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MINI-FOCUS: CORONARY PHYSIOLOGY

Zero-Flow Pressure Measured Immediately After Primary Percutaneous Coronary Intervention for ST-Segment Elevation Myocardial Infarction Provides the Best Invasive Index for Predicting the Extent of Myocardial Infarction at 6 Months

An OxAMI Study (Oxford Acute Myocardial Infarction)

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ABSTRACT

OBJECTIVES The aim of this study was to define which measure of microvascular best predicts the extent of left ventricular (LV) infarction.

BACKGROUND Microvascular injury after ST-segment elevation myocardial infarction (STEMI) is an important determinant of outcome. Several invasive measures of the microcirculation at primary percutaneous coronary intervention (PPCI) have been described. One such measure is zero-flow pressure (Pzf), the calculated pressure at which coronary flow would cease.

METHODS In 34 STEMI patients, Pzf, hyperemic microvascular resistance (hMR), and index of microcirculatory resistance (IMR) were derived using thermodilution flow/pressure and Doppler flow/pressure wire assessment of the infarct-related artery following PPCI. The extent of infarction was determined by blinded late gadolinium enhancement on cardiac magnetic resonance at 6 months post-PPCI. Infarction of ≥24% total LV mass was used as a categorical cutoff in receiver-operating characteristic curve analysis.

RESULTS Pzf was superior to both hMR and IMR for predicting ≥24% infarction area under the curve: 0.94 for Pzf versus 0.74 for hMR ($p = 0.04$) and 0.54 for IMR ($p = 0.003$). Pzf ≥42 mm Hg was the optimal cutoff value, offering 100% sensitivity and 73% specificity. Patients with Pzf ≥42 mm Hg also had a lower salvage index (61.3 ± 8.1 vs. 44.4 ± 16.8, $p = 0.006$) and 6-month ejection fraction (62.4 ± 3.6 vs. 49.9 ± 9.6, $p = 0.002$). In addition, there were significant direct relationships between Pzf and troponin area under the curve (rho = 0.55, $p = 0.002$), final infarct mass (rho = 0.75, $p < 0.0001$), percentage of LV infarction and percent transmurality of infarction (rho = 0.77 and 0.74, respectively, $p < 0.0001$), and inverse relationships with myocardial salvage index (rho = −0.53, $p = 0.01$) and 6-month ejection fraction (rho = −0.73, $p = 0.0001$).

CONCLUSIONS Pzf measured at the time of PPCI is a better predictor of the extent of myocardial infarction than hMR or IMR. Pzf may provide important prognostic information at the time of PPCI and merits further investigation in clinical studies with relevant outcome measures. (J Am Coll Cardiol Intv 2015;8:1410–21) © 2015 by the American College of Cardiology Foundation.

Primary percutaneous coronary intervention (PPCI) is the most effective reperfusion therapy for ST-segment elevation myocardial infarction (STEMI) (1,2). Although infarct-related artery (IRA) patency is achieved in a large majority, more than one-half of cases have angiographic or electrocardiographic (ECG) evidence of microvascular no-reflow, which is associated with worse outcomes (3). Several invasive parameters have been investigated to determine their value in assessment of the microcirculation, and prediction of the extent of myocardial infarction after PPCI, including zero-flow pressure (Pzf), the index of microcirculatory resistance (IMR), and hyperemic microvascular resistance index (hMR) (4–7). These parameters have not been directly compared in the same patient cohort.

Pzf is the distal coronary pressure when theoretically the flow in a coronary artery would cease. It is not possible to measure this directly as in vivo coronary flow does not cease under normal circumstances and so Pzf is extrapolated from pressure-velocity loops. Pzf is significantly higher than simply the point at which driving pressure falls to outlet pressure (i.e., coronary sinus pressure). Although hyperemia reduces Pzf, it is still considerably higher than outlet pressure principally due to microvascular tone/resistance, which is abnormally raised in microvascular dysfunction (8).

Cardiac magnetic resonance (CMR) imaging provides accurate and reproducible quantification of the extent of myocardial infarction. Left-ventricular (LV) infarction ≥24% of overall LV mass, the degree of transmural infarction, and ejection fraction (EF) <50% are independent predictors of mortality (9–12). Defining a measure available at the time of PPCI that predicts clinical outcome would provide support in its use as measure of the efficacy of reperfusion, and to guide therapeutic interventions. However, the optimal index from the measures currently available is unknown.

Accordingly, the aim of our study was to compare directly the ability of Pzf, hMR, and IMR to predict the extent of myocardial infarction after STEMI, and to identify the optimal threshold value for the most powerful parameter.

METHODS

PATIENT POPULATION. Thirty-seven patients undergoing PPCI for STEMI were recruited from 131 primary PCI calls (**Figure 1**). Diagnosis of STEMI required chest pain lasting longer than 30 min, within 12 h from onset of symptoms, and ST-segment elevation of ≥2 mm (0.2 mV) in at least 2 contiguous leads on ECG and TIMI (Thrombolysis In Myocardial Infarction) flow grade 0 on initial angiography. Exclusion criteria were presentation with cardiogenic shock, previous myocardial infarction, and previous cardiac surgery. Verbal consent was obtained at the time of PPCI, but an approved process was applied because: 1) the treatment needs to be given urgently; 2) it is necessary to take the action for the purpose of the research urgently; but 3) it is not reasonably practicable to consult before enrolling the patient (Section 32(9) of the Mental Capacity Act). The research study, including risks and benefits, were discussed. The patient was given the choice to participate or withdraw from the study at any time. In accordance with the Mental Capacity Act and the study protocol, a trained independent patient advocate witnessed patient enrollment. Full written informed consent was deferred until such time that the subject had adequate time to process verbal and written information. The study protocol and consent process was approved by the National Research Ethics Service Committee South Central Oxford (REC reference: 11/SC0397).

