index of microcirculatory resistance (IMR_{angio}), to assess coronary microvascular function in patients with STEMI based on computational flow analysis [8].

We investigated whether the utility of IMR_{angio} can be broadened across the spectrum of coronary syndrome, by assessing its diagnostic performance also in patients with non-ST-elevation acute coronary syndrome (NSTE-ACS) and CCS compared to pressure-wire-derived IMR. Furthermore, we assessed whether IMR_{angio} could retain its diagnostic accuracy also in non-hyperaemic conditions ($NH\text{-}IMR_{angio}$), thus overcoming the inherent limitation of adenosine-dependence of IMR. Moreover, we investigated the relationship of IMR_{angio} and $NH\text{-}IMR_{angio}$ with microvascular obstruction (MVO) at cardiac magnetic resonance (CMR), as a structural index of CMD and known to be related with IMR [9].

Methods

Patients admitted to the Oxford Heart Centre from September 2018 until February 2020, for a clinically-indicated invasive coronary angiography were prospectively consented for enrolment into the OxAMI (Oxford Acute Myocardial Infarction) study [4]. Exclusion criteria are reported in Supplementary Materials. OxAMI study was approved by the Oxford University Hospitals ethics committee and conducted in accordance with the Declaration of Helsinki (REC number 10/H0408/24). All patients provided informed consent for participation to the study.

Enrolled patients were divided into 3 groups according to the clinical presentation (STEMI, NSTE-ACS and CCS), defined according to the most recent recommendations (Supplementary material).

In patients with STEMI undergoing primary PCI, invasive coronary physiology assessment of the infarct related artery (IRA) was performed after flow restoration with thrombus aspiration and/or balloon dilatation (e.g. immediately before stenting) and/or at completion of primary PCI, as previously described [4] (Fig. 1).

In patients with NSTE-ACS or CCS, invasive coronary physiology assessment was performed before and/or at completion of revascularization. In a subset of patients with STEMI and NSTE-ACS, IMR was also measured in one

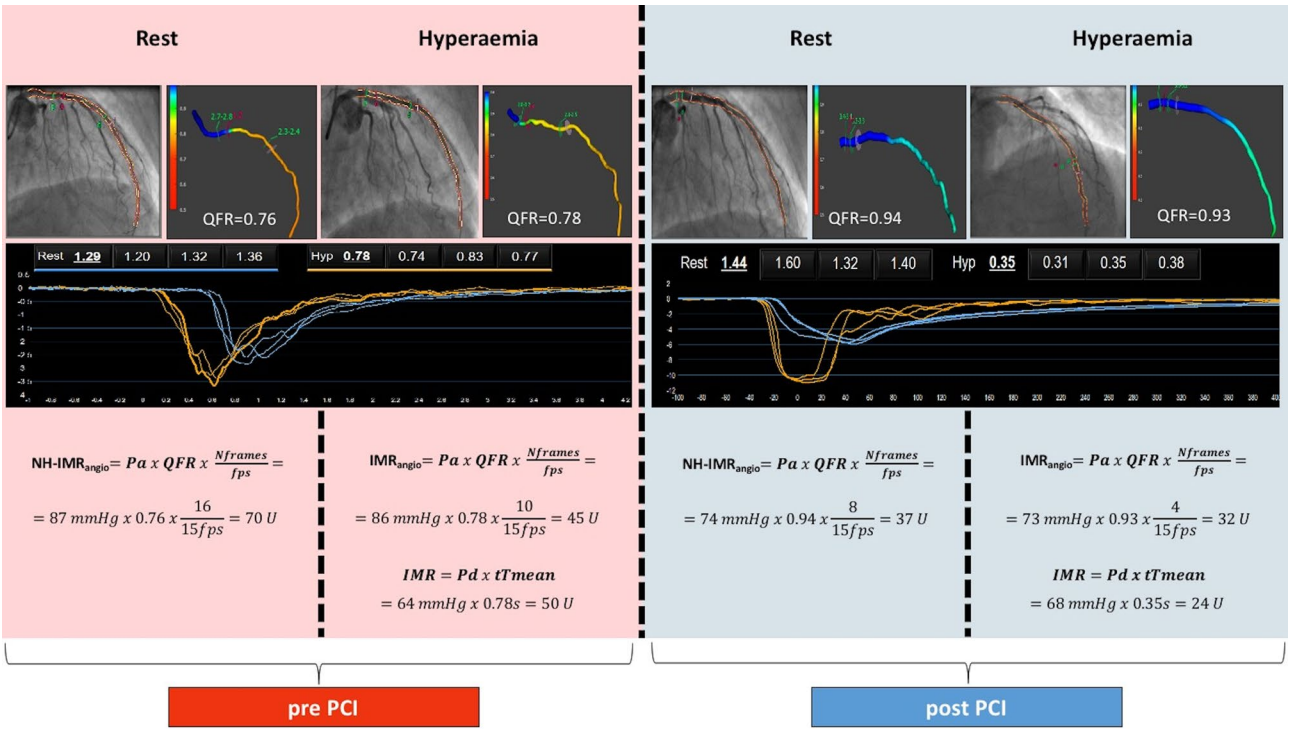


Fig. 1 Derivation of $NH\text{-}IMR_{angio}$ and IMR_{angio}

of the non-IRAs. The identification of the IRA was based on the combination of (1) lesion angiographic appearance compatible with plaque instability or presence of thrombus, (2) electrocardiographic and (3) echocardiographic findings.

In patients with CCS, microvascular angina was defined as a condition of increased IMR (> 25U) in the absence of both angiographic and functional (fractional flow reserve (FFR) > 0.8) significant epicardial stenosis [6].

Index of microcirculatory resistance and microvascular vasodilatory capacity

IMR was measured in a standard fashion using thermodilution technique and pressure wire (Abbott, Santa Clara CA) on the CoroFlow system (Coroventis, Uppsala Sweden) as previously reported [4].

Resistive reserve ratio (RRR) was calculated in all patients at the same time-points when IMR was assessed, as previously described [10] (For details see Supplementary material). RRR was measured to assess coronary microvascular vasodilatory capacity and to evaluate wheter it was associated with the diagnostic performance of IMR_{angio} and $NH\text{-}IMR_{angio}$ in different clinical settings.

Quantitative flow ratio measurement

Three-dimensional quantitative coronary angiography (3D-QCA) and then QFR were measured off-line using QAngio® XA 3D software (Medis, Leiden, the Netherlands) by two independent certified operators (RS, MS) blinded to clinical, IMR and CMR data. At each time-point, QFR was assessed both at resting and at maximal hyperaemia. See supplementary material for details.

Angiography-derived Index of microcirculatory resistance

IMR_{angio} was derived from QFR as previously described [8] and reported in details in the Supplementary material.

Briefly, IMR_{angio} was calculated as:

$$IMRangio = Pa(hyperaemia) \times QFR(hyperaemia) \times \frac{Nframes(hyperaemia)}{fps}$$

being $Pa_{(hyperaemia)}$ mean aortic pressure at hyperaemia, Nframes the number of frames for contrast dye to travel from the guiding catheter to a distal reference (corresponding to the position of the distal marker of the pressure wire) and the fps is frame-acquisition rate, set at 15 frames/second.

