Circulation: Cardiovascular Interventions

ORIGINAL ARTICLE

Risk Stratification Guided by the Index of Microcirculatory Resistance and Left Ventricular End-Diastolic Pressure in Acute Myocardial Infarction

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BACKGROUND: The index of microcirculatory resistance (IMR) of the infarct-related artery and left ventricular end-diastolic pressure (LVEDP) are acute, prognostic biomarkers in patients undergoing primary percutaneous coronary intervention. The clinical significance of IMR and LVEDP in combination is unknown.

METHODS: IMR and LVEDP were prospectively measured in a prespecified substudy of the T-TIME clinical trial (Trial of Low Dose Adjunctive Alteplase During Primary PCI). IMR was measured using a pressure- and temperature-sensing guidewire following percutaneous coronary intervention. Prognostically established thresholds for IMR (>32) and LVEDP (>18 mm Hg) were predefined. Contrast-enhanced cardiovascular magnetic resonance imaging (1.5 Tesla) was acquired 2 to 7 days and 3 months postmyocardial infarction. The primary end point was major adverse cardiac events, defined as cardiac death/nonfatal myocardial infarction/heart failure hospitalization at 1 year.

RESULTS: IMR and LVEDP were both measured in 131 patients (mean age 59±10.7 years, 103 [78.6%] male, 48 [36.6%] with anterior myocardial infarction). The median IMR was 29 (interquartile range, 17–55), the median LVEDP was 17 mm Hg (interquartile range, 12–21), and the correlation between them was not statistically significant (r=0.15; P=0.087). Fifty-three patients (40%) had low IMR (≤32) and low LVEDP (≤18), 18 (14%) had low IMR and high LVEDP, 31 (24%) had high IMR and low LVEDP, while 29 (22%) had high IMR and high LVEDP. Infarct size (% LV mass), LV ejection fraction, final myocardial perfusion grade ≤1, TIMI (Thrombolysis In Myocardial Infarction) flow grade ≤2, and coronary flow reserve were associated with LVEDP/IMR group, as was hospitalization for heart failure (n=18 events; P=0.045) and major adverse cardiac events (n=21 events; P=0.051). LVEDP>18 and IMR>32 combined was associated with major adverse cardiac events, independent of age, estimated glomerular filtration rate, and infarct-related artery (odds ratio, 5.80 [95% CI, 1.60–21.22] P=0.008). The net reclassification improvement for detecting major adverse cardiac events was 50.6% (95% CI, 2.7–98.2; P=0.033) when LVEDP>18 was added to IMR>32.

CONCLUSIONS: IMR and LVEDP in combination have incremental value for risk stratification following primary percutaneous coronary intervention.

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GRAPHIC ABSTRACT: A graphic abstract is available for this article.

Key Words: index of microcirculatory resistance ■ left ventricular end diastolic pressure ■ myocardial infarction ■ percutaneous coronary intervention ■ risk stratification

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WHAT IS KNOWN

- The index of microcirculatory resistance of the infarct-related coronary artery and left ventricular end-diastolic pressure are acute, prognostic biomarkers in patients undergoing primary percutaneous coronary intervention.
- Index of microcirculatory resistance and left ventricular end-diastolic pressure are distinct and related hemodynamic measurements and their clinical significance in combination is unknown.

WHAT THE STUDY ADDS

- A combinatory approach using index of microcirculatory resistance and left ventricular end-diastolic pressure (low and high) discriminates major adverse cardiac events and infarct size more so than if either index is used alone.
- Risk stratification using index of microcirculatory resistance and left ventricular end-diastolic pressure during primary percutaneous coronary intervention has potential to guide patient selection for targeted therapy in ST-segment–elevation myocardial infarction.

Nonstandard Abbreviations and Acronyms

CFR	coronary flow reserve
CMR	cardiovascular magnetic resonance
IMR	index of microcirculatory resistance
LV	left ventricle
LVEDP	left ventricular end-diastolic pressure
MACE	major adverse cardiac events
PCI	percutaneous coronary intervention
STEMI	ST-segment–elevation myocardial infarction
TIMI	Thrombolysis In Myocardial Infarction

Normal epicardial blood flow in the infarct-related artery is typically restored after primary percutaneous coronary intervention (PCI).[1] Microvascular injury following ST-segment–elevation myocardial infarction (STEMI) usually passes undetected in clinical practice and portends an increased risk of heart failure and death.[2] While cardiovascular magnetic resonance (CMR) imaging reveals microvascular damage following STEMI, it is not feasible acutely, and hence is not useful for early risk stratification, to guide clinical decision-making and therapeutic management.

The index of microcirculatory resistance (IMR) measured at the end of primary PCI is a prognostically validated measure of microvascular reperfusion injury in acute STEMI.[3,4] However, IMR is an imperfect prognostic biomarker since about 70% of patients with an elevated IMR do not experience a major adverse cardiac event (MACE).[5] Left ventricular end-diastolic pressure (LVEDP) is a clinically useful hemodynamic measurement in STEMI. LVEDP>18 mm Hg increases the likelihood of heart failure and death.[6]

IMR is mainly measured for research, and LVEDP is often omitted during routine primary PCI. However, both measurements are feasible and easily measured during primary PCI, therefore, there is potential for incorporation into routine clinical practice. The prognostic utility of IMR and LVEDP in combination is unknown. We aimed to assess the relative distribution of IMR and LVEDP in patients with acute STEMI, and whether the categorization of patients using predefined, prognostic cutoffs of IMR and LVEDP, would associate with MACE (primary end point) and secondary end points (infarct size, LV ejection fraction, % ST-segment resolution, coronary flow reserve [CFR], TIMI [Thrombolysis In Myocardial Infarction] flow grade, and myocardial perfusion grade at the end of PCI). We further aimed to assess whether the prognostic associations for a 4-level categorical classification would be greater than with either measurement alone.