ABBREVIATIONS AND ACRONYMS

AUC = area under the curve
CMR = cardiac magnetic resonance
ECG = electrocardiographic/electrocardiogram
EF = ejection fraction
hMR = hyperemic microvascular resistance
IMR = index of microcirculatory resistance
IRA = infarct-related artery
LGE = late-gadolinium enhancement
LV = left ventricular
MBG = myocardial blush grade
MVO = microvascular obstruction
Pa = aortic pressure
Pd = distal pressure
PPCI = primary percutaneous coronary intervention
PV = peak velocity
Pzf = zero-flow pressure
ROC = receiver-operating characteristic
STEMI = ST-segment elevation myocardial infarction

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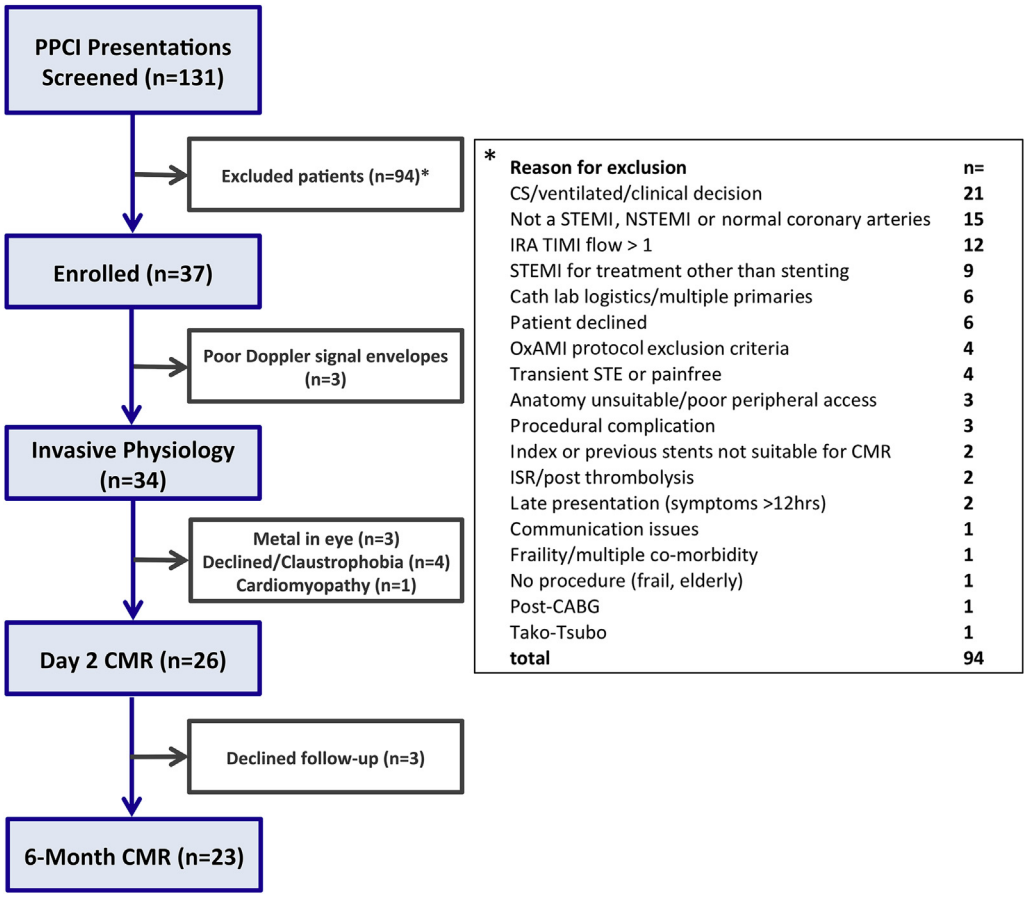
FIGURE 1 Study CONSORT Diagram



CONSORT diagram of enrollment and flow of patients through the study protocol. CABG = coronary artery bypass graft; CMR = cardiac magnetic resonance; CS = cardiogenic shock; IRA = infarct-related artery; ISR = in-stent restenosis; NSTEMI = non–ST-segment elevation myocardial infarction; OxAMI = Oxford Acute Myocardial Infarction; PPCI = primary percutaneous coronary intervention; STE = ST-segment elevation; STEMI = ST-segment elevation myocardial infarction; TIMI = Thrombolysis In Myocardial Infarction.

STUDY PROTOCOL. All patients received a standardized protocol of clopidogrel (600 mg) and aspirin (300 mg) loading before PPCI and were treated with intravenous heparin and/or bivalirudin during the procedure. Coronary catheterization and intervention were performed using a 6-F guiding catheter via radial access. Epicardial coronary reperfusion was established with a thrombus aspiration catheter with or without lesion pre-dilation. Central venous access was obtained using the femoral vein. All patients received intracoronary glyceryl trinitrate (0.5 mg to 2 mg total over a variable number of boluses), drug-eluting stent deployment, and dual antiplatelet therapy with aspirin and clopidogrel for 1 year. Appropriate secondary prevention was commenced with statins, angiotensin-converting enzyme inhibitors and beta-blockers. Venous blood sampling was performed for troponin calculation at PPCI, 6, 12, and 24 h post-intervention.