$NH\text{-}IMR_{angio}$ was derived using the same formula but replacing the hyperaemic parameters with the resting ones as follows:

$$NH - IMRangio = Pa(resting) \times QFR(resting) \times \frac{Nframes(resting)}{fps}$$

IMR_{angio} and $NH\text{-}IMR_{angio}$ were derived for all the time points when invasive IMR was measured.

QFR and IMR_{angio} were analyzed by 2 independent operators in 29 vessels, in order to assess interobserver variability. Given the satisfactory interclass coefficient (see "Results" section), the remaining 217 vessels included in the analysis was assessed by either of the two operators, blinded to the clinical characteristics including invasive coronary physiology data (FFR, IMR or CFR).

Cardiac magnetic resonance imaging in patients with acute myocardial infarction

In STEMI patients, CMR scans were performed following primary PCI but before discharge from hospital using a 3.0 T scanner (either MAGNETOM TIMTrio or MAGNETOM Verio, Siemens Healthcare, Germany). Sequence acquisitions included cine and late gadolinium enhancement (LGE) imaging was performed as previously described [11].

Microvascular obstruction (MVO) was defined as hypointense areas within the hyperenhancement region on the LGE images and was manually contoured [11]. We considered an MVO > 1.55% of LV mass as prognostically significant based on de Waha et al [12].

Statistical analysis

Continuous variables were expressed as median accompanied by interquartile range. Frequencies were compared using Fisher's exact test. Continuous variables were compared using Mann–Whitney's test or Kruskall Wallis' test, as appropriate. Wilcoxon test were used for paired samples. Correlations between variables were expressed using Spearman rho coefficients.

To assess inter-rater reliability, interclass coefficient (ICC) estimates and their 95% confident intervals were calculated based on a mean-rating ($k = 2$), absolute-agreement, 2-way mixed-effects model. The correlation of the readings of the two readers was also assessed using Spearman's Rho correlation coefficient.

The agreement between IMR_{angio}, $NH\text{-}IMR_{angio}$ and invasive IMR was assessed using Bland–Altman plot. Receiver-operating characteristic (ROC) curve analysis was used to define the diagnostic performance of IMR_{angio} and $NH\text{-}IMR_{angio}$ in detecting CMD. In STEMI, CMD was defined as IMR > 40U or MVO > 1.55%. In NSTE-ACS and CCS

patients, CMD was defined as IMR > 25U [6]. Areas under the ROC curves (AUC) were compared using the DeLong method.

In STEMI, a hybrid algorithm using both NH-IMR_{angio} and IMR_{angio} was developed to define the presence of significant CMD (IMR > 40 U) in the IRA territory. Lower and upper NH-IMR_{angio} cut-offs were identified as ≥ 90% negative predictive value (NPV) and ≥ 90% positive predictive value (PPV), respectively, for an IMR > 40 U.

Statistical analysis was performed using SPSS 25.0 (Inc Chicago, Illinois) and MedCalc (Ostend, Belgium). A p value < 0.05 was considered statistically significant.

Results

Clinical and procedural characteristics

A total of 145 patients were included in the current analysis, including 66 STEMI, 43 NSTEMI and 36 CCS patients. Clinical and procedural characteristics are presented in Table1. Consequently, the agreement between angiography-derived and thermodilution-derived IMR was assessed in a total of 246 measurements (189 coronary vessels) (Fig. 2).

Coronary microvascular dysfunction across the spectrum of coronary syndromes

Before intervention, IMR was significantly higher in the IRA of STEMI patients (IMR 46.2 [24.6–68.3]) compared with NSTE-ACS (22.3 [18.1–29.0]) and CCS (20.5 [14.1–32.9]; p < 0.0001) (Table 1 and Supplementary Figure 1), whilst no significant differences in IMR were observed between patients with NSTE-ACS and CCS.

IMR decreased post-PCI in patients with STEMI (IMR 46.2 [24.6–68.3] vs 30.9 [19.2–51.1], p = 0.001) but not in patients with NSTE-ACS and CCS (Supplementary Figure 1).

Overall, in patients with STEMI, IMR was significantly higher in the IRA compared with the non-IRAs (35.8 [20.2–60.0] vs 18.9 [12.8–26.9], p < 0.0001). No difference in IMR was observed between the IRA and non-IRA in NSTE-ACS (22.7[17.2–28.9] vs 18.6[13.3–28.5], p = 0.27) (Supplementary Figure 2).

In the CCS group 15 coronary vessels in 12 patients presented an abnormal FFR (≤ 0.80). Within the CCS group a condition of microvascular angina (FFR > 0.80 and IMR > 25U) was observed in 10 out of 36 patients (22.2%), whist 14 out of 36 (38.9%) did not show either significant epicardial stenosis (FFR > 0.80) or presence of microvascular impairment (IMR < 25U). Notably, a substantial agreement was observed between IMR and $IMR_{corrected}$ as shown in the Supplementary Figure 3.

IMR_{angio} across the spectrum of coronary syndromes

Satisfactory ICC was observed for IMR_{angio} (0.97, 95% CI 0.93–0.99; F = 31.8, p < 0.0001).

Before intervention IMR_{angio} was significantly higher in the IRA of STEMI patients (39.6 [26.1–50.9]) compared with NSTE-ACS (25.3[16.6–42.3]) and CCS (20.1[14.4–30.6], p < 0.0001) (Table 1 and Fig. 3). As IMR, IMR_{angio} also decreased significantly post-PCI in STEMI (39.6 [26.1–50.9] vs 31.8 [21.0–45.2], p = 0.002) but did not change significantly in NSTE-ACS and CCS (Fig. 3).

Notably in the subgroup of CCS patients without obstructed coronary disease (FFR > 0.80) IMR_{angio} was significantly higher in patients with microvascular angina (defined as invasive IMR > 25U) compared to those without (31.0[25.3–42-5] vs 16.6[14.1–19.7] p < 0.001) (Fig. 4).

Overall, IMR_{angio} and invasive IMR were significantly correlated (rho = 0.78, p < 0.0001).

Notably, the correlation was maintained across the whole spectrum of coronary syndromes, both before and after PCI, as well as in the IRA as in the non-IRA for STEMI and NSTE-ACS (Fig. 5). The Bland Altman analysis showed a significant agreement between IMR and IMR_{angio} especially in cases with IMR below 75 U. Conversely, the absolute numerical values of the two indices were less related in cases of severe microvascular dysfunction (Fig. 6). The correlation between IMR_{angio} and IMR in LAD vs non-LAD vessels is presented in the Supplementary Figure 4.

Non-Hyperaemic-IMR_{angio} across the spectrum of coronary syndromes

Satisfactory ICC was observed for NH-IMR_{angio} (0.90, 95% CI 0.64–0.92; F = 11.7, p < 0.0001).

