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ORIGINAL PAPER

Impact of the use of plaque modification techniques on coronary microcirculation using an angiography-derived index of microcirculatory resistance

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Abstract

Many lesions in patients undergoing percutaneous coronary intervention (PCI) exhibit significant calcification. Several techniques have been developed to improve outcomes in this setting. However, their impact on coronary microcirculation remains unknown. The aim of this study is to evaluate the influence of plaque modification techniques on coronary microcirculation across patients with severely calcified coronary artery disease. In this multicenter retrospective study, consecutive patients undergoing PCI with either Rotablation (RA) or Shockwave-intravascular-lithotripsy (IVL) were included. Primary endpoint was the impairment of coronary microvascular resistances assessed by Δ angiography-derived index of microvascular resistance (ΔIMRangio) which was defined as the difference in IMRangio value post- and pre-PCI. Secondary endpoints included the development of peri procedural PCI complications (flow-limiting coronary dissection, slow-flow/no reflow during PCI, coronary perforation, branch occlusion, failed PCI, stroke and shock developed during PCI) and 12-month follow-up adverse events. 162 patients were included in the analysis. Almost 80% of patients were male and the left descending anterior artery was the most common treated vessel. Both RA and IVL led to an increase in ΔIMRangio

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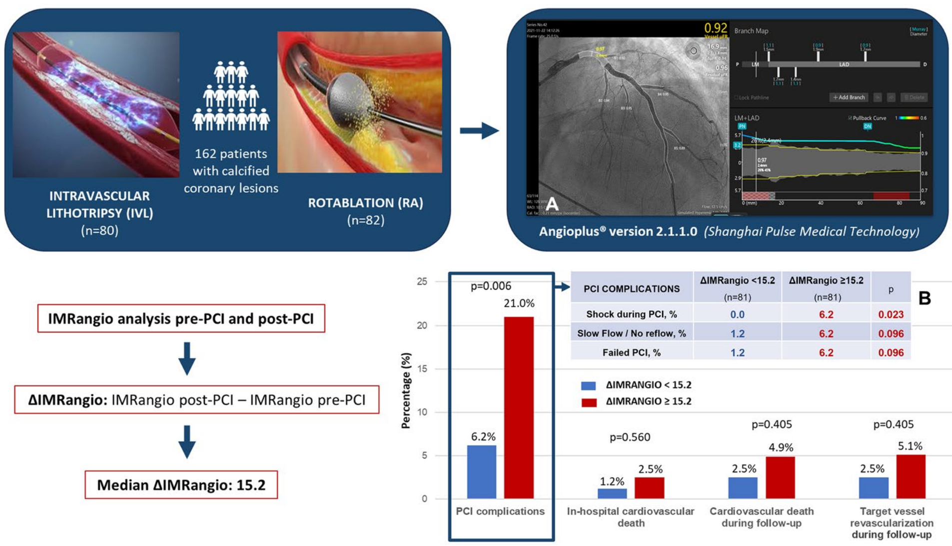
(22.3 and 10.3; p = 0.038, respectively). A significantly higher rate of PCI complications was observed in patients with ΔIMRangio above the median of the cohort (21.0% vs. 6.2%; p = 0.006). PCI with RA was independently associated with higher ΔIMRangio values (OR 2.01, 95% CI: 1.01–4.03; p = 0.048). Plaque modification with IVL and RA during PCI increases microvascular resistance. Evaluating the microcirculatory status in this setting might help to predict clinical and procedural outcomes and to optimize clinical results.

Graphical abstract

Impact of plaque modification techniques on coronary microcirculation assessed with an angiography-derived index of microvascular resistance (IMRangio). **A** 3-dimensional quantitative coronary angiography analysis and the Murray law based quantitative flow ratio (μFR) computation of left anterior descending coronary artery with Angioplus® version 2.1.1.0 (Shanghai Pulse Medical Technology). **B** Patients with ΔIMRangio ≥15.2 showed a higher percentage of complications during PCI with plaque modification techniques mainly due to a higher percentage of cardiogenic shock developed during PCI, slow flow and no reflow. *IMRangio* angiography-derived index of microvascular resistance, *PCI* percutaneous coronary intervention



Keywords Microcirculatory dysfunction · Index of microcirculatory resistance (IMR) · Angiography-derived IMR · Severe calcified coronary artery disease · Plaque modification techniques · Rotablation · Shockwave-intravascular lithotripsy

Abbreviations

ACS	Acute coronary syndrome
CAD	Coronary artery disease
CAG	Coronary angiography
FFR	Fractional flow reserve
IMR	Index of microvascular resistance
IMRangio	Angiography-derived index of microvascular resistance
IVL	Intravascular-lithotripsy
RA	Rotablation
LAD	Left descending anterior artery
LCx	Left circumflex artery
RCA	Right coronary artery
TIMI	Thrombolysis in myocardial infarction
TLR	Target lesion revascularization
μFR	Murray law based quantitative flow ratio

Introduction

Percutaneous coronary intervention (PCI) is the most common method of revascularization in patients with coronary artery disease (CAD). Moderate or severe coronary artery calcification is reported in about 30% of the patients undergoing PCI [1]. This represents a major challenge when performing PCI and complicate both short- and long-term outcomes following revascularization [2–4], especially due to underexpansion that ultimately leads to stent thrombosis or restenosis [5, 6]. Several techniques, including balloon-based and atheroablative technologies, have been developed to improve outcomes in this setting. Yet, they have potential hazards including the alteration of microcirculation due to embolization [7] which becomes relevant since the microcirculation provides coronary flow to the myocardium [8].