METHODS

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

T-TIME (Trial of Low Dose Adjunctive Alteplase During Primary PCI) was a randomized, placebo-controlled, clinical trial of low-dose (10 and 20 mg) intracoronary alteplase in 440 patients with STEMI.[7] The trial protocol encouraged achieving TIMI flow grade ≥2, using balloon angioplasty/aspiration thrombectomy, before randomization. The 20 mL volume of study drug was then manually infused into the culprit artery, over 5 to 10 minutes, proximal to the culprit lesion, using an intracoronary/guiding catheter, prestent implantation. A physiology substudy was designated in 3 sites and found no associations between alteplase and LVEDP or IMR.[8] Enrollment occurred from 2016 to 2017 and was based on eligibility criteria, operator experience, and logistics at the point-of-care. The study was approved by the West of Scotland Research Ethics Committee (reference 13-WS-0119) and all participants gave informed consent.

Eligibility

Patients were eligible to participate if they presented with persistent ST-segment elevation or recent left bundle branch block, ≤6 hours from symptom onset and with an occluded infarct-related artery, TIMI 1 flow (contrast passes beyond the obstruction but fails to opacify the entire coronary bed distally), or reduced coronary flow (TIMI 2 flow, slow but complete filling), in the presence of TIMI thrombus grade ≥2. Key exclusion criteria (Data Supplement) included a functional coronary collateral supply (Rentrop grade ≥2) to the infarct-related artery and cardiogenic shock.

Coronary Physiology

IMR and CFR were measured using a pressure- and temperature-sensing guidewire (Abbott, Vascular, CA) at the end of

PCI.[3,4,9] Intracoronary nitroglycerin (200 μg) was administered into the infarct-related artery. A calibrated wire was equalized to guide catheter pressure, then advanced to the distal third of the infarct-related artery. Using standard thermodilution methods, the mean transit time of a hand injected 3 mL bolus of room temperature saline was measured in triplicate at rest and during steady-state maximal hyperemia, induced by intravenous adenosine (140 μg/kg per minute).

The cardiologists were blinded to IMR, by obscuring the display of the RadiAnalyzer Xpress monitor. Physiology technicians recorded and quality-assured the thermodilution data. The physiology data were analyzed in a central laboratory by blinded researchers using Coroventis software (Coroventis Research AB, Uppsala, Sweden). IMR was defined as distal coronary pressure × mean transit time during steady-state hyperemia.[3] A predefined threshold of 32 was used to dichotomize IMR, because IMR>32 is prognostically significant[3,4] and is also being used to select patients for inclusion in clinical trials.[10] CFR was quantified by dividing resting mean transit time by hyperemic mean transit time.[9] A threshold of 2.0 was used to dichotomize CFR because based on published literature a CFR ≤2.0 is abnormal.[9]

Left Ventricular End-Diastolic Pressure

Measurement of LVEDP was recommended in the T-TIME protocol. Having positioned a right Judkins/pigtail catheter in the LV, the LVEDP was measured at the Z-point of change in the upstroke of the ventricular pressure that coincided with the R wave on the ECG.[11] A prognostically significant predefined threshold of 18 mm Hg was used to dichotomize LVEDP.[6]

Angiographic and ECG Analyses

Angiographic and ECG end points were determined by blinded core laboratory analysis. The absolute percentage ST-segment resolution on ECGs obtained 60 minutes after reperfusion (ie, after initial restoration of flow in the infarct-related artery) compared with prereperfusion was calculated.

CMR Imaging

CMR was performed at 1.5 Tesla, and the analysis was done by blinded researchers in a central laboratory. The presence of acute infarction was established based on abnormalities in cine wall motion, rest first-pass myocardial perfusion, and late gadolinium enhancement imaging, in 2 imaging planes. The myocardial mass of late gadolinium was quantified using a 5 SD semiautomated method and expressed as % of total LV mass. Myocardial salvage was calculated by subtraction of percent infarct size from percent area-at-risk (as reflected by the extent of edema), and the myocardial salvage index was calculated by dividing the myocardial salvage area by the initial area-at-risk. The CMR protocol has previously been described in detail.[7]

Health Outcomes

Information on serious adverse events during follow-up was obtained by site research staff. These events were independently reviewed and adjudicated by a clinical events committee. Clinical events were assessed at 1 year. MACE, defined as cardiac death, nonfatal MI, or hospitalization for heart failure. Hospitalization for heart failure was defined as follows: (1) new or worsening signs/symptoms of heart failure requiring the initiation of, or increase in heart failure directed treatment (including intravenous therapy), or occurring in a patient already receiving maximal heart failure therapy or (2) confinement to bed predominantly due to heart failure symptoms or (3) pulmonary edema sufficient to cause tachypnea and distress (not occurring in the context of an acute MI, worsening renal function [that is not wholly explained by worsening heart failure], or as the consequence of arrhythmia without worsening heart failure) or (4) cardiogenic shock.

Statistics

Continuous data were summarized using mean±SD, or median and interquartile ranges if skewed. Categorical variables were reported as frequency and percentages.

The study end points were compared in a 4-category combination of high/low LVEDP and IMR, using the Kruskal-Wallis test (for skewed continuous end points), 1-way ANOVA (for normally distributed continuous end points), or the χ^2 test (for categorical end points).