Before intervention, NH-IMR_{angio} did not differ significantly between STEMI (39.9[28.3–60.4]), NSTE-ACS (42.7[25.5–62.8]) and CCS (36.7[23.5–44.4], p = 0.110) (Table 1 and Supplementary Figure 5). However, in STEMI patients NH-IMR_{angio} was significantly higher in the IRA compared with the non-IRA (39.9[28.3–60.4] vs 22.5[21.2–43.3], p = 0.031).

Overall, NH-IMR_{angio} showed a significant correlation with IMR in STEMI (rho = 0.64, p < 0.0001, Fig. 5), a modest correlation in CCS (rho = 0.33, p = 0.018) and it was not correlated with IMR in NSTE-ACS (rho = 0.23, p = 0.121) (Supplementary Figures 6 and 7).

Notably, in the STEMI cohort, the correlation between NH-IMR_{angio} and IMR was maintained when analysis was restricted to the IRA either pre-PCI (rho = 0.68, p < 0.0001), or post-PCI (rho = 0.67, p < 0.0001) but not in the non-IRA (rho = 0.33, p = 0.21).

Table 1 Clinical, procedural and haemodynamic data

	STEMI	NSTE-ACS	CCS	p-value
Clinical data				
Age, years	63.5(56.0–71.0)	63.0(56.0–71.2)	67.0(59.0–74.0)	0.244
Sex male, n (%)	56(84.8)	26(60.5)	24(66.6)	0.014
Hypertension, n (%)	33(50.0)	26(60.5)	24(66.6)	0.424
Hypercholesterolaemia, n (%)	24(36.4)	14(32.6)	17(47.2)	0.397
Diabetes, n (%)	9(13.6)	6(13.9)	6(16.7)	0.938
Current smoker, n (%)	34(51.5)	20(46.5)	14(38.9)	0.279
*Target vessel**				
LAD, n (%)	29(43.9)	24(55.8)	27(77.1)	0.016
LCX, n (%)	7(10.6)	8(18.6)	1(2.9)	
RCA, n (%)	28(42.4)	9(20.9)	6(17.1)	
Intermediate, n (%)	2(3.0)	2(4.7)	1(2.9)	
TIMI Flow—pre-PCI				
0	44(66.7)	2(4.6)	0(0.0)	< 0.0001
1	6(9.0)	1(2.3)	0(0.0)	
2	10(15.3)	13(30.2)	0(0.0)	
3	6(9.0)	27(62.8)	52(100)	
TIMI Flow—post-PCI				
0	0(0.0)	0(0.0)	0(0.0)	< 0.001
1	2(3.0)	0(0.0)	0(0.0)	
2	10(15.2)	3(7.0)	0(0.0)	
3	54(81.8)	40(93.0)	52(100)	
Ischemic time, min	196(127–425)	–	–	–
*Coronary physiology data—pre-PCI***				
FFR	0.75(0.61–0.86)	0.85(0.80–0.94)	0.83(0.73–0.90)	0.008
QFR	0.78(0.72–0.84)	0.83(0.78–0.93)	0.87(0.77–0.93)	0.002
CFR	1.30(1.10–1.91)	3.00(1.37–4.46)	2.10(1.58–3.90)	0.001
RRR	1.60(1.33–1.94)	3.00(2.12–4.89)	2.78(1.61–4.28)	< 0.0001
IMR	47.5(24.4–68.2)	22.3(17.7–28.9)	20.5(14.7–31.8)	< 0.0001
IMRangio	39.6(26.1–50.9)	25.3(16.6–42.3)	20.1(14.4–30.6)	< 0.0001
NH-IMRangio	39.9(28.3–60.4)	42.7(25.5–62.8)	36.7(23.5–44.4)	0.110
*Coronary physiology data—post-PCI***				
FFR	0.94(0.89–0.98)	0.88(0.84–0.96)	0.87(0.82–0.93)	0.015
QFR	0.96(0.91–0.99)	0.94(0.86–0.97)	0.93(0.88–0.99)	0.182
CFR	1.80(1.41–2.65)	2.59(2.03(3.35)	2.10(1.58–3.47)	0.004
RRR	2.04(1.63–2.81)	2.86(2.00–4.09)	2.41(1.64–3.70)	0.003
IMR	29.7(19.8–49.3)	22.7(15.7–28.4)	15.8(11.9–34.8)	0.035
IMRangio	31.8(21.0–45.2)	24.8(16.5–33.0)	23.9(8.1–27.7)	0.018
NH-IMRangio	45.5(31.7–67.6)	45.1(22.4–58.1)	39.7(23.1–42.6)	0.316

*Target vessel in STEMI and NSTE-ACS corresponds to IRA; **Complete physiology data is available in Supplementary Table 1

The Bland Altman analysis confirmed the good agreement between NH-IMRangio and invasive IMR in STEMI, up to severe degree of microvascular dysfunction (Fig. 6, Supplementary Figures 6 and 7). The correlation between $NH\text{-}IMR_{angio}$ and IMR in LAD vs non-LAD vessels is presented in the Supplementary Figure 8.