Wire-derived index of microvascular resistance (IMR), which is the most common tool to evaluate microvascular dysfunction, can predict adverse clinical outcomes and the extent of myocardial injury in patients with both chronic and acute CAD [9–15]. However, it requires additional PCI time, costs and high-tech software solutions [16]. In this regard, pressure-wire-free and angiography-based IMR (IMRangio), has been developed and validated to assess coronary microvascular function based on computational flow analysis [17–19]. Its fast and reproducible computation intends to overcome the limitations of wire-based physiology and to increase the use of physiology-based decision-making in CAD.

The aim of this study is to evaluate the impact of the use of RA and IVL on coronary microcirculation in patients with severely calcified CAD using IMRangio as well as to investigate the prognostic information that the evaluation of IMRangio may provide in this setting.

Methods

Study population

The present study is a retrospective multicenter study that included consecutive patients with severely calcified coronary artery disease who underwent PCI using plaque modification techniques such as rotablation (RA) or Shockwave-intravascular-lithotripsy (IVL) at three tertiary centers. Since IVL was only available as of 2019 in all participating centers, the inclusion period was defined from January 2019 until June 2022.

All inclusion criteria had to be met: (1) age older than 18 years old and (2) appropriate angiographic views for IMRangio analysis. Exclusion criteria were: (1) patients undergoing PCI in chronic total occlusions; (2) patients with epicardial stenosis with significant collaterals (those that could be seen in angiogram due to the severity of the lesion); (3) patients with TIMI flow grade pre-PCI < 2; (4) patients who underwent more than one plaque modification technique in the same procedure and (5) patients in cardiogenic shock before PCI were performed.

The study was conducted according to the guidelines of the Declaration of Helsinki and received the approval of the Institutional Review Board (Ref.: 2023/5042).

Study variables

Patient's demographics, cardiovascular risk factors and clinical history were collected from medical reports at admission and discharge. Left ventricle ejection fraction (LVEF) was assessed by echocardiography using the biplane Simpson method at admission. Treatments and procedures performed during hospital stay were also reported.

Coronary angiography, μFR and IMRangio computation

Hemodynamic data during PCI and the reason for coronary angiography (CAG) were registered. CAGs were performed either by femoral or radial access. Angiographic views as well as mean aortic pressure were obtained before and after performing RA or IVL.

The degree of coronary artery calcification that was classified as none/mild, moderate (radiopacities noted only during the cardiac cycle before contrast injection) or severe (radiopacities noted without cardiac motion before contrast injection involving both sides of the arterial lumen) [20] was also extracted from the medical record system.

A certified reader performed the 3-dimensional quantitative coronary angiography analysis and the quantitative flow ratio (μFR) computation in the CoreLab at the MedStar Cardiovascular Research Network using the Angioplus® software version 2.1.1.0 (Shanghai Pulse Medical Technology, INC). Murray law based QFR (μFR) is a novel computational method that uses artificial intelligence to estimate the fractional flow reserve (FFR) based on the analysis of a single angiographic projection with an excellent reproducibility [21].

Briefly, one angiographic projection with minimal overlap was selected, ensuring at least TIMI flow pre-PCI 2 was achieved, to estimate the IMRangio. The entire treated vessel was analyzed. Using ECG guidance, the end-diastolic frame was chosen. The software automatically detected the vessel contours and reconstructed a 3D anatomical vessel model for the 3D-QCA analysis. The analyst made corrections to the segment length and contours when needed. The number of frames (Nframes) required for contrast dye to travel from the proximal to the distal reference was recorded for the μFR analysis. IMRangio was assessed using the previously validated formula [17, 18] as follows:

$$IMRangio = Mean\,aortic\,pressure\,(rest) \times \mu FR\,(rest) \times \frac{N\,frames\,(rest)}{frame\,adquisition\,rate}$$

IMRangio was estimated for each patient before PCI and after performing the selected plaque modification technique. RA or IVL selection was left at the discretion of the treating physician.

ΔIMRangio was the chosen metric to assess the impact RA or IVL to mitigate the potential influence of pre-existing impaired microvascular resistances. ΔIMRangio was calculated as follows:

$$\Delta IMRangio : IMRangio\ postPCI - IMRangio\ prePCI$$

Outcomes during hospitalization and follow-up

Endpoints were defined according to The Academic Research Consortium-2 Consensus Document [22]. PCI complications, in-hospital mortality, death during follow-up and target lesion revascularization (TLR) during follow-up were investigated.