Analyses were also performed for associations between study end points and LVEDP>18 mm Hg or IMR>32 as binary predictors, using linear regression (continuous parameters), or logistic regression (categorical parameters). In regression models, logarithmic transformations were used where necessary to improve model residual distributions. The multivariable models were built by stepwise selection of baseline characteristics, with entry criteria set at the $P<0.1$ level. In addition to LVEDP and IMR, the following covariates were included in the multivariable model of infarct size at 3 months: body mass index, ischemic time, and infarct-related artery, and the following covariates were included in the multivariable model of MACE: age, estimated glomerular filtration rate, and infarct-related artery. Associations with health outcomes were evaluated using odds ratios derived from logistic regression. Furthermore, the incremental predictive ability of LVEDP>18, or IMR>32 for detecting health outcomes, was evaluated by the continuous net reclassification improvement.

All tests were 2-tailed, and a P value of <0.05 was considered statistically significant. Data were analyzed using R (version 3.6.1, R Development Core Team, Auckland, New Zealand) and SPSS (version 25.0, SPSS, IBM, Armonk, NY).

RESULTS

Population

One hundred and thirty-one patients (mean age 59±10.7 years, 103 [78.6%] male, 48 [36.6%] with anterior MI) had IMR and LVEDP measured at the end of primary PCI (Table 1; Figure 1). The primary mode of reperfusion was balloon angioplasty or aspiration thrombectomy in 111 (84.7%) and 20 (15.3%) patients, respectively. The clinical and treatment characteristics of these participants were generally similar to the trial population, although some differences were observed (Table I in the Data Supplement).

Table 1. Clinical and Procedural Characteristics of the Study Population

	All (n=131)	LVEDP/IMR category				*P* value
		LVEDP low/IMR low (n=53)	LVEDP high/IMR low (n=18)	LVEDP low/IMR high (n=31)	LVEDP high/IMR high (n=29)	
Age, y	59.0±10.7	56.8±9.2	56.9±10.7	60.3±11.8	63.2±11.1	0.070
Male	103 (78.6%)	46 (86.8%)	11 (61.1%)	24 (77.4%)	22 (75.9%)	0.156
Current smoker	64 (48.9%)	29 (22.1%)	8 (44.4%)	18 (58.1%)	9 (31.0%)	0.044
Diabetes*	15 (11.5%)	5 (9.45%)	2 (11.1%)	4 (12.9%)	4 (13.8%)	0.939
Hypertension	37 (28.2%)	13 (24.5%)	2 (11.1%)	10 (32.3%)	12 (41.4%)	0.127
Body mass index, kg/m^2, median [IQR]	28.1 [24.8–30.4]	27.3 [24.5–29.5]	29.2 [24.9–31.6]	27.2 [24.41–29.4]	29.4 [26.7–32.7]	0.072
Previous MI	8 (6.15%)	2 (3.8%)	0	3 (9.7%)	3 (10.3%)	0.416
Estimated glomerular filtration rate,† mL/min per 1.73 m^2	90.0 [76.7–102.8]	90.2 [84.0–101.0]	95.0 [78.0–102.0]	90.1 [78.0–111.0]	80.1 [68.0–103.0]	0.388
Ischemic time, h, median [IQR]	2.9 [2.1–3.9]	2.7 [2.0–3.8]	2.8 [1.9–4.3]	3.3 [2.8–4.3]	2.4 [2.0–3.5]	0.049
Infarct-related coronary artery						
Left anterior descending	49 (37.4%)	15 (28.3%)	9 (50.0%)	11(35.5%)	14 (48.3%)	0.441
Right coronary	59 (45.0%)	28 (52.8%)	5 (27.8%)	15 (48.4%)	11 (37.9%)	
Circumflex	23 (17.6%)	10 (18.9%)	4 (22.2%)	5 (16.1%)	4 (13.8%)	
Initial TIMI thrombus grade						
3	3 (2.3%)	2 (3.8%)	0	1 (3.2%)	0	0.348
4	23 (17.6%)	8 (15.1%)	1 (5.6%)	9 (29.05)	5 (17.2%)	
5	105 (80.2%)	43 (81.1%)	17 (94.4%)	21 (67.7%)	24 (82.8%)	
Initial culprit artery TIMI flow grade						
0	103 (78.6%)	42 (79.2%)	16 (88.9%)	21 (67.7%)	24 (82.8%)	0.577
1	13 (9.9%)	5 (9.4%)	0	5 (16.1%)	3 (10.3%)	
2	15 (11.5%)	6 (11.3%)	2 (11.1%)	5 (16.1%)	2 (6.9%)	
3	0	0	0	0	0	
PCI with stent implantation	131 (100.0%)	53 (100.0%)	18 (100.0%)	31 (100.0%)	29 (100.0%)	…
Aspirin loading dose						
300 mg	129 (100.0%)	53 (100.0%)	16 (100.0%)	31 (100.0%)	29 (100.0%)	…
None	0	0	0	0	0	
Other antiplatelet medication						
Clopidogrel	78 (59.5%)	34 (64.2%)	10 (55.6%)	17 (54.8%)	17 (58.6%)	0.227
Ticagrelor	51 (38.9%)	19 (35.8%)	6 (33.3%)	14 (45.2%)	12 (41.4%)	
None	2 (1.5%)	0	2 (11.1%)	0	0	
Intracoronary alteplase during PCI						
10 mg	40 (30.5%)	15 (28.3%)	11 (61.1%)	3 (9.7%)	11 (37.9%)	0.015
20 mg	44 (33.6%)	18 (34.0%)	3 (16.7%)	15 (48.4%)	8 (27.6%)	
None	47 (35.9%)	20 (37.7%)	4 (22.2%)	13 (41.9%)	10 (34.5%)	

Data are mean±SD, or n (%) unless otherwise stated. *P* values are derived from the 1-way ANOVA, Kruskal-Wallis, or χ^2 tests. IMR indicates index of microcirculatory resistance; IQR, interquartile range; LVEDP, left ventricular end-diastolic pressure; MI, myocardial infarction; PCI, percutaneous coronary intervention; and TIMI, Thrombolysis In Myocardial Infarction.