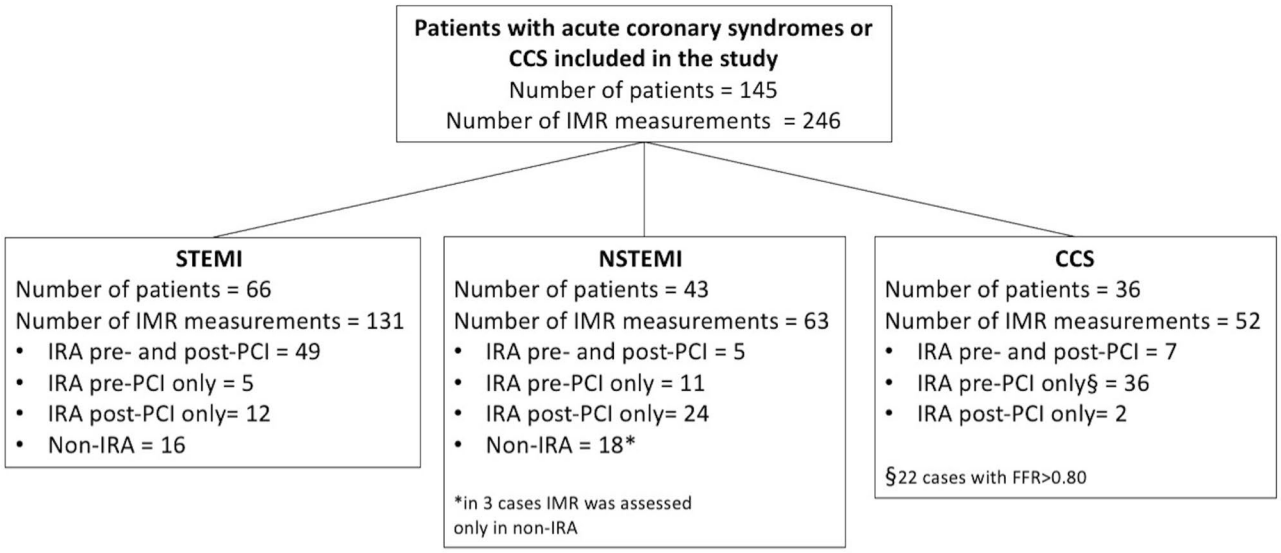


Fig. 2 Study flow chart

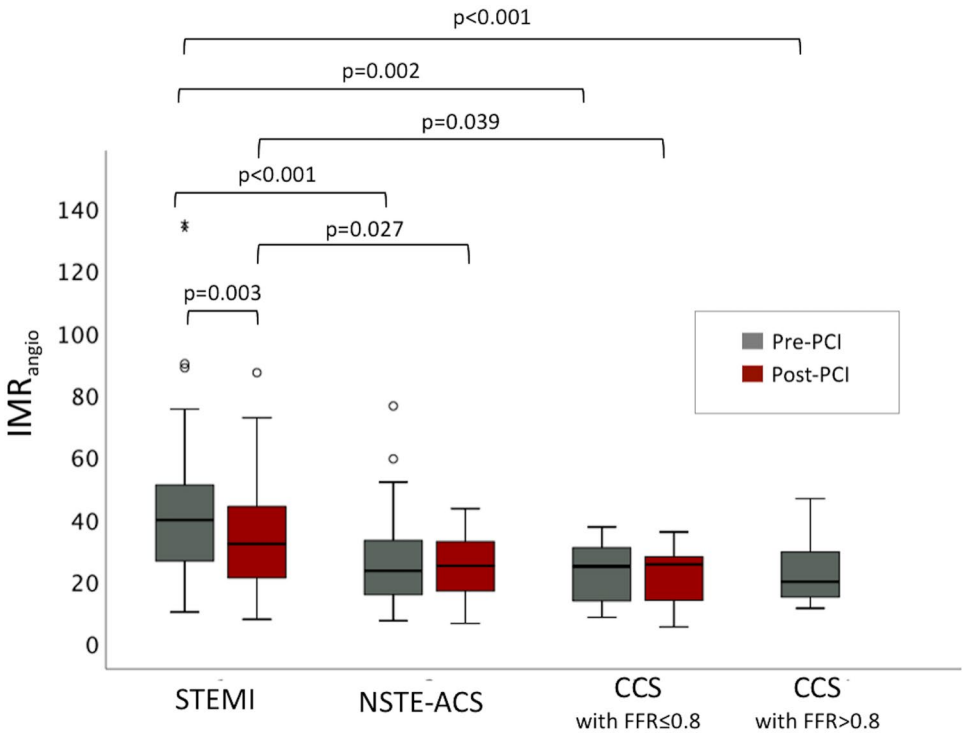


Fig. 3 IMR_{angio} across the spectrum of coronary syndromes. Box plots depict IMR_{angio} median values in patients with STEMI, NSTE-ACS and CCS before and after PCI. CCS cases with FFR > 0.80 at baseline did not undergo PCI. p-value is provided for statistically significant differences between the subgroups. Other comparisons were not statistically significant

Microvascular vasodilatory capacity and angiography-derived microcirculatory resistance indices

RRR was significantly lower in patients with STEMI compared with NSTE-ACS and CCS patients, indicating a more severe impairment of microvascular vasodilatory capacity in the STEMI group (Table 1 and Supplementary Figure 6). No significant differences in RRR were observed between NSTE-ACS and CCS (Table 1 and Supplementary Figure 9).

The median RRR value in the whole cohort was 2.18, with higher proportion of STEMI patients (67.3%) presenting impaired RRR (<2.18) in the IRA, compared with NSTE-ACS (27.9%), CCS (43.7%) and the non-IRA (32.2%, p < 0.001).

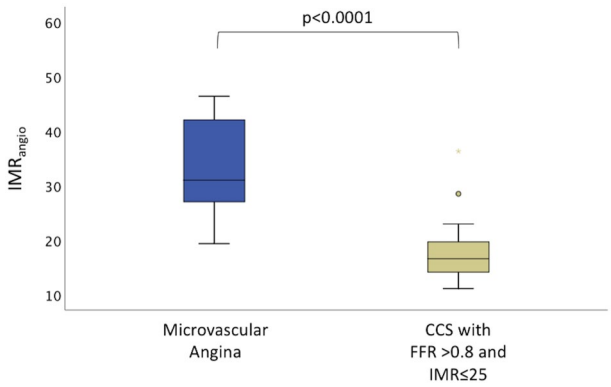


Fig. 4 IMR_{angio} in patients with microvascular angina (defined as FFR > 0.8 and IMR > 25 U) vs patients with unobstructed coronary artery disease (FFR > 0.8) but normal microcirculatory function (IMR ≤ 25 U)

IMR_{angio} maintained a good correlation with IMR both in the group with low (rho = 0.80, p < 0.001) as in the group with high RRR (rho = 0.64, p < 0.001) (Supplementary Figure 10).

Conversely, NH-IMR_{angio} and thermodilution-derived IMR were well related (rho = 0.66, p < 0.001) in patients with low RRR (< 2.18) but less well correlated (rho = 0.36, p < 0.001) in patients with high RRR (≥ 2.18) (Supplementary Figure 10).

Diagnostic performance of IMR_{angio} and NH-IMR_{angio}

In patients with STEMI, IMR_{angio} predicted IMR > 40 U with an AUC of 0.93 (CI 95%: 0.88–0.98, p < 0.0001) (Fig. 7). The best IMR_{angio} cut-off to predict IMR > 40 U was 40 (Youden index = 0.79). IMR_{angio} > 40 U presented a