PCI complications were defined as the composite of flow-limiting coronary dissection, slow-flow/no reflow during PCI, coronary perforation, branch occlusion, failed PCI, shock developed during PCI, stroke during PCI and/or cardiac arrest during PCI.

Cardiovascular death was defined as any death by acute MI (myocardial infarction), sudden cardiac arrest, heart failure, stroke, cardiovascular procedures, cardiovascular hemorrhage or other cardiovascular cause.

Non-cardiovascular death was defined as any death resulting from malignancy, infection (including sepsis), accident/trauma, non-cardiovascular organ failure or other non-cardiovascular cause.

Adverse events during the follow-up period were defined as the composite of overall mortality and TLR.

Follow-up and event adjudication were performed by the study investigators reviewing the patients' medical records through the territorial health network and with phone calls, if necessary. One-year follow-up was available for 162 patients (100%).

Statistical analysis

Data are presented as mean ± standard deviation for continuous variables with a normal distribution, median and interquartile range (IQR) for continuous variables with a non-Gaussian distribution and with counts and percentages for categorical data. Normality of the variables was evaluated using the Shapiro–Wilk test.

Patients were stratified into two groups based on the employed technology (RA or IVL). Categorical variables were compared using the chi-squared test or Fisher's exact test, while continuous variables were analyzed with the *t*-test or ANOVA for normally distributed data, and the Mann–Whitney U-test or Kruskal–Wallis test for non-normally distributed data.

To assess variables associated with the impairment of coronary microvascular resistances we divided our cohort in 2 groups according to ΔIMRangio median values. Both univariate and multivariate logistic regression were conducted to identify factors associated with a greater deterioration of the microvascular status. Multivariate logistic regression analysis was adjusted for several variables, including those previously reported to influence microvascular circulation (gender, age, diabetes mellitus, vasculopathy, active smoking status, presentation as acute coronary syndrome, pre-PCI TIMI flow grade < 3), as well as those with significance at $p < 0.1$ in the univariate analysis. The threshold of $p < 0.1$ was chosen to be more inclusive of variables that may have a meaningful impact on microvascular circulation. Odds ratios (OR) were calculated for each case, accompanied by a 95% confidence interval. Statistical significance was set at two-tailed $p < 0.05$.

Statistical analyses were performed with the Stata software version 16.1 (College Station, TX).

Results

Initially, 192 patients were eligible for enrollment. Thirty patients were not included based on the exclusion criteria (Fig. 1). No significant differences were observed between patients included and excluded from the study (Table 1S from the supplementary material).

A total of 162 patients were finally included in the analysis. Median age was 75.8 years (IQR 68.1–81.9), 20.4% were female, 61.7% had diabetes mellitus, 21.0% were active smokers and 43.3% had prior history of coronary artery disease. In 66.7% of the patients, PCI was performed in the

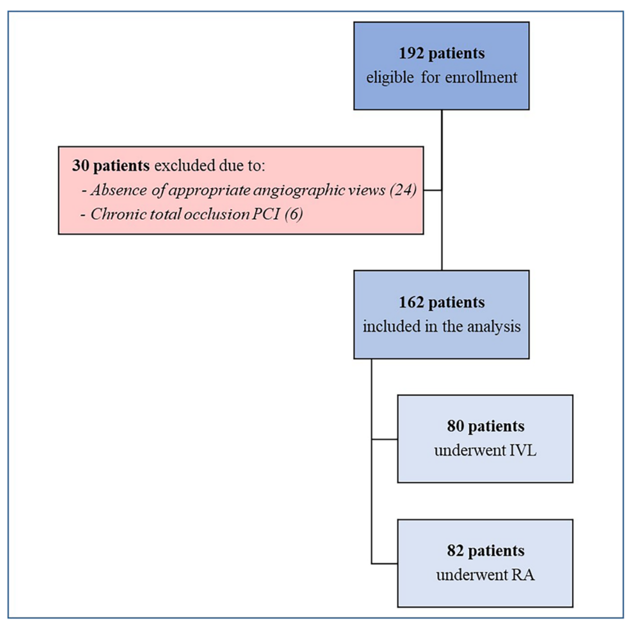


Fig. 1 Patients flow chart. *PCI* percutaneous coronary intervention, *IVL* intravascular-lithotripsy, *RA* rotablation

setting of ACS. The left descending anterior (LAD) artery was the most frequently treated vessel (38.9%).

Clinical characteristics of the study population based on utilized plaque modification technique

IVL was used in 80 patients (49.4%) with a median number of pulses of 80.0 (IQR 50.0–80.0) while RA was performed in 82 patients (50.6%), 63.4% of them with a 1.5 mm burr.