INVASIVE CORONARY PHYSIOLOGY MEASURES AND ANALYSIS. Indices of coronary physiology of the IRA were assessed immediately following coronary stenting at PPCI. Single measures were obtained. Aortic pressure (Pa) was recorded from the guiding catheter. IMR was defined as the mean distal pressure multiplied by the mean hyperemic transit time as previously described (7,13), and obtained using a coronary PressureWire (St. Jude Medical, St. Paul, Minnesota). A dual sensor pressure and Doppler flow-velocity guidewire (ComboWire, Volcano Corporation, Rancho Cordova, California) was used to

determine hMR and Pzf. Following calibration and equalization with aortic pressure, the guidewire was placed distal to the stented lesion, and small rotational movements made to produce the most-dense Doppler envelope. Simultaneous ECG, Pa, distal pressure (Pd) and instantaneous peak velocity (PV) recordings were obtained using the ComboMap Pressure and Flow System (Volcano Corporation) at baseline and at hyperemia induced by a 140 μg/kg/min intravenous infusion of adenosine. Recordings were transferred for offline analysis. Recordings of 5 to 15 consecutive cycles at baseline and at hyperemia were identified, and source data for instantaneous Pd and PV were exported using ComboMap Study Manager (Volcano Corporation). These data were analyzed using custom software packages designed on MATLAB (MathWorks, Natick, Massachusetts). Average Pd, Pa, and PV of consecutive beats at rest and during hyperemia were used to calculate hMR (defined as the ratio of average Pd and average PV during hyperemia) (14). Pzf was determined using automated algorithms developed on MATLAB. Data from several cardiac cycles during hyperemia were used to construct ensembled average Pd and PV against time plots (**Figure 2A**). The automated algorithm then determined the mid-diastolic period of the averaged cardiac cycle (**Figure 2B**), and sampled this diastolic phase (shown in black on **Figure 2B** and **Figure 2C**) of the resultant pressure-velocity loop. A line of regression is drawn automatically from the diastolic data points, and Pzf is the pressure at which this line crosses the x-axis (15). This is the extrapolated distal coronary pressure at which flow would cease in the IRA.

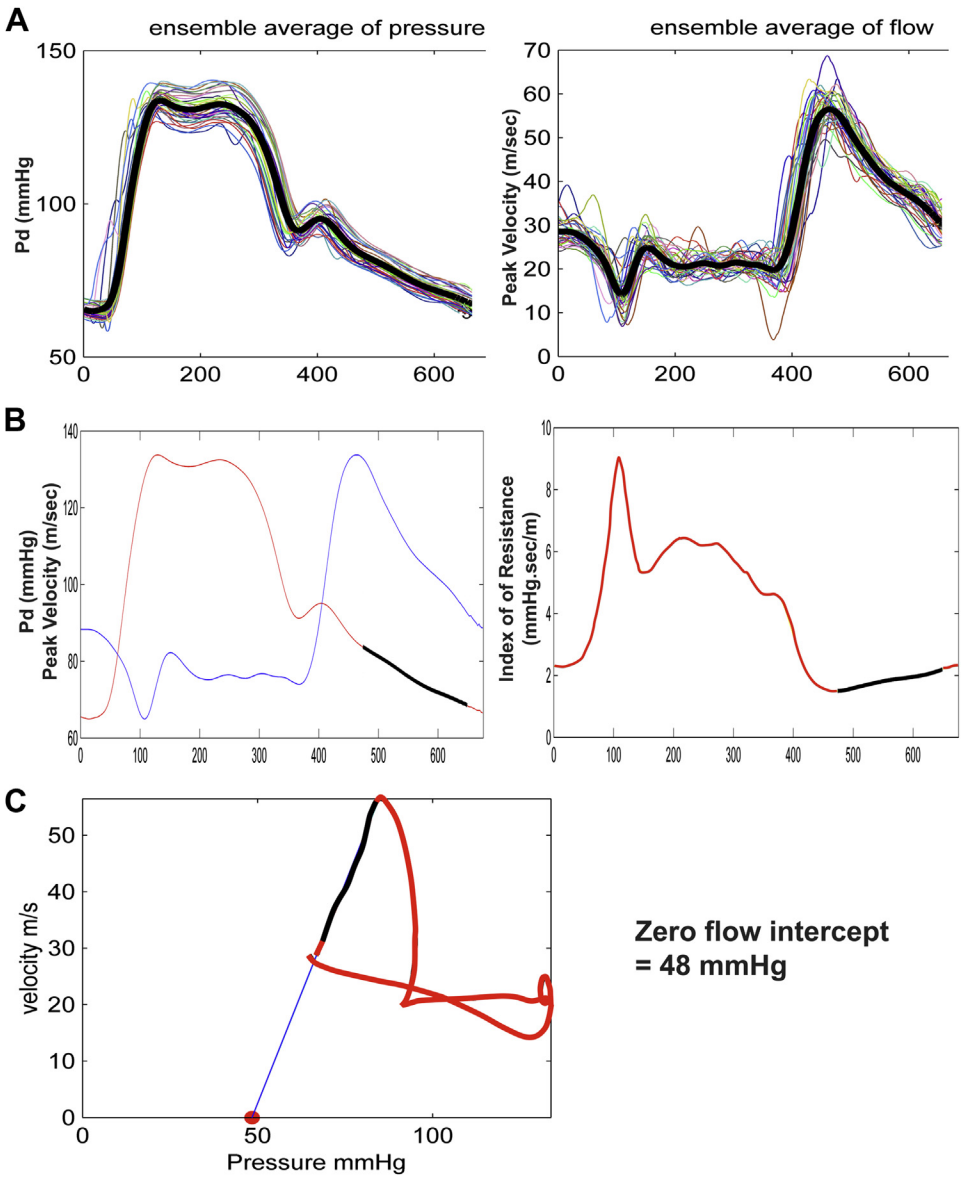
ANGIOGRAPHIC ASSESSMENT. Coronary flow was graded using the standard TIMI criteria (16). Myocardial blush grade (MBG) at the end of the procedure was evaluated according to van't Hof (17). Angiographic no-reflow was defined as TIMI flow grade <3 and/or TIMI flow grade 3 with MBG <2 at completion of the procedure. Two interventional cardiologists blinded to clinical and outcome parameters performed the angiographic analyses, and differences were resolved by consensus. Quantitative blush evaluator software (QuBE; open source) assessment was performed as described previously (18,19).