*Diabetes was defined as a history of diet-controlled or treated diabetes.

†Missing data: estimated glomerular filtration rate—1 subject.

IMR and LVEDP appeared to have skewed distributions (Figure I in the Data Supplement). The median IMR was 29 (interquartile range, 17–55), and the median LVEDP was 17 mm Hg (interquartile range, 12–21). The correlation between LVEDP and IMR was not statistically significant (Spearman ρ 0.15; *P*=0.087). The characteristics that were associated with higher LVEDP, on multivariable linear regression, were higher body mass index (*P*<0.001), higher initial thrombus grade (*P*=0.003), and infarct-related artery (left anterior descending versus circumflex versus right coronary; *P*<0.001). The distribution of patients according to the predetermined cutoffs was LVEDP low (≤18 mm Hg) and IMR low (≤32), n=53 (40%); LVEDP low and IMR high, n=31 (24%); LVEDP

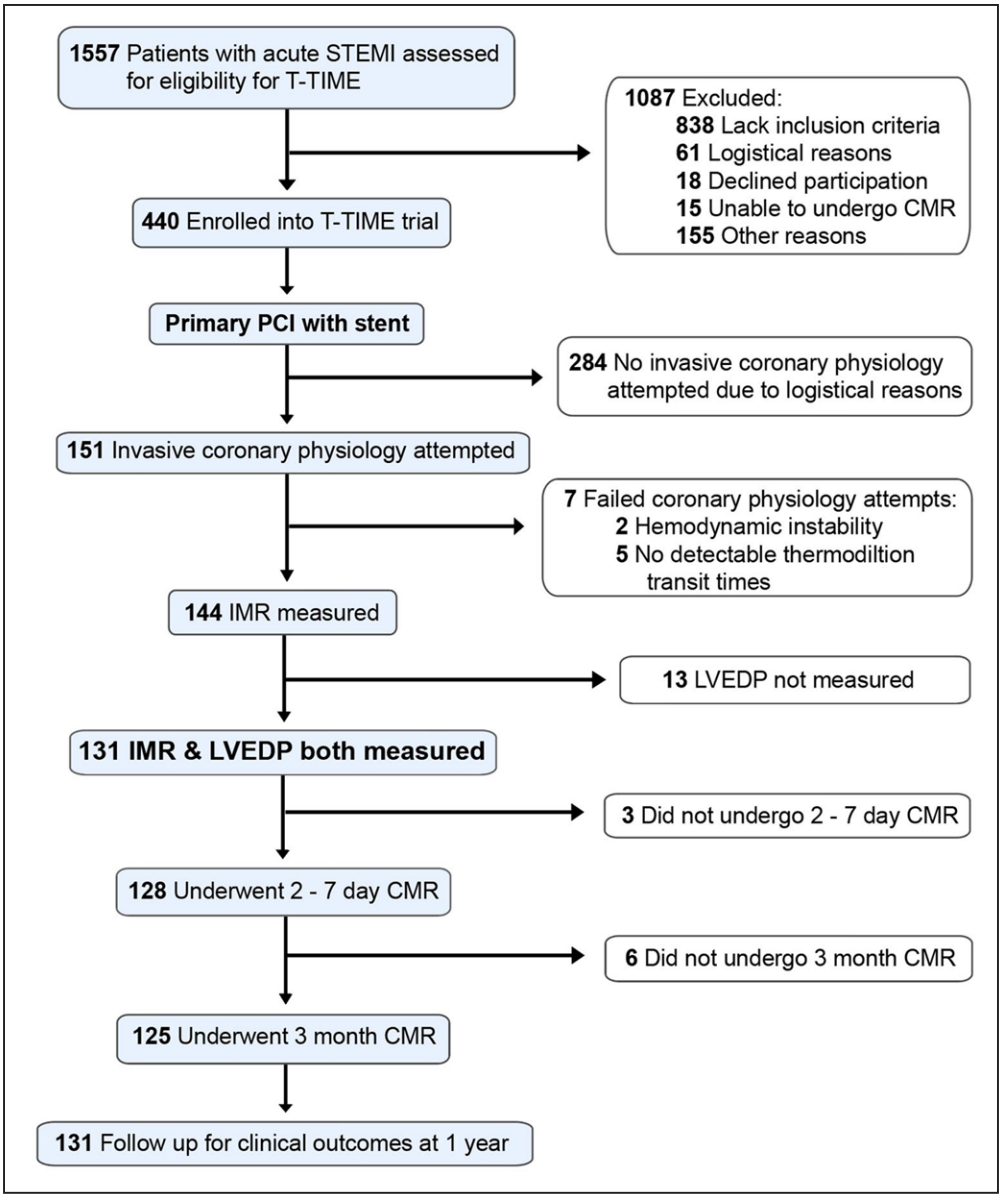

Figure 1. Flow of subjects through the study.
CMR indicates cardiovascular magnetic resonance; IMR, index of microcirculatory resistance; LVEDP, left ventricular end-diastolic pressure; PCI, percutaneous coronary intervention; and STEMI, ST-segment–elevation myocardial infarction.

high and IMR low, n=18 (14%); LVEDP high and IMR high, n=29 (22%).

CMR, Angiographic, and ECG End Points

The CMR findings at 2 to 7 days and 3 months for a 4-category combination of IMR and LVEDP (low and high) are shown in Table 2. Also shown are angiographic end points CFR and % ST-segment resolution (Table 2).

A 4-category combination of IMR and LVEDP (low and high) had discriminative value for predicting infarct size, myocardial savage index, and LV ejection fraction at 2 to 7 days and 3 months (Table 2). The CMR end points differed particularly when IMR and LVEDP were both low versus both high (Figures 2 and 3 and Table 2). When multivariable linear regression was performed, LVEDP>18 and IMR>32 combined was associated with 3-month infarct size, when compared with the low-risk group (LVEDP≤18 and IMR≤32 combined; Table 3).