Patients in the RA group were older (78.0 vs. 71.6 years; p = 0.004) while there was a higher percentage of previous ACS and previous PCI in the IVL group (52.5% vs. 34.2%; p = 0.018 and 46.3% vs. 29.3%; p = 0.026, respectively). In addition, there was a non-significant trend to a higher percentage of women in the RA group (26.8% vs. 13.6%; p = 0.051). The ANOVA analysis revealed that the treated vessel did not influence on selecting RA or IVL (F = 0.96, p = 0.470). Detailed characteristics of the study cohort are presented in Table 1.

Differences in microvascular status and outcomes based on the plaque modification technique used

Mean aortic pressure pre-PCI and post-PCI did not differ between groups. The percentage of angiographic stenosis pre-PCI was 81.7% in the overall population, with no differences between the IVL and the RA group (80.6% vs. 82.0%; p = 0.452). Post-PCI residual stenosis was 26.6%, again with no differences between the IVL and the RA group (26.4% vs. 26.7%; p = 0.539).

Both median μFR and IMRangio values pre-PCI did not differ between groups. In the overall population, median IMRangio value was higher post-PCI than pre-PCI (49.2

Table 1 Differences in basal characteristics between patients based on plaque modification technique (n = 162 patients)

	Global (n = 162)	IVL (n = 80)	Rotablation (n = 82)	p
Baseline characteristics				
Age (years)	75.8 (68.1–81.9)	71.6 (65.3–81.4)	78.0 (72.5–82.9)	0.004
Female gender, % (n)	20.4 (33)	13.6 (11)	26.8 (22)	0.051
Hypertension, % (n)	90.8 (147)	90.0 (72)	91.5 (75)	0.748
Hyperlipidemia, % (n)	78.4 (127)	75 (60)	81.7 (67)	0.343
Diabetes Mellitus, % (n)	61.7 (100)	58.8 (47)	64.6 (53)	0.441
Smoker, % (n)				0.878
No	42.6 (69)	42.5 (34)	42.7 (35)	
Yes	21.0 (34)	22.5 (18)	19.5 (16)	
Ex-smoker	36.4 (59)	35 (28)	37.8 (31)	
Vasculopathy, % (n)	18.5 (30)	18.8 (15)	18.2 (15)	0.940
Chronic kidney disease, % (n)	21.6 (35)	18.8 (15)	24.4 (20)	0.447
Previous ACS, % (n)	43.3 (70)	52.5 (42)	34.2 (28)	0.018
Previous PCI, % (n)	37.7 (61)	46.3 (37)	29.3 (24)	0.026
LVEF (%)	54.0 (42–60)	55.0 (40–60)	50.0 (45–60)	0.656
Onsetting characteristics				
Reason PCI, % (n):				0.024
Stable angina	14.2 (23)	15.0 (12)	13.4 (11)	0.825
Unstable angina	15.4 (25)	21.3 (17)	9.8 (8)	0.051
NSTEMI	39.5 (64)	27.5 (22)	51.2 (42)	0.002
STEMI	11.7 (19)	12.5 (10)	11.0 (9)	0.811
Other	19.1 (31)	23.8 (19)	14.6 (12)	0.165
Acute coronary syndrome, % (n)	66.7 (108)	61.3 (49)	72.0 (59)	0.149
Treated vessel, % (n)				0.319
Left main	16.7 (27)	13.8 (11)	19.5 (16)	0.325
LAD	38.9 (63)	46.3 (37)	31.7 (26)	0.058
LCx	11.1 (18)	11.3 (9)	11.0 (9)	0.956
RCA	33.3 (54)	28.8 (23)	37.8 (31)	0.222
Multivessel disease, % (n)	69.1 (112)	70.0 (56)	68.3 (56)	0.814

Continuous variables are expressed as median (IQR) and categorical data as % (n)

IVL intravascular lithotripsy, *ACS* acute coronary syndrome, *PCI* percutaneous coronary intervention, *LVEF* left ventricular ejection fraction, *LAD* left anterior descending artery, *LCx* left circumflex artery, *RCA* right coronary artery vs. 33.7; $p < 0.001$), and post-PCI IMRangio values were higher in the RA group than in the IVL group (52.0 vs. 48.0; $p = 0.035$). Patients undergoing RA showed higher ΔIMRangio values than those undergoing IVL (22.3 vs. 10.3; $p = 0.038$).

Twenty-two patients (13.6%) experienced periprocedural PCI complications, with a higher percentage observed in the RA group compared to the IVL group (19.5% vs. 7.5%; $p = 0.026$), mainly due to higher rates of shock developed during PCI (6.1% vs. 0.0%, $p = 0.025$). Pre- and post-PCI TIMI flow grade did not show differences between groups.

In-hospital mortality was 2.5% (4 patients) with no differences between groups. During the follow-up period, mortality was 6.8% (3.7% cardiovascular and 2.5% non-cardiovascular death) and there was a rate of TLR of 3.8% at 1-year follow-up, without differences between groups.

Detailed results about microvascular status and outcomes based on the utilized plaque modification technique are detailed in Table 2.