ELECTROCARDIOGRAPHIC ANALYSIS OF ST-SEGMENT RESOLUTION. For assessment of pre-procedural ST-segment elevation the ECG with the maximal ST-segment elevation (performed by paramedics or in the emergency department) was taken. For post-procedural ST-segment analysis, an ECG was recorded 60 min after PPCI. Two readers blinded to clinical and outcome parameters performed measurements. The absolute level of ST-segment elevation was measured with digital calipers to the nearest 0.01 mV, 20 ms after the end of the QRS interval. The sum of pre-procedural and post-procedural ST-segment elevation was calculated for anterior (leads V_1 to V_6, I, and aVL) and non-anterior (leads II, III, aVF, V_5, V_6) infarctions. For statistical analysis, summed ST-segment resolution parameters were categorized as complete (≥70%) and incomplete (<70%).

TROPONIN ANALYSIS. Cardiac troponin I was quantified using an automated chemiluminescent immunoassay technique, and the area under the curve (AUC) was calculated using the trapezoidal method.

CMR IMAGE ACQUISITION AND ANALYSIS. All patients were examined at rest with a 3.0-T CMR scanner (either MAGNETOM TIM-Trio or MAGNETOM Verio, Siemens Healthcare, Erlangen, Germany) using a phased-array 32-channel coil. Patients were scanned on day 2 (n = 26) and again at 6 months post-PPCI (n = 23; 3 patients withdrew consent). Identical short-axis images at matching slice position with functional images were acquired using steady-state free precession for cine imaging, T2-prep steady-state free precession single-shot sequence with coil signal intensity correction for edema imaging, and T1-weighted segmented inversion-recovery gradient echo-phase sensitive-inversion recovery sequence for late-gadolinium enhancement (LGE) imaging as previously described. LGE images were acquired 15 min after administration of 0.1 mmol/kg gadodiamide contrast agent (Omniscan, GE Healthcare, Amersham, United Kingdom) and analyzed following adjustment of the inversion time to optimize nulling of remote normal myocardium (20). CMR image analysis was performed using certified software (cmr^{42}, Circle Cardiovascular Imaging, Calgary, Alberta, Canada). For objective quantification of both edema and LGE, a reference region of interest was placed in remote myocardium. The signal intensity threshold indicating edema/LGE was imposed 2 standard deviations above the mean intensity of the reference region of interest (21). Microvascular obstruction (MVO) was included in the measurement of edema and LGE. MVO was quantified by manual delineation of hypodense areas within LGE (22,23) and expressed as percentage fraction of area at risk. The Myocardial Salvage Index was defined as the difference between the area of edema at day 2 and the final infarct size assessed by LGE at 6 months. The standard American Heart Association 17-segment model was used to determine the IRA subtended myocardium, and average values of wall thickness, thickening, motion,

FIGURE 2 Computer Algorithm for Determination of Pzf



(A) Assembled average of several cardiac cycles. **(B)** Automated determination of the diastolic period (in **black**). **(C)** Determination of zero-flow pressure (Pzf) by construction of a pressure-velocity loop and linear regression of the diastolic segment of the cardiac cycle (in **black**). Output of this automated process is the pressure at zero flow (x-axis intercept). Pd = diastolic pressure.

edema, and transmurality of infarction (LGE) are presented for IRA territories (apical segments were excluded from analysis due to motion artefact and considerable variability in blood supply) (24).

STATISTICAL METHODS. Normally distributed metrics are reported as mean ± SD, and the Student *t* test used for comparisons. Nonparametric distributions are reported as median (interquartile range), and the Mann-Whitney test used for unpaired data. The Fisher exact chi-square test was used for binary variables. Correlations between continuous variables were made using the Spearman rho correlation. Receiver-operating characteristic (ROC) curves were compared using the Delong method, and a p value of <0.05 was considered statistically significant (25). ROC analyses were performed on MedCalc 13.2.1.0 (Ostend, Belgium). The Youden index was used to

identify the ideal cutoff values from ROC curves. For multiple testing, the Benjamini and Hochberg method of type 1 error control was applied, and a p value of <0.01 was considered statistically significant (26). All tests were 2-tailed. All other statistics were performed on SPSS version 22.0 (IBM, Chicago, Illinois), and figures were generated with GraphPad Prism 6.0 (GraphPad Software, La Jolla, California).

RESULTS

A total of 37 patients were recruited. Pzf could not be measured in 3 patients due to poor Doppler envelopes. Data from 34 patients were analyzed. The baseline characteristics of the cohort are presented in Table 1. Approximately one-half of the patients underwent PPCI to the left anterior descending coronary artery, approximately two-thirds achieved angiographic reflow at the end of the procedure, and the mean percent of LV final infarction was 24.3 ± 12.6%.

RELATIONSHIPS OF INVASIVE PARAMETERS OF MICROVASCULAR FUNCTION TO ANGIOGRAPHIC, ST-SEGMENT RESOLUTION, BIOCHEMICAL, AND CMR IMAGING MEASURES.