A 4-category combination of IMR and LVEDP (low and high) also predicted myocardial perfusion grade, TIMI flow grade, and CFR≤2 at the end of PCI (Table 2). Although a 4-category combination of IMR and LVEDP (low and high) was not associated with ST-segment resolution overall (Table 2), there was a significant difference in % ST-segment resolution when patients with low IMR and LVEDP were compared with patients with high IMR and LVEDP (coefficient: −19.0 [95% CI, −36.9 to −1.08]; *P*=0.038).

Table 2. CMR, ECG, and Angiographic End Points and Clinical Outcomes in 131 Participants in the T-TIME Trial Grouped According to a 4-Category Combination of High and Low LVEDP (>18 and ≤18) and IMR (>32 and ≤32)

	All (n=131)	LVEDP/IMR category				*P* value
		LVEDP low/IMR low (n=53)	LVEDP high/IMR low (n=18)	LVEDP low/IMR high (n=31)	LVEDP high/IMR high (n=29)	
ECG, angiography, and coronary physiology						
% ST-segment resolution 60 minutes postreperfusion relative to baseline	46.1±41.4	54.3±40.0	53.3±30.5	38.1±51.6	35.3±34.6	0.133
TIMI flow grade ≤2 after PCI	15 (11.5%)	1 (1.9%)	0	5 (16.1%)	9 (31.0%)	<0.001
MPG ≤1 after PCI	42 (32.1%)	11 (20.8%)	3 (16.7%)	12 (38.7%)	16 (55.2%)	0.005
CFR at the end of PCI	1.4 [1.1–2.0]	1.8 [1.2–2.1]	1.8 [1.3–2.4]	1.2 [1.1–1.7]	1.2 [1.1–1.5]	0.001
CMR at day 2–7						
Infarct size (% LV)	23.1 [15.9–32.3]	19.8 [11.9–26.6]	25.4 [18.8–32.8]	25.4 [20.2–31.4]	31.2 [18.9–39.2]	0.016
Myocardial salvage index	0.4 [0.2–0.6]	0.5 [0.2–0.7]	0.4 [0.2–0.6]	0.3 [0.2–0.4]	0.3 [0.2–0.5]	0.010
LV ejection fraction, %	45.0 [40.2–49.7]	47.3 [42.1–51.1]	45.2 [42.4–47.2]	45.5 [39.3–50.8]	40.9 [32.5–46.4]	0.027
CMR at 3 mo						
Infarct size (% LV)	15.9 [7.5–24.6]	12.8 [2.8–18.7]	14.4 [7.5–20.7]	16.2 [11.6–25.3]	22.4 [14.8–28.3]	0.002
Myocardial salvage index	0.6 [0.4–0.8]	0.7 [0.5–0.9]	0.7 [0.5–0.8]	0.4 [0.4–0.7]	0.4 [0.3–0.7]	0.001
LV ejection fraction %	50.3 [45.7–54.6]	51.1 [47.5–55.1]	50.6 [49.1–55.2]	50.2 [46.4–54.0]	46.6 [38.5–50.9]	0.030
Health outcomes at 1 y						
MACE, n (%)	21 (16.0%)	4 (7.5%)	5 (16.1%)	3 (16.7%)	9 (31.0%)	0.051
All-cause death, n (%)	2 (1.5%)	1 (1.9%)	0 (0.0%)	1 (5.6%)	0 (0.0%)	0.465
Heart failure hospitalization, n (%)	18 (13.7%)	3 (5.7%)	5 (16.1%)	2 (11.1%)	8 (27.6%)	0.045

Values are median [IQR] unless otherwise stated. *P* values are derived from the 1-way ANOVA, Kruskal-Wallis, or χ^2 tests. Missing data: CMR findings at 2–7 days—3 subjects; infarct size or myocardial salvage index at 3 mo—8 subjects; LV ejection fraction at 3 mo—6 subjects; and ST-segment resolution—3 subjects. CFR indicates coronary flow reserve; CMR, cardiovascular magnetic resonance; IMR, index of microvascular resistance; LV, left ventricle; LVEDP, left ventricular end-diastolic pressure; MACE, major adverse cardiac events; MPG, myocardial perfusion grade; PCI, percutaneous coronary intervention; T-TIME, Trial of Low Dose Adjunctive Alteplase During Primary PCI; and TIMI, Thrombolysis In Myocardial Infarction.

The results for the associations between CMR, angiographic, or ECG end points with LVEDP>18 mm Hg and IMR>32 as binary predictors are reported in Tables II and III in the Data Supplement. The multivariable associates of infarct size at 3 months are described in Table 3.

Health Outcomes

A 4-category combination of IMR and LVEDP (low and high) had discriminative value for predicting MACE and hospitalization for heart failure at 1 year, particularly when IMR and LVEDP were both low versus both high (Table 2 and Figures 2 and 3). When multivariable logistic regression was performed, LVEDP>18 and IMR>32 combined was associated with MACE, when compared with the low-risk group (LVEDP≤18 and IMR≤32 combined; Table 3).

The overall net reclassification improvement, reflecting the incremental predictive accuracy for detecting MACE, was 50.6% (95% CI, 2.7–98.2; *P*=0.033) when LVEDP>18 was added to a baseline model incorporating IMR>32. When IMR>32 was added to LVEDP>18, the net reclassification improvement for detecting MACE was 49.7% (95% CI, 5.3–92.2; *P*=0.031).

When LVEDP>18 was added to a baseline model incorporating IMR>32, the overall net reclassification improvement for detecting heart failure hospitalization was 45.6% (95% CI, −5.7 to 97.9; *P*=0.081). When the baseline model incorporated LVEDP>18, the overall net reclassification improvement for detecting heart failure hospitalization was 61.3% (95% CI, 13.0–104.5; *P*=0.010) when IMR>32 was added.