Impact of coronary microvascular deterioration during PCI after using plaque modification techniques

The median ΔIMRangio value in the cohort was 15.2. No differences were found in baseline characteristics between patients above or below the median value of ΔIMRangio. Patients with ΔIMRangio ≥ 15.2 presented a significant higher rate of PCI complications (21.0% vs. 6.2%, $p = 0.006$) mainly due to a higher percentage of cardiogenic shock developed during PCI (6.2% vs. 0.0%, $p = 0.023$) and a non-significant trend to a higher percentage of slow-flow/no-reflow and failed PCI (6.2% vs. 1.2%; $p = 0.096$ and 6.2% vs. 1.2%; $p = 0.096$, respectively). TIMI flow grade deterioration post-PCI did not differ between groups but there was a higher percentage of post-PCI TIMI flow grade < 3 in patients with ΔIMRangio ≥ 15.2 (13.9% vs. 4.0%; $p = 0.030$). Patients with higher ΔIMRangio values also needed more frequently the use of inotropic treatment during PCI (9.9% vs. 1.2%; $p = 0.016$). Regarding the plaque modification technique, there was a higher percentage of RA in the group with higher ΔIMRangio values (59.3% vs. 40.7%; $p = 0.028$). No significant differences were found either in-hospital mortality or in adverse events during follow-up between groups. Detailed results about microvascular status and outcomes based on the median ΔIMRangio are shown in Table 3.

A multivariate logistic regression analysis including age, male gender, diabetes mellitus, smoking, history of vasculopathy, presence of ACS, use of inotropic treatment and pre-PCI TIMI flow grade < 3 was performed. After adjustment for covariates RA remained as an independent predictor of a greater ΔIMRangio following PCI (OR 2.01, 95% CI 1.01–4.03, $p = 0.048$). Detailed results are presented in Table 4.

Discussion

To the best of our knowledge, this is the first study to evaluate the impact of plaque modification techniques on the coronary microcirculation status through an angiography-derived index of microvascular resistance. The main findings of our study are: (1) plaque modification techniques such as IVL and RA increase coronary microvascular resistances and (2) higher ΔIMRangio values might be considered as a marker of higher risk of PCI complications regardless of the selected technology.

In recent years, there has been a growing interest towards plaque modification technologies addressing the complexities of calcified CAD PCI. However, there is evidence suggesting that the manipulation of plaques using these tools could significantly affect the microcirculation status and thus, the prognosis of these patients [23–26]. IMR is the most used, precise and reproducible measure of the coronary microcirculation status [14]. Nevertheless, it requires a dedicated pressure–temperature sensor wire and the induction of hyperemia, which limits its use in daily practice. Hence, new methods have arisen to address these drawbacks such as angiography-derived IMR (IMRangio) that has demonstrated a good correlation and diagnostic performance in prior research compared with wire based IMR [19, 27]. As previously mentioned, we aimed to assess the impact of plaque modification techniques on coronary microcirculation by means of IMRangio and evaluate the information given by this measurement in terms of prognosis.

First, in our study, both treatments (RA and IVL) increased post-PCI IMRangio values. However, since non-hyperemic IMRangio estimates the resting microvascular resistance, whose value does not inform of the presence or ausence of microvascular dysfunction by itself [28–31], we analyzed the ΔIMRangio rather than only the post-PCI IMRangio in an attempt to minimize the potential influence of the basal status of coronary microcirculation. We observed that ΔIMRangio values were higher in the RA group compared to the IVL group (22.3 vs. 10.3; $p = 0.038$) being RA independently associated with higher ΔIMRangio after PCI (OR 2.01, $p = 0.048$). This might be explained by their distinct mechanisms: RA high-speed burr can pulverize the calcified plaque, increasing the likelihood of generating micro-sized fragments that may embolize while, in contrast, IVL's controlled acoustic pulses create fewer microcracks, leading to fewer embolic particles [32]. Nevertheless, it's important to note that the use of RA and IVL is not interchangeable. IVL may not be

Table 2 Differences in coronary microvascular status and complications between patients based on plaque modification technique (n = 162)