1. Relationships of Pzf to angiographic, ST-segment resolution, biochemical, and CMR imaging parameters: Pzf was significantly lower in those with MBG >II (39.4 ± 16.9 mm Hg vs. 59.4 ± 22.8 mm Hg, p = 0.01). Furthermore, it correlated with both ST-segment resolution (rho = −0.64, p = 0.001) and troponin AUC (rho = 0.55, p = 0.002). There were significant direct relationships between Pzf and MVO mass (rho = 0.49, p = 0.02), final infarct mass (rho = 0.75, p < 0.0001), percentage of LV infarction and percent transmurality of infarction (rho = 0.77 and 0.74, respectively, p < 0.0001), and inverse relationships with myocardial salvage index (rho = −0.53, p = 0.01) and 6-month EF (rho = −0.73, p = 0.0001) (Figure 3).
2. Relationships of IMR to angiographic, ST-segment resolution, biochemical, and CMR imaging parameters: In contrast to Pzf, IMR was no different in those with MBG >II (20.2 [4.8 to 67.3] vs. 34.6 [23.0 to 65.1], p = 0.10). There were no significant relationships between IMR and ST-segment resolution (rho = −0.27, p = 0.15) or troponin AUC (rho = 0.24, p = 0.2) and also no significant relationships between IMR and MVO mass, final infarct mass, percentage of LV infarction, percent transmurality of infarction, or to myocardial salvage index. Additionally, there were no significant differences in ECG, biochemical, or imaging parameters of infarction when the cohort was stratified based on the previously reported IMR prognostic cutoff of 40 (7).
3. Relationships of hMR to angiographic, ST-segment resolution, biochemical, and CMR imaging parameters: hMR was not significantly different in those with MBG >II (2.2 [1.9 to 3.1] vs. 2.5 [2.2 to 3.9], p = 0.69). However, there were no

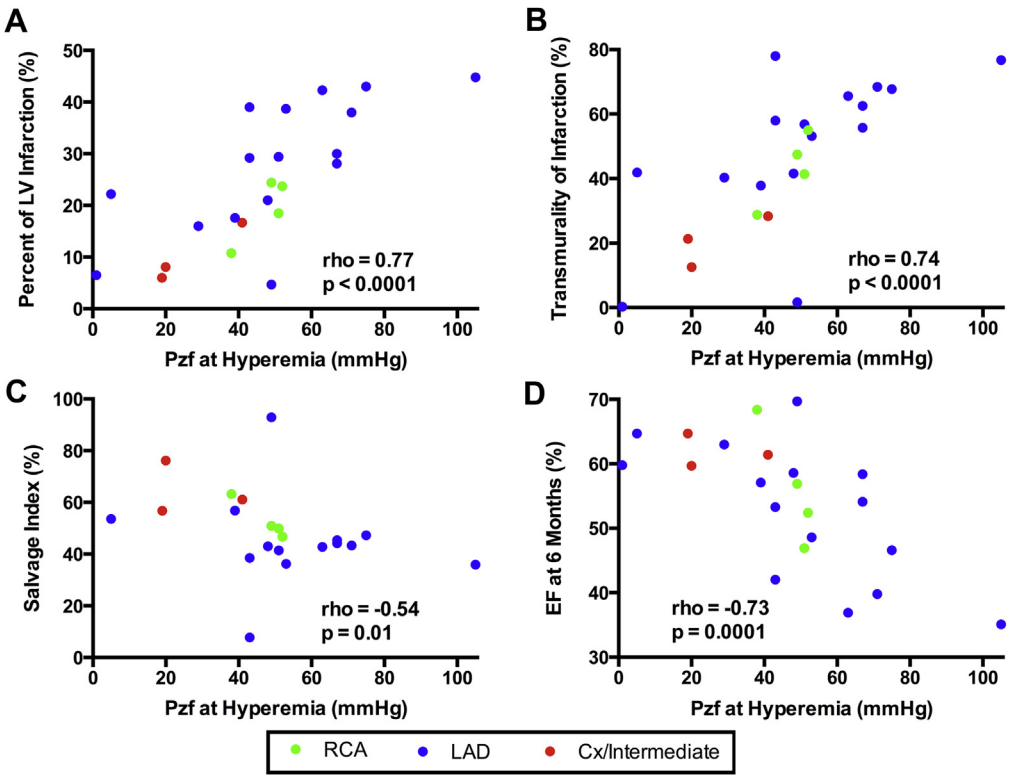
TABLE 1 Clinical Characteristics of the Study Population, N = 34

Presentation	Age, yrs	61.0 ± 10.6
	Male	26 (76.5%)
	Pain-to-balloon time, h	2.9 (1.9–4.6)
	Door-to-balloon time, min	22 (17–34)
	Systolic/diastolic BP mm Hg	125/79 ± 25/21
	Heart rate, beats/min	80 ± 18
Coronary risk factors	Dyslipidemia	18 (52.9%)
	Current smoker	14 (41.2%)
	Ex-smoker	16 (47.1%)
	Diabetes mellitus	2 (5.9%)
	Hypertension	11 (32.4%)
	BMI	28.0 ± 4.0
Procedural antithrombotic	Unfractioned heparin	23 (67.6%)
	Bivalirudin	32 (94.1%)
	Abciximab	0 (0.0%)
IRA	LAD	18 (52.9%)
	LCX	2 (5.9%)
	RCA	12 (35.3%)
	OM	1 (2.9%)
	Intermediate	1 (2.9%)
	APPROACH JS	31.8 (26.7–51.0)
PCI characteristics	Radial approach	34 (100.0%)
	Thrombectomy device use	32 (94.1%)
	Direct stenting	5 (14.7%)
	Drug eluting stent use	30 (88.2%)
	Stented segment length	20.0 (20.2–25.0)
	Post-dilation	19 (55.9%)
Post-PCI outcomes	TIMI flow grade III	26 (76.5%)
	MBG II or III	24 (70.6%)
	Angiographic reflow	23 (67.6%)
	$APV_{resting}$, cm/s^{-1}	23.0 ± 10.9
	$APV_{hyperemia}$, cm/s^{-1}	28.6 ± 10.2
	$Pd_{resting}$, mm Hg	88 ± 15
	$Pd_{hyperemia}$, mm Hg	72 ± 16
	Doppler CFR	1.4 ± 0.6
	Thermodilution CFR	1.9 ± 1.1
	$Pzf_{resting}$, mm Hg	46.5 ± 21.6
	$Pzf_{hyperemia}$, mm Hg	44.8 ± 20.1
	IMR	28.6 (20.0–43.5)
	hMR	2.32 (2.01–3.54)

Values are mean ± SD, median (interquartile range), or n/N (%). Angiographic reflow was defined as TIMI III and MBG ≥II.