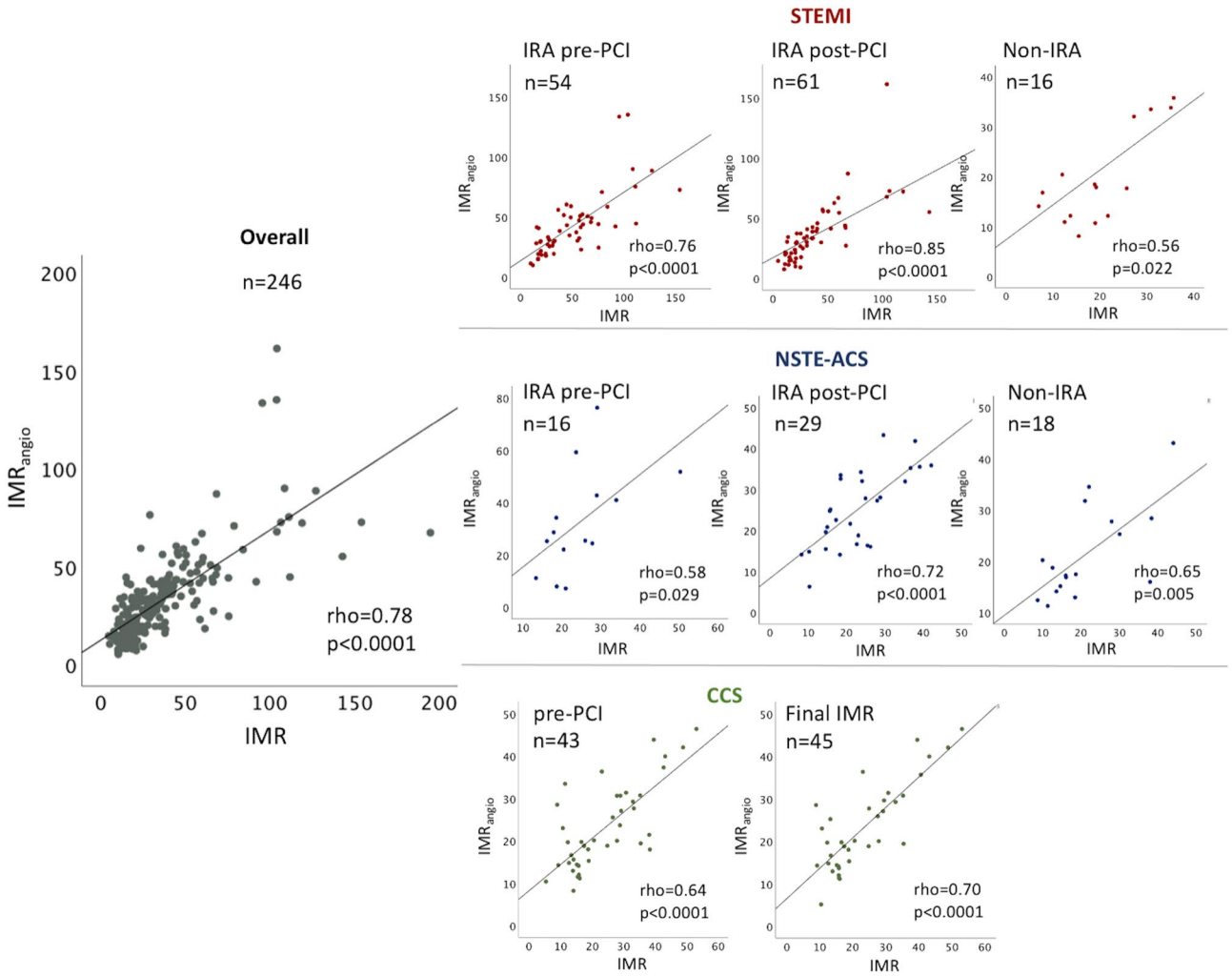


Fig. 5 Correlation between IMR_{angio} and IMR. Scatter plots summarise correlations between IMR_{angio} and IMR in patients with STEMI, NSTE-ACS and CCS. Final IMR for CCS include baseline measurements for patients with FFR > 0.8 and post-PCI values for patients with FFR ≤ 0.8 who underwent PCI

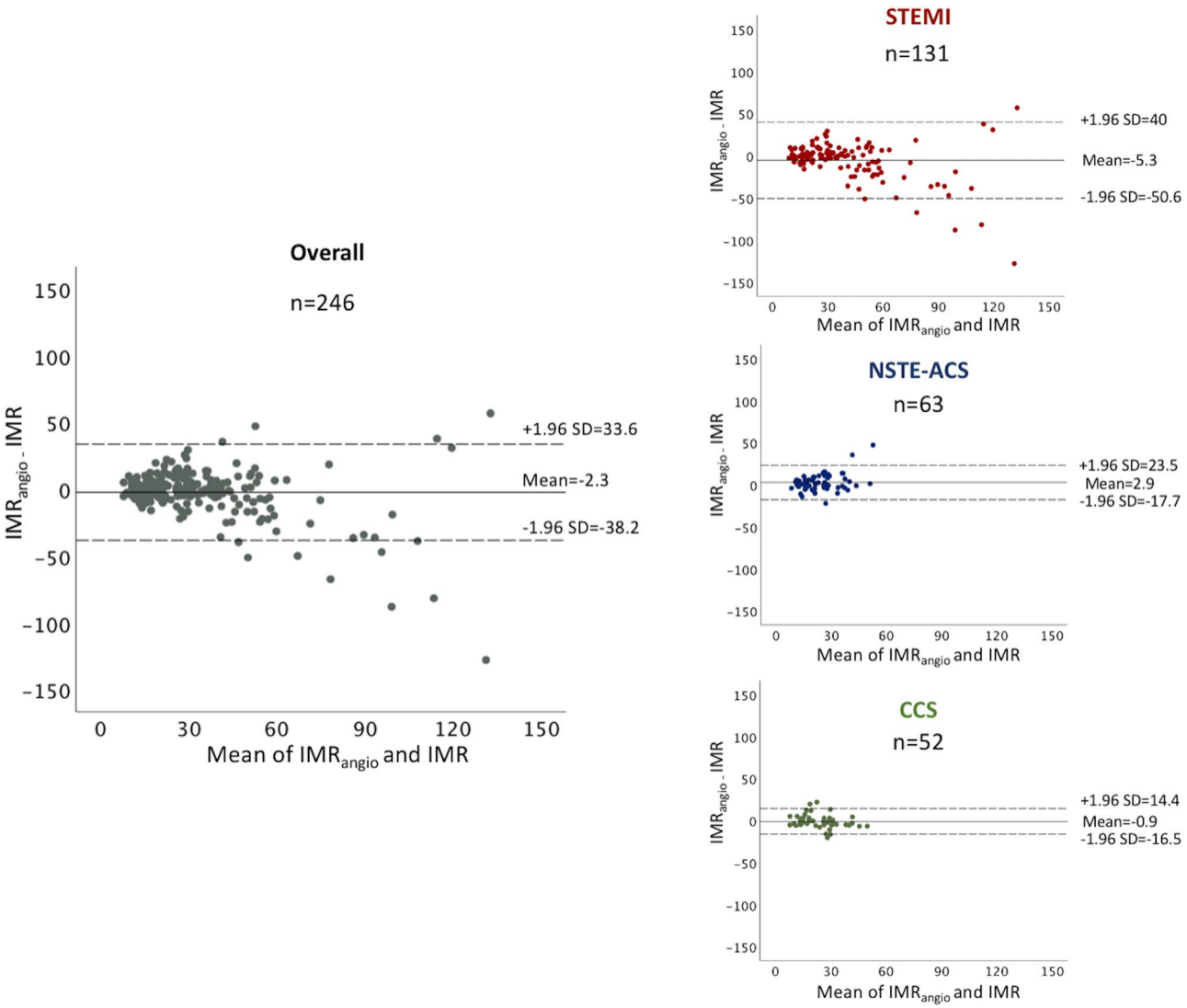


Fig. 6 Bland–Altman plots. Bland–Altman plots summarise agreement between IMR_{angio} and IMR in STEMI and NSTEMI/CCS patients

diagnostic accuracy of 88.6%, NPV of 87.9%, PPV of 89.6%, sensitivity of 84.3% and specificity of 92.1%.