	Global (n = 162)	IVL (n = 80)	Rotablation (n = 82)	p
Microvascular status				
Pre-PCI μFR	0.64 (0.43–0.75)	0.62 (0.43–0.75)	0.65 (0.44–0.75)	0.666
Post-PCI μFR	0.92 (0.86–0.95)	0.92 (0.86–0.95)	0.92 (0.87–0.95)	0.987
Pre-PCI IMRangio	33.7 (20.1–51.6)	33.0 (17.9–50.6)	35.0 (24.6- 52.7)	0.076
Post-PCI IMRangio	49.2 (32.2–67.2)	48.0 (30.7–63.0)	52.0 (36.7–72.1)	0.035
ΔIMRangio	15.2 (0.1–31.1)	10.3 (− 3.8/29.0)	22.3 (1.0–33.3)	0.038
ΔIMRangio > 15.2, % (n)	50.0 (81)	41.3 (33)	58.5 (48)	0.028
Pre-PCI % of angiographic stenosis	81.7 (75.4–86.6)	80.6 (74.7–86.8)	82.0 (77.7–86.4)	0.452
Percentatge of residual angiographic stenosis, (%)	26.6 (16.5–34.9)	26.4 (16.4–33.7)	26.7 (16.9–36.7)	0.539
Pre-PCI TIMI flow grade < 3, % (n)	23.2 (36)	25.6 (20)	20.8 (16)	0.474
Post-PCI TIMI flow grade < 3, % (n)	9.0 (14)	9.0 (7)	9.1 (7)	0.980
TIMI flow grade deterioration during PCI, % (n)	3.9 (6)	5.1 (4)	2.6 (2)	0.423
Mean blood pressure (mmHg)				
Pre PCI	92.9 (82.0–101.0)	95.3 (84.4–103.2)	90.6 (80.0–98.0)	0.080
Post PCI	91.1 (79.0–102.0)	92.1 (81.8–101.3)	90.1 (78.6–102.0)	0.869
In-hospital complications				
Inotropic treatment during PCI	5.6 (9)	1.3 (1)	9.8 (8)	0.018
PCI complications, % (n):	13.6 (22)	7.5 (6)	19.5 (16)	0.026
Flow-limiting coronary dissection	1.9 (3)	1.3 (1)	2.4 (2)	0.575
Slow-Flow / no-Reflow	3.7 (6)	1.3 (1)	6.1 (5)	0.102
Coronary perforation	0.0 (0)	0.0 (0)	0.0 (0)	1.000
Branch occlusion	3.1 (5)	3.8 (3)	2.4 (2)	0.680
Failed PCI	3.7 (6)	2.5 (2)	4.9 (4)	0.423
Shock developed during PCI	3.1 (5)	0.0 (0)	6.1 (5)	0.025
Stroke during PCI	0.6 (1)	1.2 (1)	0.0 (0)	0.322
Cardiac arrest during PCI	1.2 (2)	0.0 (0)	2.4 (2)	0.160
In-Hospital mortality, % (n)	2.5 (4)	1.3 (1)	3.7 (3)	0.323
Cardiovascular	1.9 (3)	1.3 (1)	2.4 (2)	0.575
Non-cardiovascular	0.6 (1)	0.0 (0)	1.2 (1)	0.322
1 year follow-up				
NYHA class, % (n):				0.357
I	35.5 (43)	31.2 (19)	40.0 (24)	
II	50.4 (61)	50.8 (31)	50.0 (30)	
III	14.1 (17)	18.9 (11)	10.6 (6)	
IV	0.0 (0)	0.0 (0)	0.0 (0)	
TLR, % (n)	3.8 (6)	2.5 (2)	5.1 (4)	0.681
Mortality, % (n)	6.8 (10)	5.0 (4)	8.5 (6)	0.371
Cardiovascular	3.7 (6)	2.5 (2)	4.9 (4)	0.423
Non-cardiovascular	2.5 (4)	2.5 (2)	2.5 (2)	0.980
Adverse events, % (n)	9.9 (16)	7.5 (6)	12.2 (10)	0.317

Continuous variables are expressed as median (IQR) and categorical data as % (n)

IVL intravascular lithotripsy, *IMRangio* angiography-derived index of microcirculatory resistance, *PCI* percutaneous coronary intervention, *μFR* Murray law based quantitative flow ratio *NYHA* New York Heart Association, *TLR* target lesion revascularization

suitable for uncrossable lesions, whereas RA might be a preferable option in cases involving uncrossable, long, or diffuse lesions. Consequently, lesions treated with RA may inherently be more complex, which could in part explain the higher ΔIMRangio values found in our study in this group.

Second, we observed that patients with a ΔIMRangio above the median of the population at study (15.2) presented higher PCI complication rates (21.0% vs. 6.2%, p = 0.006).

Table 3 Clinical and procedural variables associated with coronary microvascular deterioration based on ΔIMRangio (n = 162)