APPROACH JS = Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease jeopardy score; APV = average peak velocity; BMI = body mass index; BP = blood pressure; CFR = coronary flow reserve; hMR = hyperemic microvascular resistance; IMR = index of microcirculatory resistance; IRA = infarct-related artery; LAD = left anterior descending coronary artery; LCX = left circumflex coronary artery; MBG = myocardial blush grade; OM = obtuse marginal; PCI = percutaneous coronary intervention; Pd = diastolic pressure; Pzf = zero-flow pressure; RCA = right coronary artery; TIMI = Thrombolysis In Myocardial Infarction.

FIGURE 3 Pzf Correlations With CMR Measures of Outcomes



Correlations between zero-flow pressure (Pzf) and infarct size as a percentage of left ventricular (LV) mass **(A)**, percentage transmurality of infarction **(B)**, salvage index **(C)**, and ejection fraction (EF) **(D)** at 6 months post-presentation. CMR = cardiac magnetic resonance; Cx = circumflex coronary artery; LAD = left anterior descending coronary artery; RCA = right coronary artery.

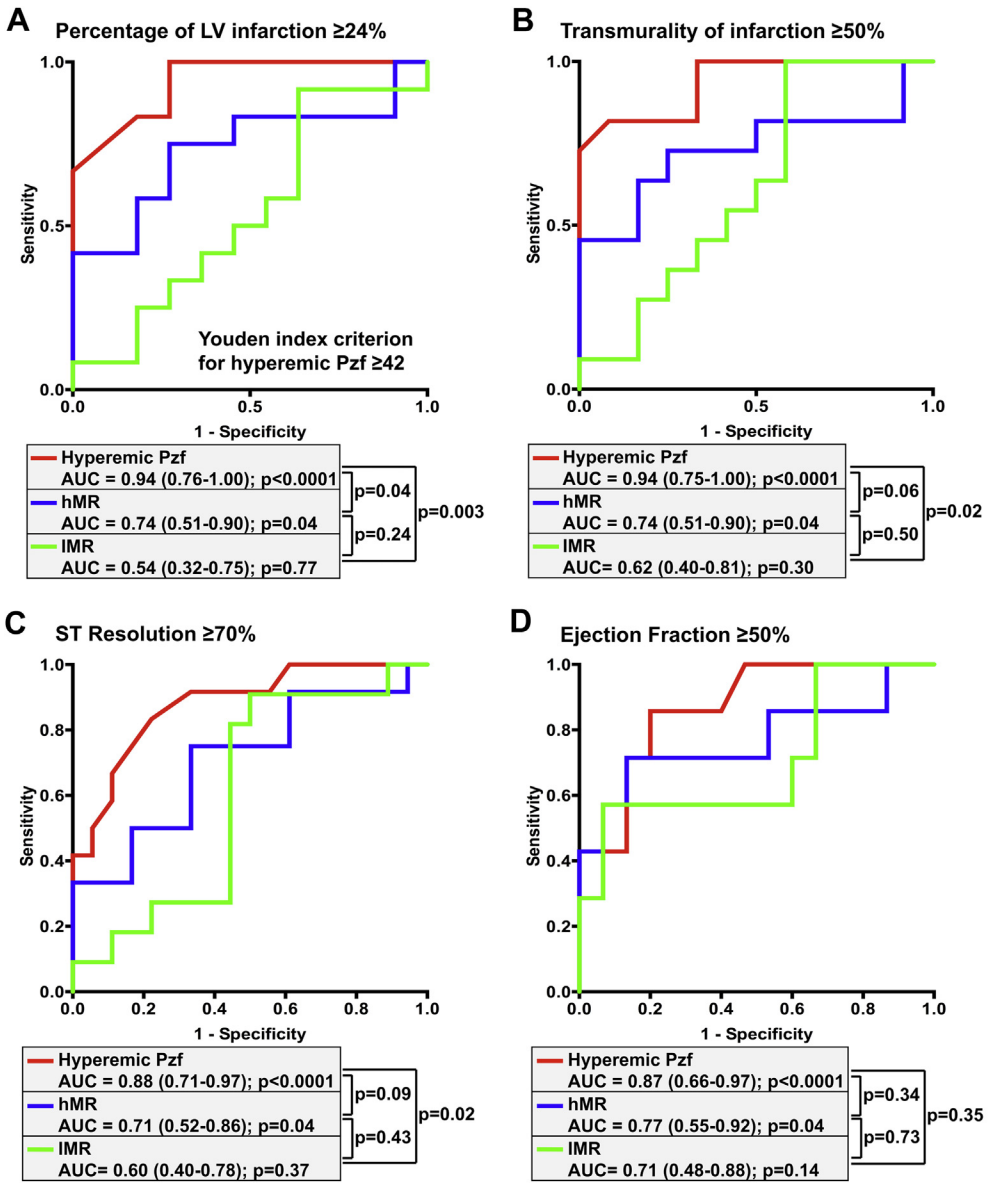
significant relationships to ST-segment resolution (rho = −0.31, p = 0.09) or troponin AUC (rho = 0.36, p = 0.05). There were significant relationships with final infarct mass (rho = 0.47, p = 0.03), percentage of LV infarction and percent transmurality of infarction (rho = 0.54 and 0.48, p = 0.009 and 0.02, respectively), but myocardial salvage index failed to reach significance (rho = −0.39, p = 0.08). There was, however, a close inverse relationship to 6-month EF (rho = −0.62, p = 0.002). Stratifying the cohort based on a previously reported cutoff value of ≥3.25 (4) identified a group with significantly higher troponin AUC (2,586 [2,035 to 5,070] vs. 4,522 [2,973 to 9,272]; p = 0.04), larger percentage of infarction (19.7 ± 11.2% vs. 33.0 ± 10.8%, p = 0.01), and lower EF at 6 months (58.7 ± 7.5% vs. 45.2 ± 8.4%, p = 0.004).