The results for the associations between clinical outcome and LVEDP>18 mm Hg and IMR>32 as binary predictors are reported in Tables II and III in the Data Supplement.

DISCUSSION

We described the associations and prognostic significance of IMR and LVEDP combined as a 4-level categorical variable. We observed that MACE and the CMR, ECG and angiographic end points differed particularly when IMR and LVEDP were both low versus both high. We undertook multivariable analyses, which showed that LVEDP>18 and IMR>32 had incremental predictive utility for detecting MACE. There were consistent, directional associations for infarct size and the IMR/LVEDP category, providing a mechanism to explain the associations with MACE and LV ejection fraction. Our analysis identifies IMR/LVEDP in combination as a novel biomarker for risk stratification during primary PCI. If future studies

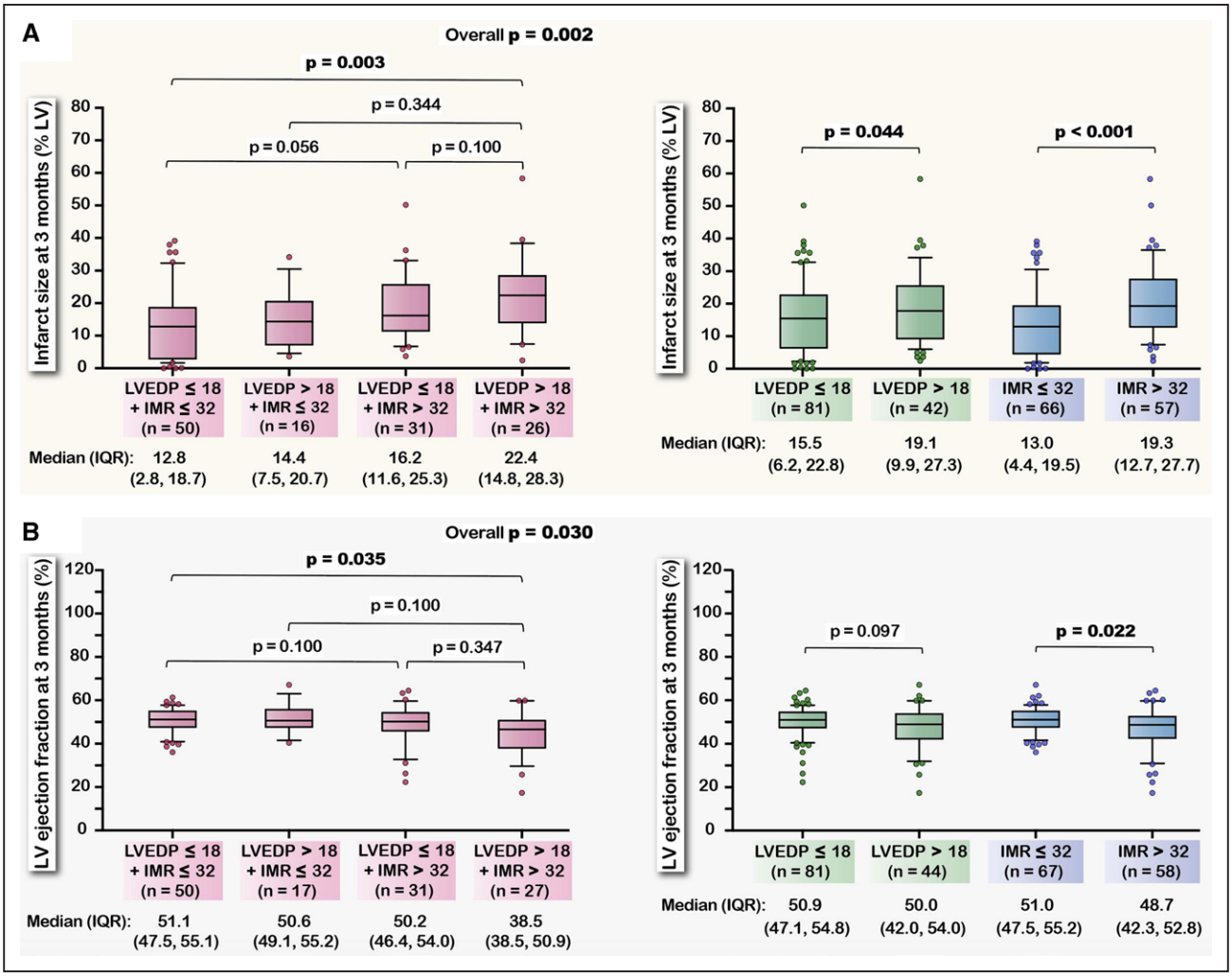

Figure 2. Box and whisker plots for infarct size and left ventricular (LV) ejection fraction.
Differences in infarct size (**A**) and left ventricular (LV) ejection fraction (**B**) at 3 mo following primary percutaneous coronary intervention (PCI), between the 4-category groups of high/low left ventricular end-diastolic pressure (LVEDP; >18 and ≤18) and index of microcirculatory resistance (IMR; >32 and ≤32), and for LVEDP>18 and IMR>32 as independent binary factors. Boxes represent the median and interquartile range (IQR; values provided), with whiskers at the 10th and 90th percentiles. Values outside the 10th and 90th percentiles are presented as individual data points.

confirm this result, then IMR and LVEDP combined may represent a novel theragnostic biomarker for clinical and research purposes.