	Global (n = 162)	ΔIMRangio < 15.2 (n = 81)	ΔIMRangio ≥ 15.2 (n = 81)	p-value
Baseline characteristics				
Age (years)	75.8 (68.1–81.9)	74.9 (68.4–81.7)	77.0 (67.4–82.3)	0.931
Female gender, % (n)	20.4 (33)	23.5 (19)	17.3 (14)	0.329
Hypertension, % (n)	90.8 (147)	92.6 (75)	88.9 (72)	0.416
Hyperlipidemia, % (n)	78.4 (127)	75.3 (61)	81.5 (66)	0.340
Diabetes mellitus, % (n)	61.7 (100)	55.6 (45)	67.9 (55)	0.106
Smoker, % (n)	21.0 (34)	25.9 (21)	16.1 (13)	0.123
Vasculopathy, % (n)	18.5 (30)	17.3 (14)	19.8 (16)	0.686
Chronic kidney disease, % (n)	21.6 (35)	18.5 (15)	24.7 (20)	0.340
Previous ACS, % (n)	43.3 (70)	43.2 (35)	43.2 (35)	1.000
Previous PCI, % (n)	37.7 (61)	43.2 (35)	32.1 (26)	0.144
LVEF (%)	54.0 (42–60)	55 (44–64)	55 (45–60)	0.652
Onsetting characteristics				
Reason PCI, % (n):				0.650
Stable angina	14.2 (23)	17.3 (14)	11.1 (9)	0.260
Unstable angina	15.4 (25)	16.1 (13)	14.8 (12)	0.828
NSTEMI	39.5 (64)	34.6 (28)	44.4 (36)	0.199
STEMI	11.7 (19)	11.1 (9)	12.4 (10)	0.807
Other	19.1 (31)	21.0 (17)	17.3 (14)	0.549
Acute coronary syndrome, % (n)	66.7 (108)	61.7 (50)	71.6 (58)	0.182
Procedural variables				
Treated vessel, % (n):				
Left main	16.7 (27)	16.1 (13)	17.3 (14)	0.833
LAD	38.9 (63)	43.2 (35)	34.6 (28)	0.259
LCx	11.1 (18)	11.1 (9)	11.1 (9)	1.000
RCA	33.3 (54)	29.6 (24)	37.0 (30)	0.317
Multivessel disease, % (n)	69.1 (112)	66.7 (54)	71.6 (58)	0.496
Pre-PCI TIMI flow grade < 3, % (n)	23.2 (36)	24.7 (19)	21.8 (17)	0.671
Post-PCI TIMI flow grade < 3, % (n)	9.0 (14)	4.0 (3)	13.9 (11)	0.030
TIMI flow grade deterioration during PCI, % (n)	3.9 (6)	2.6 (2)	5.1 (4)	0.423
Plaque modification technique, % (n):				0.028
IVL	49.4 (80)	58.0 (47)	40.7 (33)	
Rotablator	50.6 (82)	42.0 (34)	59.3 (48)	
Inotropic treatment during PCI	5.6 (9)	1.2 (1)	9.9 (9)	0.016
In-hospital complications				
PCI complications, % (n):	13.6 (22)	6.2 (5)	21.0 (17)	0.006
Flow-limiting coronary dissection	1.9 (3)	1.2 (1)	2.5 (2)	0.560
Slow-Flow / no-Reflow	3.7 (6)	1.2 (1)	6.2 (5)	0.096
Coronary perforation	0.0 (0)	0.0 (0)	0.0 (0)	1.000
Branch occlusion	3.1 (5)	42.5 (2)	3.7 (3)	0.650
Failed PCI	3.7 (6)	1.2 (1)	6.2 (5)	0.096
Shock developed during PCI	3.1 (5)	0.0 (0)	6.2 (5)	0.023
Stroke during PCI	0.6 (1)	1.2 (1)	0.0 (0)	0.316
Cardiac arrest during PCI	1.2 (2)	0.0 (0)	2.5 (2)	0.155
TIMI flow grade deterioration post-PCI, % (n)	3.9 (6)	2.6 (2)	5.1 (4)	0.423
Post-PCI TIMI flow grade < 3, % (n)	9.0 (14)	4.0 (3)	13.9 (11)	0.030
In-hospital mortality, % (n)	2.5 (4)	2.5 (2)	2.5 (2)	1.000
Cardiovascular	1.9 (3)	1.2 (1)	2.5 (2)	0.560
Non-cardiovascular	0.6 (1)	1.2 (1)	0.0 (0)	0.316

Table 3 (continued)

	Global (n = 162)	ΔIMRangio < 15.2 (n = 81)	ΔIMRangio ≥ 15.2 (n = 81)	p-value
1 year follow-up				
NYHA class, % (n)				0.493
I	35.5 (43)	39.1 (25)	31.6 (18)	
II	50.4 (61)	50.0 (32)	50.9 (29)	
III	14.1 (17)	10.9 (7)	17.5 (10)	
IV	0.0 (0)	0.0 (0)	0.0 (0)	
TLR, % (n)	3.8 (6)	2.5 (2)	5.1 (4)	0.405
Mortality, % (n)	6.8 (11)	6.2 (5)	7.4 (6)	0.755
Cardiovascular	3.7 (6)	2.5 (2)	4.9 (4)	0.405
Non-cardiovascular	3.1 (5)	3.7 (3)	2.5 (2)	0.650
Adverse events, % (n)	10.5 (17)	8.6 (7)	12.3 (10)	0.598

Continuous variables are expressed as median (IQR) and categorical data as % (n)

IVL intravascular lithotripsy, *RA* rotablation, *PCI* percutaneous coronary intervention, *IMRangio* angiography-derived index of microcirculatory resistance, *ACS* acute coronary syndrome, *LVEF* left ventricular ejection fraction, *LCx* left circunflex artery, *LAD* left anterior descending artery, *RCA* right coronary artery, *PCI* percutaneous coronary intervention, *NYHA* New York Heart Association, *TLR* target lesion revascularization

Table 4 Multivariable logistic regression to assess variables related to a higher deterioration of coronary microvascular status