In summary, Pzf and hMR are related to biochemical and imaging assessments of infarction, and Pzf was also inversely related to salvage index.

CONSTRUCTION OF RECEIVER-OPERATING CHARACTERISTIC CURVE ANALYSIS. ROC curve analysis was used to compare the performance of the coronary physiology parameters (Pzf, hMR, and IMR) to predict: 1) ≥24% LV infarction; 2) ≥50% transmural myocardial infarction; 3) <70% ST-segment resolution; and 4) ≥50% LVEF at 6 months.

1. Predicting ≥24% LV infarction at 6 months: The AUC were 0.94 (p < 0.0001) for Pzf, 0.54 (p = 0.77) for IMR, and 0.74 (p = 0.04) for hMR (Figure 4A). Direct comparison of the AUC confirmed that Pzf was significantly better than hMR (p = 0.04) and IMR (p = 0.003). The optimal cutoff for predicting ≥24% of LV infarction was ≥42 mm Hg, with a sensitivity of 100% and specificity 73%.
2. Predicting ≥50% transmural myocardial infarction at 6 months: The AUC were 0.94 (p < 0.0001) for Pzf, 0.62 (p = 0.30) for IMR, and 0.74 (p = 0.04) for hMR (Figure 4B). Direct comparison of the AUC confirmed that Pzf was significantly better than

FIGURE 4 ROC Curves for Prediction of Parameters of Myocardial Infarction and Function



Receiver-operating characteristic (ROC) curves for zero-flow pressure (Pzf), hyperemic microvascular resistance (hMR), and index of microcirculatory resistance (IMR) in predicting infarct size as a percentage of left ventricular (LV) mass ≥24% **(A)**, ≥50% percentage transmurality of infarction **(B)**, ≥70% ST resolution **(C)**, and normal ejection fraction (defined as ≥50%) **(D)** at 6 months. AUC = area under the curve.

IMR ($p = 0.02$). The optimal cutoff for predicting >50% transmural LV infarction was ≥50 mm Hg. A threshold value of ≥42 mm Hg (optimal for ≥24% of LV infarction) returns a sensitivity of 100% and specificity 67%.

3. Predicting ≥70% ST-segment resolution: The AUC were 0.88 ($p < 0.0001$) for Pzf, 0.62 ($p = 0.26$) for IMR, and 0.71 ($p = 0.04$) for hMR (Figure 4C). Direct comparison of the AUC confirmed that Pzf was significantly better than IMR ($p = 0.02$). The optimal cutoff for predicting ≥70% ST-segment resolution was ≤43 mm Hg. A value of <42 mm Hg returns a sensitivity of 61% and specificity 92%.
4. Predicting LVEF at 6 months (defined as ≥50%): The AUC were 0.87 ($p < 0.0001$) for Pzf, 0.77 ($p = 0.04$) for hMR, and 0.71 ($p = 0.14$) for IMR (Figure 4D). The optimal cutoff for predicting EF ≥50% was ≤49 mm Hg (sensitivity 80%, specificity

TABLE 2 Clinical, Angiographic, Physiological, And Imaging Parameters in Patients Stratified by Pzf Value of 42 mm Hg