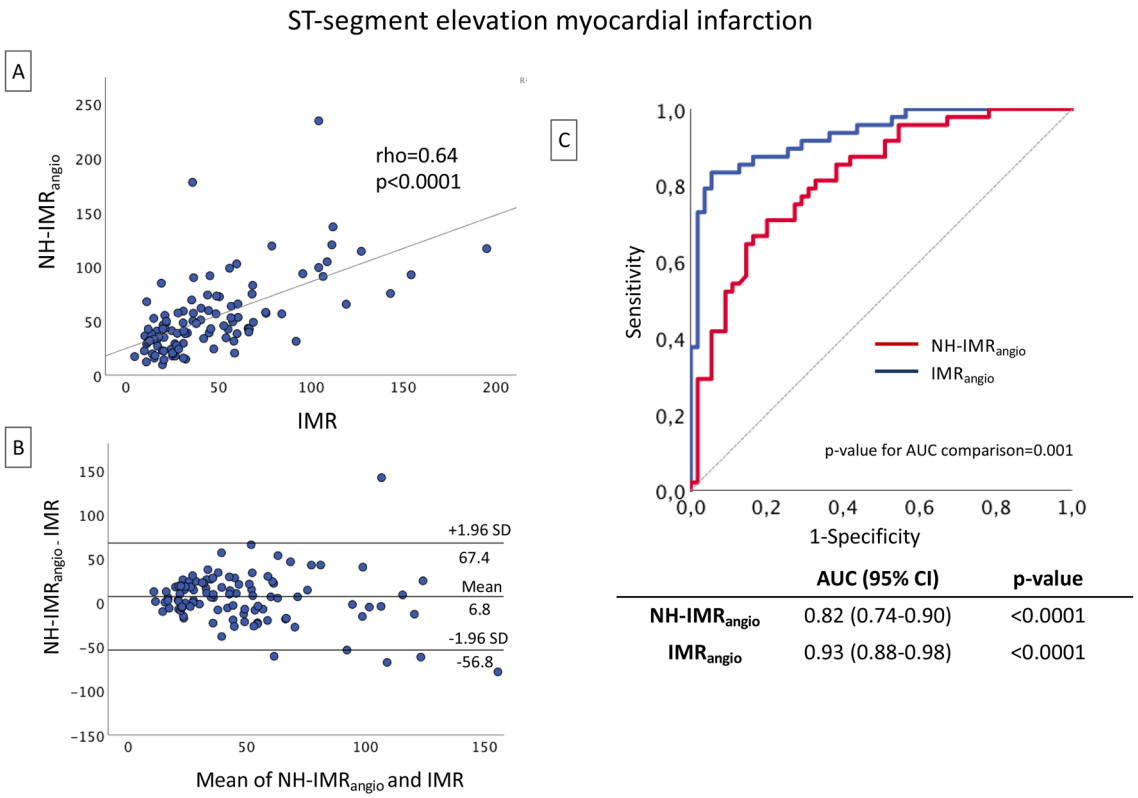
A good accuracy of IMR_{angio} was also maintained in NSTE-ACS. IMR_{angio} predicted an invasive-IMR > 25 U with an AUC of 0.78 (CI 95%: 0.64–0.93, p < 0.0001) (Supplementary Figure 7). The best IMR_{angio} cut-off in NSTE-ACS was 25 and demonstrated a diagnostic accuracy of 73.3%, NPV of 87.1%, PPV of 58.6%, sensitivity of 80.9% and specificity of 69.2%.

In patients with CCS, IMR_{angio} predicted IMR > 25 U with an AUC of 0.88 (CI 95%: 0.79–0.97, p < 0.0001) (Supplementary Figure 8). The best IMR_{angio} cut-off in CCS was 25 and demonstrated a diagnostic accuracy of 78.4%, NPV of 80.0%, PPV of 76.2%, sensitivity of 72.7% and specificity of 82.8%.

In STEMI patients, NH-IMR_{angio} demonstrated a good diagnostic performance in predicting IMR > 40 U in the IRA (AUC = 0.82, 95% CI 0.74–0.90, p < 0.0001), but was less accurate when compared with IMR_{angio} (p = 0.001) (Fig. 7). The diagnostic performance of NH-IMR_{angio} was however suboptimal in patients with NSTE-ACS (AUC = 0.64, 95% CI 0.47–0.81, p = 0.11) and CCS (AUC = 0.63, 95% CI 0.48–0.79, p = 0.10) (Supplementary Figures 7 and 8).

IMR_{angio}, NH-IMR_{angio} and MVO

CMR imaging was performed in 49 STEMI patients (Supplementary Table 1). MVO > 1.55% was present in 18 (36.7%) cases. Patients with MVO ≥ 1.55% showed both higher IMR_{angio} (41.0[29.5–64.3] vs 27.4[15.7–38.4], p = 0.008)



	AUC (95% CI)	p-value
NH-IMR$_{angio}$	0.82 (0.74-0.90)	<0.0001
IMR$_{angio}$	0.93 (0.88-0.98)	<0.0001

Fig. 7 Non-Hyperaemic-IMR$_{angio}$ in the infarct-related-artery of STEMI. Scatter plot (**a**) and Bland Altman (**b**) analysis summarise significant correlation and agreement between NH-IMR$_{angio}$ and IMR in patients with STEMI. Panel C shows the ROC curve analysis for IMR$_{angio}$ and NH-IMR$_{angio}$ in predicting a pressure-wire IMR > 40 U in the IRA of STEMI

and NH-IMR$_{angio}$ (58.9[42.6–90.8] vs 43.4[30.1–59.1], p = 0.026) compared with patients with MVO < 1.55% (Supplementary Figure 11). IMR$_{angio}$ (AUC = 0.76, 95% CI: 0.61–0.91, p = 0.007) and NH-IMR$_{angio}$ (AUC = 0.71, 95% CI: 0.54–0.87, p = 0.033) presented fair and comparable diagnostic accuracy in predicting the presence of MVO > 1.55% (Supplementary Figure 11).

Hybrid IMR$_{angio}$ algorithm to assess coronary microvascular dysfunction in STEMI infarct-related artery

A cut-off value of < 30U of NH-IMR$_{angio}$ presented a NPV = 92.3% in excluding an IMR > 40 U. Conversely, a NH-IMR$_{angio}$ > 90U presented a PPV = 93.3% in detecting an IMR > 40U.

A hybrid decision-making strategy in which IMR$_{angio}$ was measured only in vessels presenting NH-IMR$_{angio}$ higher than 30U and lower than 90U, yielded an 88.0% agreement with IMR classification, sparing the administration of adenosine in 38.0% of the cases (Fig. 8).

Discussion

The main results of our analysis are the following:

1. IMR$_{angio,}$ is a hyperaemic, angiography-based and pressure-wire-free index, with good diagnostic accuracy in defining an abnormal value of invasively measured pressure-wire-derived IMR.
2. The diagnostic accuracy of IMR$_{angio}$ is maintained across the whole spectrum of coronary syndromes, including STEMI, NTE-ACS and CCS. In STEMI, its diagnostic value is further confirmed by its correlation with MVO on CMR.
3. NH-IMR$_{angio,}$ a non-hyperaemic resting version, maintains a good diagnostic performance in STEMI whilst the same does not hold true in the non-IRA and in NSTE-ACS and CCS. This is likely to be due to the depleted vasodilatory capacity of the coronary microcirculation in STEMI, as reflected by a lower RRR.