Variables	OR (95% CI)	p-value
Age	1.00 (0.99–1.01)	0.547
Male gender	2.09 (0.88–4.92)	0.093
Diabetes mellitus	1.73 (0.85–3.52)	0.128
Active smoker	0.45 (0.18–1.09)	0.076
History of vasculopathy	0.88 (0.35–2.19)	0.788
Presence of acute coronary syndrome	1.54 (0.73–3.26)	0.259
Inotropic treatment	6.31 (0.71–56.0)	0.098
Pre-PCI TIMI flow grade < 3	0.71 (0.31–1.65)	0.426
Rotablation	2.01 (1.01–4.03)	0.048

OR odds ratio, *CI* confidence interval, *PCI* percutaneous coronary intervention

This was mostly due to significantly higher rates of development of cardiogenic shock during PCI (6.2% vs. 0.0%, p = 0.023) but also, despite not reaching statistical significance, due to a higher percentage of slow-flow/no-reflow and failed PCI (6.2% vs. 1.2%). Only a few studies prior to the one that we present have associated the value of IMRangio after PCI and the occurrence of PCI complications. Wang et al. [33] noticed that a higher IMRangio value after RA in 118 stable patients was an independent predictor of MACE and target vessel revascularization. Moreover, previous reports have associated increased IMR values with negative clinical outcomes in obstructive (in both stable and unstable clinical scenarios) and non-obstructive CAD [32, 34–37] as well as with the severity and extent of the myocardial damage after an acute coronary syndrome or post elective PCI [12, 38–43]. Recently, Scarsini et al. [44] showed that, in a cohort of STEMI patients, post primary PCI IMRangio could identify patients at risk for early cardiovascular complications and therefore, the authors hypothetize that this measurement could lead to the implementation of early-discharge strategies for those with low IMRangio or longer observation hospitalization for the opposite setting. In this line, other previous studies assessing the use of different preventive strategies based on IMRangio have demonstrated improvements in outcomes for patients with microcirculatory dysfunction [27, 45]. In our study, despite the impairment in coronary microcirculation, no differences were found in terms of clinical adverse events either based on the ΔIMRangio (8.6% with ΔIMRangio < 15.2 vs. 12.3% with ΔIMRangio ≥ 15.2, p = 0.598) or on the plaque modification technique utilized (7.5% with IVL vs. 12.2% with RA, p = 0.317). It has to be noted that these observations may not be extrapolated to the setting of ANOCA (angina with non obstructive coronary artery disease) since, in that population, resting microvascular resistance indexes such non-hyperemic IMRangio may not detect appropriately the status of microcirculation [28–31]. Moreover, our results should be taken with caution due to the small sample size and event rate and larger trials should be performed to further evaluate the hypothesis mentioned above.

Study limitations

First, it is a retrospective study which has limitations inherent to its own nature. Second, although the event rate in the present study was low, limiting the possibility of achieving conclusive results, it represents one of the first attempts to evaluate coronary microvascular status following RA or IVL and its exploratory goal establishes the foundation for additional prospective investigations. In fact, a recent publication introduced a prospective randomized trial protocol exploring this aspect, thereby enhancing the relevance of the present investigation [46]. Third, the event adjudication was done by the study investigators. However, the investigators were blind to the results, since the IMRangio evaluation was performed after the adjudication of the events. Additionally, as mentioned above, the use of RA and IVL is not interchangeable and, consequently, lesions treated with RA may have been inherently more complex, which could potentially introduce bias. Fourth, as IMRangio relies on angiography, its accuracy depends on the quality of images. To minimize this limitation, we only considered optimal angiographic images for analysis. Fifth, the utilization of computationally derived IMR represents a novel technique with limited outcome data, particularly lacking comparison to invasive IMR in the context of plaque modification techniques during PCI. However, IMRangio has shown good performance in assessing the microcirculation status compared to invasive IMR in prior research in both acute and chronic coronary syndromes [17, 47]. Sixth, μFR was incorporated instead of QFR in the formula for computing IMRangio. Although it should be noted that the combination of IMRangio with μFR has not undergone validation, an excellent agreement between QFR, typically used to estimate IMRangio, and μFR has been reported [48]. Finally, a significant proportion of the patients presented with TIMI flow < 3 prior to PCI. In those cases, the increase in IMRangio value could be a consequence of microvascular injury during PCI or changes in flow. Despite it being difficult to ascertain which component played a major role in the increase in IMRangio in each patient, having a pre-PCI TIMI flow grade < 3 was not associated with a higher deterioration of IMRangio in our cohort (Table 4). Furthermore, when we excluded patients with pre-PCI TIMI flow grade < 3 (Table 2S from the supplementary material) results did not differ.

Conclusions

IVL and RA seems to have a noticeable effect on coronary microcirculation status. The assessment of coronary microvascular resistance using IMRangio in patients undergoing PCI with plaque modification techniques could help predict clinical and procedural outcomes and therefore guide adjunctive therapies to optimize clinical outcomes.

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Declarations

Conflict of interest The authors declare no competing interests.

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