In our study,[7] the distribution of IMR and LVEDP was similar to those of other populations.[6,12,13] The associations between IMR/LVEDP category with the CMR and angiographic surrogates, and health outcomes were directionally consistent. The coherence of these results, derived from distinct methodologies, implies that a type 2 statistical error is unlikely and the findings are plausible. Furthermore, fatal and nonfatal cardiovascular events were independently adjudicated by a clinical events committee blind to the LVEDP and IMR measurements, which strengthens the reliability of our findings.

Hospitalization for heart failure represented the majority of the MACE. Heart failure forms part of the natural history of acute MI and is a typical mode of death. Sudden cardiac death is directly related to infarct scar tissue and LV failure. The goal of effective reperfusion is to limit infarct size, preserve LV systolic function, and prevent heart failure. Although heart failure post-MI may be considered a soft outcome, we suggest that it is a highly undesirable outcome post-MI, mechanistically linked to the efficacy of myocardial reperfusion[2] and a key target for secondary prevention therapy.[1]

For the first time, we provide information on the prognostic utility of LVEDP in combination with IMR. Therefore, our study extends previous reports on associations between LVEDP and health outcomes, in patients with STEMI.[6,11–13] In the HORIZONS-AMI trial (Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction), LVEDP>18 mm Hg (median) during primary PCI was associated with increased rates of reinfarction and death at 30 days and at 2 years (hazard ratio:

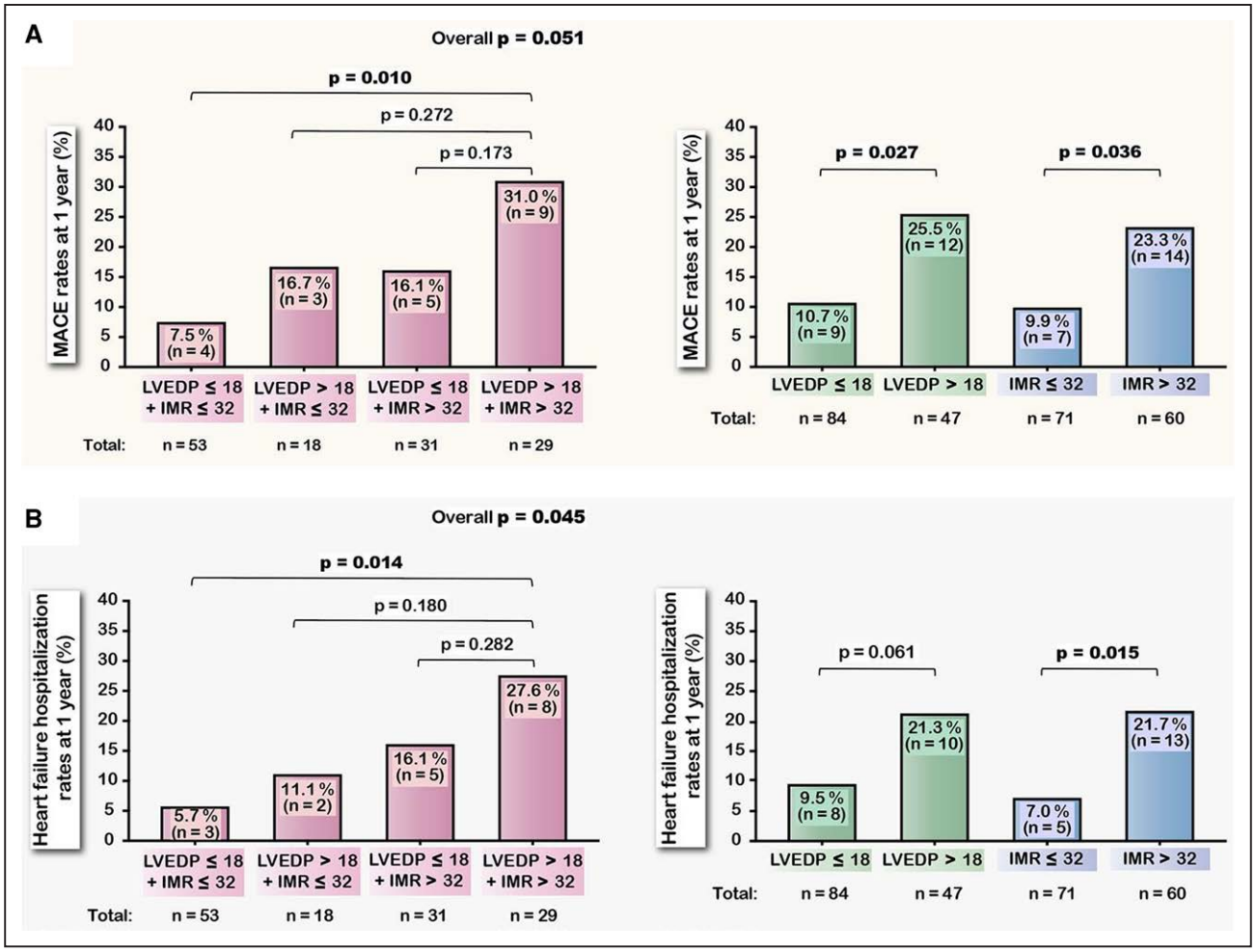

Figure 3. Bar charts showing rates of major adverse cardiac events (MACE) and heart failure hospitalization.
Differences in major adverse cardiac events (MACE; **A**) and heart failure hospitalization (**B**) rates 1 y following primary percutaneous coronary intervention (PCI), between the 4-category groups of high/low left ventricular end-diastolic pressure (LVEDP; >18 and ≤18) and index of microcirculatory resistance (IMR; >32 and ≤32), and for LVEDP>18 and IMR>32 as independent binary factors.