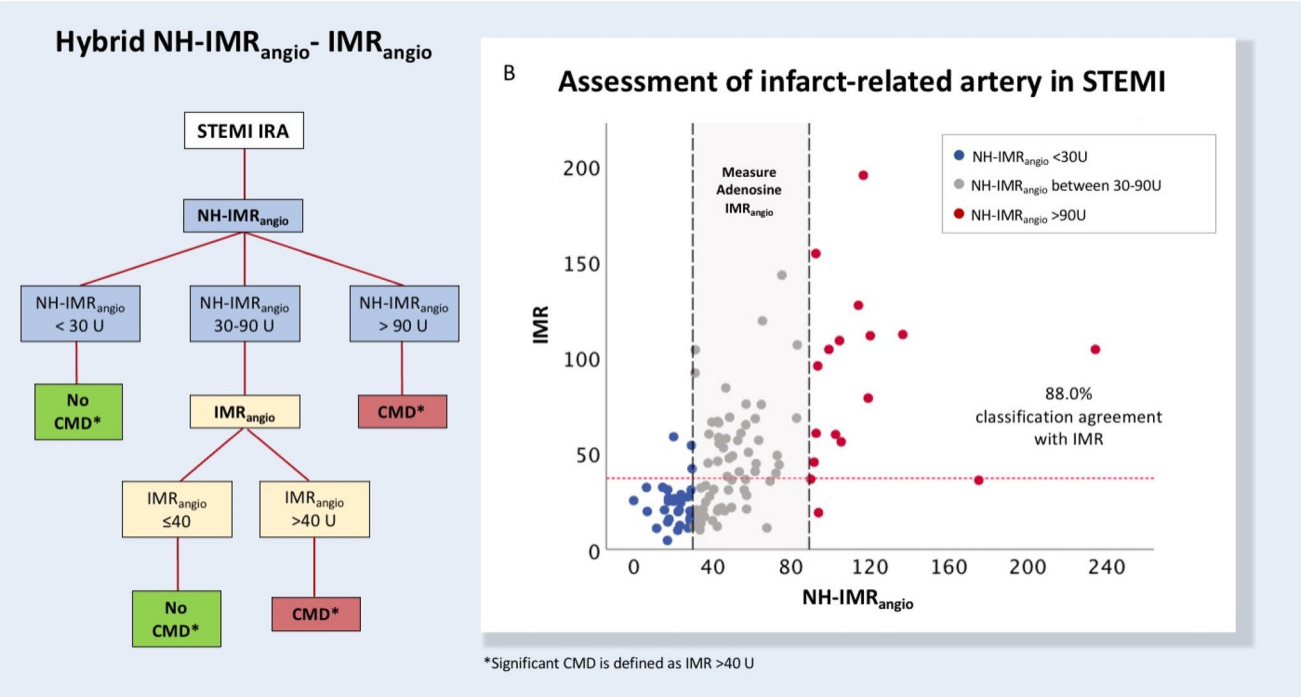


Fig. 8 Hybrid IMR$_{angio}$ algorithm in STEMI. Panel A shows the flow-chart of microcirculatory assessment of the IRA in STEMI patients using a "hybrid" NH-IMR$_{angio}$/IMR$_{angio}$ decision making strategy. Details of lesion distribution are shown in B. Overall, 38% of the lesions can be assed with high-accuracy by means of NH-IMR$_{angio}$ only. A NH-IMR$_{angio}$ cut-off of 30U presents a NPV of 92% in excluding IMR > 40U. Conversely, a NH-IMR$_{angio}$ cut-off of 90U presents a PPV of 93% in detecting IMR > 40U. The algorithm offers a diagnostic accuracy in predicting invasive IMR of 88.0%

Besides the well-established assessment of the epicardial segment of the coronary tree, a comprehensive physiological evaluation of CMD has important prognostic and therapeutic implications [6, 7]. Specifically, in patients with STEMI, the presence of microvascular injury has been associated with an increased risk of adverse outcome [5, 11, 13]. More recently, IMR has also been proposed as an accurate tool to early identify STEMI patients at increased risk of suboptimal reperfusion, who have potential benefit from additional therapies or closer monitoring [2]. Nevertheless, the application of CMD assessment in routine clinical practice remains extremely limited. This has been attributed to the requirement for a pressure-wire assessment and the associated additional procedural time, procedural cost and increased procedural complexity. The need of inducing hyperaemia with adenosine infusion is also a limiting factor.

In order to overcome some of these limitations, we have recently developed and validated IMR$_{angio}$ as an angiography-derived and pressure-wire-free index to assess CMD [8]. However, its validation was limited to a relatively small cohort of STEMI patients. In this study we have extended those observations and shown that IMR$_{angio}$ maintains an excellent diagnostic performance also in patients with NSTE-ACS and CCS compared with pressure-wire-derived IMR.

To the best of our knowledge, this represents one of the few available reports comparing the degree of CMD, measured by pressure-wire derived IMR across the spectrum of coronary syndromes. However, this is the first time it has been done with the newly proposed angiography-derived IMR (IMR$_{angio}$).

Unsurprisingly, STEMI presentations were characterized by a higher degree of CMD (high IMR) and reduced microvascular vasodilatory capacity (low RRR) compared to NSTE-ACS and CCS.

Notably, IMR, IMR$_{angio}$ and RRR were not significantly different in NSTE-ACS and CCS and they did not differ between the IRA and non-IRA. This is in line with previous observations that microvascular impairment in the non-IRA, when present, is usually not severe and that the observed values of IMR are not significantly different from those measured in patients with CCS [14, 15].

Importantly, IMR$_{angio}$ closely reproduced the measured invasive IMR across the spectrum of coronary syndromes. Notably, on Bland Altman analysis, the agreement between IMR$_{angio}$ and invasive IMR was very close in NSTE-ACS and CCS, whereas it appeared more scattered in STEMI. This different behaviour is clearly due to the inherently higher biological variability of IMR in STEMI, in which

the degree of CMD ranges from low to very high. This is in line with our previous observation that the absolute numerical values of IMR and IMR_{angio} are less correlated in cases of extreme (very high IMR) microvascular dysfunction [8]. Consistently, it has been previously shown that the agreement between QFR and FFR is negatively affected by the presence of severe microvascular impairment [16]. Nonetheless, even though the difference between IMR and IMR_{angio} values tends to widen with the severity of microvascular impairment, it remains a clinically meaningful concordance between the two measures using standard conventional thresholds for IMR. In particular, the classification agreement between IMR_{angio} and IMR remains excellent (88.6%) in STEMI, when using the established cut-off of > 40 U for both parameters. Similarly, in patients with STEMI patients, the numeric agreement between NH-IMRangio and IMR remains strong up to extreme degrees of microvascular dysfunction, where the correlation between the two indices scatters.

In this study we also tested the accuracy of a non-hyperaemic and adenosine-free version of $IMR_{angio,}$ named NH-IMR_{angio} against IMR. We observed that it reliably detects abnormal IMR in the IRA in STEMI but it did not do so in the non-IRA and in NSTE-ACS and in CCS. The good correlation of NH-IMR_{angio} in the IRA in STEMI is dependent on a blunted vasodilatory response of the microcirculation to the hyperaemic agent, as reflected by a low RRR. This important observation is a further reflection of the different functional status of coronary microcirculation across the clinical presentations of STEMI, NSTE-ACS and CCS. When the vasodilatory response to adenosine is blunted, the RRR is exhausted and the difference between basal/non-hyperaemic and hyperaemic resistance is minimal, as observed in the IRA of STEMI [17]. This explains why in this setting, the agreement between a non-hyperaemic index of microvascular resistance (NH-IMR_{angio}) and the invasive (hyperaemic) IMR is maintained. Conversely, when the microvascular vasodilatory capacity is intact and the vasodilatory reserve is preserved, the vascular tone changes significantly after the administration of adenosine. In this case, a non-hyperaemic index of microvascular resistance does not reliably reflect the minimal level of resistance achievable at maximal hyperaemia. This is why in our study, the agreement between NH-IMR_{angio} and IMR was poor in the non-IRA of STEMI patients, and in NSTE-ACS and CCS, since the corresponding vascular beds were characterised by relatively preserved RRR and IMR.

Interestingly, when assessed against CMR-derived MVO, NH-IMR_{angio} and IMR_{angio} showed similar correlations. Importantly, similar prediction of MVO is a further proof that NH-IMR_{angio} and IMR_{angio} could be used, to a certain extent, interchangeably in the IRA of patients with STEMI.

Whether the two angiography-derived indices have similar long-term prognostic value needs to be tested in dedicated studies measuring validated clinical outcomes.

Our data suggest that NH-IMR_{angio} can be a valid and a more practical alternative to assess CMD in the IRA of STEMI undergoing primary PCI. Indeed, when incorporated and combined with IMR_{angio} into a hybrid decision-making algorithm, NH-IMR_{angio} would allow an adenosine-free microvascular assessment in nearly half of the cases (Fig. 8).

Whilst the prognostic value of CMD in STEMI patients is well documented, its prognostic relevance in patients with CCS or with unobstructed coronary disease has only recently been considered [18]. In this setting, a dedicated assessment of the coronary microvascular function in the catheterization laboratory was shown to be effective in reducing symptoms and increasing quality of life and treatment satisfaction [6]. In our study we showed that IMR_{angio} was significantly higher in patients with unobstructed coronary arteries but with high IMR. This means that IMR_{angio} is a potential tool in the assessment of CMD in patients with microvascular angina, in whom the adoption of physiology-based assessment is sometimes perceived as problematic because of the necessity to manipulate with a pressure-wire an unobstructed epicardial coronary artery.

Limitations

The relatively small sample limits the conclusions of our analysis. In particular, the final sample size for each clinical subgroup (STEMI, NSTE-ACS and CCS) has to be acknowledged as a potential limiting factor of our analysis. Secondly, in our study, IMR was used to define CMD with different cut-offs in STEMI and in NSTE-ACS/CCS. The IMR cut-off of 40 is a well-established and validated threshold to define CMD in STEMI [5, 13]. An IMR > 25 U has been previously proposed to define an abnormal coronary microcirculatory function in patients with CCS [6]. However, an analogous reference threshold for NSTE-ACS is missing. In our study we applied the same IMR threshold of 25 U used for CCS in NSTE-ACS, and this could explain the lower PPV and NPV observed for IMR_{angio} in NSTE-ACS compared to CCS. In the presence of severe epicardial disease and particularly when FFR is lower than 0.60, IMR tends to overestimate the true microvascular resistance because of the distal vessel underfilling and the collapse of microvessels with consequent falsely elevated microvascular resistance [19, 20]. Moreover, the contribution of collateral flow may cause a falsely increased value of distal coronary pressure measured by the pressurewire [21]. A slight overestimation of the IMR values cannot be excluded by our analysis since the coronary wedge pressure (Pw) was not available in

this series. Nevertheless, only 5.7% of the coronary vessels included in the analysis presented a severe epicardial stenosis (FFR < 0.60). Moreover, the corrected IMR obtained applying the Yong formula presented a substantial agreement with the IMR values (Supplementary Figure 3). Therefore, we did not anticipate a significant overestimation of the true IMR in the vast majority of the assessed coronary vessels [4, 21].

In this study the angiographic views for IMR_{angio} analysis were prospectively acquired immediately after invasive IMR measurement. However, in the everyday practice, it may be difficult to be sure of the achievement of the maximal hyperemic status without the use of a pressure-wire. We anticipate that continuous i.v. adenosine infusion for a standardized time > 1 min should guarantee the achievement of the maximal hyperemic status. This approach needs to be tested in future dedicated studies.

Lastly, other novel angiography-derived indices of microvascular function have been recently developed. In particular, Tebaldi and colleagues proposed an index that included the vessel length and correction for epicardial disease [22]. In this study, IMR_{angio} was not compared with other angiography-derived indices and future dedicated studies are warranted to explore these aspects of angiography-derived CMD assessment.

Conclusions

IMR_{angio} measured at maximal hyperaemia is a viable and pressure-wire-free alternative to IMR, with the potential of significantly simplifying the assessment of CMD in patients with acute and chronic coronary syndromes. NH-IMR_{angio} represents a reasonable alternative to IMR in the IRA of patients with STEMI, who usually have a blunted response to adenosine, as a consequence of the intra and peri-procedural microvascular injury. Both IMR_{angio} and NH-IMR_{angio} correlated well with MVO on CMR in STEMI patients.

When combined with IMR_{angio} in a hybrid decision-making algorithm, NH-IMR_{angio} can limit the need of inducing hyperaemia in nearly half of the cases, making the assessment of CMD in patients with STEMI even simpler and hence more easily adoptable in future research and clinical practice.

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Author contributions RS and MS co-ordinated the study, recruited patients, collected data, performed QFR analysis and prepared the manuscript. RS performed the statistical analysis. GLDM and APB conceived and designed the study, recruited patients and helped prepare the manuscript. AB performed CMR image analysis. RAK and DTP recruited patients, collected data and performed QFR analysis. JL, AL and KC contributed to study design, recruited patients and collected data. VMF helped design the study and supervised image analysis. HMGG and FR contributed to study's conception and design. All authors critically appraised the manuscript.

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Data availability The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Conflict of interest Dr RS is on the scientific advisory board for Abbott Laboratories. Dr GLDM has received grants for Abbott Laboratories and Miracor Medical SA. AB reports institutional funding for fellowship from Boston Scientific and speaker fees from Boston Scientific, Miracor Medical SA, Medtronic and Abbott. All other authors report no conflict.

Consent to participate All patients provided informed consent for participation in the OxAMI study.

Consent for publication All patients provided informed consent for anonymous publication of the results of the study.

Ethical approval OxAMI study was approved by the Oxford University Hospitals ethics committee and conducted in accordance with the Declaration of Helsinki (REC number 10/H0408/24).

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