1.45 [95% CI, 1.14–1.85] *P*=0.002; n=2797).[6] Therefore, an LVEDP threshold of 18 mm Hg was used in our article. A smaller study (n=1909) reported that an LVEDP>22 mm Hg (median) was associated with increased heart failure rates at 90 days after primary PCI for.[12] In a further study, higher LVEDP predicted mortality at 8 years following primary PCI (hazard ratio: 1.18 [95% CI, 1.02–1.36] *P*=0.022, for 5 mm Hg incremental increase in LVEDP).[13]

It is mechanistically plausible that IMR and LVEDP used together may have greater prognostic utility than either parameter alone since these are distinct yet complimentary prognostic parameters. IMR is a specific measure of microvascular injury following STEMI. Microvascular injury has been implicated in worse health outcomes, due to impaired delivery of macrophages/promoters needed for optimal infarct healing,[14,15] and extravasation of blood when capillary integrity is compromised, leading to deposition of cytotoxic levels of iron in the myocardium, triggering inflammation, and fibrosis.[16,17] When IMR is measured immediately following primary PCI, reversible edema may contribute to microvascular injury, which may partly explain why not all patients with elevated IMR have MACE.

In contrast, LVEDP measured during primary PCI reflects acute LV pump function, including the extent of ischemic injury, filling, contractility, and compliance. Because of the proximity of the vascular and myocardial compartments, intramyocardial vessels may be susceptible to changes in LV cavity pressure.[18] An increased pressure in the LV cavity may result in transmitted external compressive forces on the microcirculation, thereby increasing endocardial capillary pressure, which may, in turn, lead to decreased perfusion pressure, with subsequent impairment of microvascular perfusion in the territory of the infarct-related artery.[18,19] This concept is supported by correlations between LVEDP with zero-flow pressure.[20] Other factors that may potentially affect LVEDP in acute STEMI include intravascular volume status[21,22] and vasodilatory drugs, for example, nitrate, which may transiently reduce LVEDP.

Considering clinical translation, LVEDP and IMR are relatively straightforward to measure and well within the skill-sets of interventional cardiologists who perform

Table 3. Multivariable Associations for LVEDP and IMR With Infarct Size at 3 Months, and MACE at 1 Year Following Primary PCI, Derived From Linear or Logistic Regression

Infarct size at 3 months	Coefficient (95% CI)	*P* value	MACE at 1 year	OR (95% CI)	*P* value
Model A			Model A		
LVEDP>18	1.07 (−3.09 to 5.24)	0.347	LVEDP>18	1.57 (0.53 to 4.65)	0.245
IMR>32	6.23 (2.60 to 9.86)	0.001*	IMR>32	1.98 (0.66 to 5.97)	0.195
Infarct-related artery*	4.48 (2.47 to 6.48)	<0.001*	Age	1.08 (1.03 to 1.13)	0.003
Ischemic time	1.60 (0.29 to 2.91)	0.017*	Infarct-related artery*	2.37 (1.30 to 4.33)	0.005
Body mass index	0.26 (0.11 to 0.63)	0.109	Estimated glomerular filtration rate	0.98 (0.96 to 1.01)	0.246
Model B			Model B		
Continuous LVEDP	3.19 (−1.72 to 8.10)	0.926*	Continuous LVEDP	2.64 (0.59 to 11.90)	0.117
IMR>32	6.23 (2.60 to 9.86)	0.001*	IMR>32	1.94 (0.65 to 5.84)	0.195
Infarct-related artery*	4.48 (2.47 to 6.48)	<0.001*	Age	1.08 (1.03 to 1.13)	0.003
Ischemic time	1.60 (0.29 to 2.91)	0.017*	Infarct-related artery*	2.37 (1.30 to 4.33)	0.005
Body mass index	0.19 (−0.18 to 0.57)	0.981	Estimated glomerular filtration rate	0.99 (0.96 to 1.01)	0.246
Model C			Model C		
LVEDP>18 + IMR>32 combined†	8.43 (3.20 to 13.66)	0.002*	LVEDP>18 + IMR>32 combined†	5.80 (1.60 to 21.11)	0.008
Infarct-related artery*	4.40 (1.64 to 7.15)	0.002*	Age	1.07 (0.99 to 1.16)	0.070
Ischemic time	2.58 (0.69 to 4.47)	0.008*	Infarct-related artery*	2.06 (0.94 to 4.54)	0.059
Body mass index	0.22 (−0.34 to 0.78)	0.434	Estimated glomerular filtration rate	1.00 (0.97 to 1.04)	0.939

Continuous LVEDP was analyzed on a log transformed scale. IMR indicates index of microcirculatory resistance; LVEDP, left ventricular end-diastolic pressure; MACE, major adverse cardiac events; OR, odds ratio; and PCI, percutaneous coronary intervention.

*Left anterior descending versus circumflex versus right coronary artery.

†LVEDP>18 + IMR>32 combined versus LVEDP≤18 and IMR≤32 combined.

primary PCI. LVEDP is a well-established hemodynamic biomarker, whereas clinicians are generally less familiar with IMR and potential barriers to measuring IMR include the cost of the guidewire and use of intravenous adenosine. More research is needed to clarify whether LVEDP and IMR when used together might lead to improved patient outcomes, and if so, at what cost.

Limitations

The T-TIME population was selected for participation in a clinical trial, and LVEDP/IMR were not measured consecutively in all patients. The low MACE rate limited power to detect statistically significant associations, therefore the findings should be interpreted as exploratory/hypothesis generating and not definitive. Moreover, continuous net reclassification improvement may overestimate the incremental value of a biomarker,[23] hence further research is needed to validate the findings. A further limitation is that the participants would not have withheld from caffeine because the procedures were performed in the emergency setting, which could have affected response to adenosine and thus maximal hyperemia could not be guaranteed in all patients.

Conclusions

IMR and LVEDP in combination have potential additive utility for immediate risk stratification during primary PCI for STEMI. Further research seems warranted.

ARTICLE INFORMATION

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Disclosures

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