	Pzf at PPCI		
	<42 mm Hg (n = 14)	≥42 mm Hg (n = 20)	p Value
Clinical			
Age, yrs	62.4 ± 11.2	59.9 ± 10.2	0.50
Male	11/14 (78.6%)	15/20 (75.0%)	0.81
Ischemia time, h	2.5 (1.9–7.6)	3.0 (1.9–3.9)	0.99
First heart rate, beats/min	70 (70–80)	80 (70–100)	0.10
Systolic BP, mm Hg	122.4 ± 27.6	127.0 ± 24.6	0.63
Diastolic BP, mm Hg	71.6 ± 24.7	83.9 ± 16.3	0.10
Door to balloon time, h	20.0 (17.0–29.0)	24.0 (18.3–82.8)	0.57
Percentage ST-segment resolution	85.6 ± 19.8	67.3 ± 15.7	**0.009**
Troponin AUC	2,040 (839–3,119)	4,991 (3,080–7,341)	0.02
Angiographic			
LAD territory	5/14 (35.7%)	13/20 (65.0%)	0.09
APPROACH JS	28.8 (26.4–37.3)	39.2 (31.0–51.0)	0.09
TIMI flow grade 3	13/14 (92.9%)	13/20 (65.0%)	0.10
MBG III	9/14 (64.3%)	3/20 (15.0%)	**0.005**
QuBE	15.5 ± 5.4	10.5 ± 3.7	**0.003**
Physiology			
FFR	0.95 ± 0.04	0.95 ± 0.05	0.92
IMR	24.4 (14.2–40.7)	33.8 (22.0–46.4)	0.20
hMR	2.07 (1.87–2.48)	2.65 (2.12–4.49)	0.03
Pzf	28.1 ± 13.6	56.5 ± 15.1	**<0.0001**
CMR			
At day 2			
Myocardial edema, g	29.4 ± 14.4	47.7 ± 19.1	0.04
Myocardial edema, % of LV	33.6 ± 11.6	51.9 ± 16.3	0.02
MVO mass, g	0.0 (0.0–0.9)	2.5 (0.0–3.7)	0.16
MVO, % of AAR	0.9 (0.0–3.0)	3.1 (0.0–5.9)	0.22
IRA territory wall edema, %	60.6 (48.2–67.5)	86.5 (70.7–92.7)	**0.006**
IRA territory wall motion, mm	6.0 (4.3–7.5)	3.1 (2.6–3.9)	**0.001**
IRA territory wall thickness, mm	8.0 (7.5–8.9)	8.4 (7.5–8.9)	1.00
IRA territory wall thickening, %	45.2 ± 25.0	22.0 ± 12.6	**0.005**
EDV, mm^3	132.3 ± 36.0	165.4 ± 36.8	0.10
ESV, mm^3	65.6 ± 25.7	98.3 ± 26.1	**0.01**
EF, %	53.5 ± 8.9	40.9 ± 5.5	**<0.0001**
At 6 months			
Infarct mass, g	12.3 (4.9–15.6)	31.2 (21.1–39.4)	**0.001**
Infarct size, % of LV	13.0 ± 6.0	30.3 ± 11.0	**<0.0001**
Salvage index	61.3 ± 8.1	44.4 ± 16.8	**0.006**
Transmurality of infarction, %	26.4 ± 14.5	55.3 ± 18.5	**0.001**
IRA territory wall motion, mm	7.8 ± 2.1	5.2 ± 2.1	**0.008**
IRA territory wall thickness, mm	6.4 ± 1.1	6.8 ± 1.0	0.38
IRA territory wall thickening, %	67.7 ± 20.0	40.0 ± 28.1	0.02
EDV, mm^3	133.6 ± 22.9	178.5 ± 26.8	**0.001**
ESV, mm^3	52.1 ± 11.7	90.4 ± 26.8	**0.001**
EF, %	62.4 ± 3.6	49.9 ± 9.6	**0.002**

Values are mean ± SD, median (interquartile range), or n (%). Statistically significant p values using the Benjamini and Hochberg method of type 1 error control are highlighted in **bold**.

AAR = area at risk (edema CMR imaging); AUC = area under the curve; CMR = cardiac magnetic resonance imaging; EDV = end-diastolic volume; EF = ejection fraction; ESV = end-systolic volume; FFR = fractional flow reserve; LV = left ventricle; MVO = microvascular obstruction; PPCI = primary percutaneous coronary intervention; other abbreviations as in Table 1.

86%). A value of <42 mm Hg returns a sensitivity of 53% and specificity 100%.

CLINICAL CHARACTERISTICS OF PATIENTS WITH Pzf ≥42 mm Hg. Twenty of 34 patients had Pzf ≥42 mm Hg (Table 2). This group had significantly lower ST-segment resolution, lower QuBE score, features of adverse LV remodeling, and larger CMR myocardial infarction. In addition, there was more extensive transmural infarction and less recovery of IRA region function as assessed by wall motion. This translated to significantly lower 6-month EF. Importantly, there was also a significantly lower salvage index.

DISCUSSION

Our study has measured both thermodilution and Doppler-based parameters of microvascular function in the same cohort after STEMI and therefore allows an important direct comparison of the utility of these measures. We demonstrate that Pzf is the most sensitive invasive coronary physiology index currently available for the assessment of the microcirculation at the time of PPCI for predicting the final extent of global and regional irreversible myocardial injury and LV function at 6 months. It is significantly better than hMR and IMR. Pzf is also correlated to ECG characteristics, biochemical markers, and imaging parameters for final infarct size and myocardial salvage index.

There has been a longstanding interest in developing an understanding of the microcirculation after STEMI, and advances in technology have allowed measures to be developed for a number of important physiological parameters in the context of contemporary PPCI. Both coronary flow reserve (27,28) and IMR have been used to assess altered microcirculatory states. Recently, IMR has gained attention due to its perceived simpler methodology. A number of studies have confirmed that IMR measured at the time of PPCI is an important predictor of infarct size (5,6), and that using a categorical value of 40, allows identification of a group with adverse prognosis (7). However, specific indices derived from combined pressure/flow data of the IRA vessel may provide more detailed assessments of the microcirculation. In 2003, Shimada and colleagues (29) studied Pzf using a Doppler wire and assessing arterial pressure from the guiding catheter in patients undergoing PPCI for anterior STEMI, and showed that Pzf correlated with ^{18}F-fluorodeoxyglucose-positron emission tomography delineated myocardial viability. In 2007, Van Herck et al. (30) confirmed that Pzf values were

increased after myocardial infarction. More recently hMR, Pzf, and Doppler coronary flow reserve were derived using a combined pressure/flow wire in 27 patients after anterior STEMI (4). All measures correlated with peak creatinine kinase-myocardial band and CMR measures of infarct size, and Pzf was found to be higher in those with >75% infarct transmurality. However, CMR was performed early after infarction at only 13 days, and although LGE soon after infarction may predict final infarct size several weeks to months later, it is preferable to determine final infarct size and LV function after maturation of healing processes and remodeling (21,31,32).

Against this background of a series of studies interrogating combined pressure/flow data using different methods and different outcomes, our cohort was unselected on the basis of IRA and endpoints were selected to relate to later prognosis. We also used an automated algorithm for detection of the analysis period for calculation of Pzf. Importantly, this requires phasic signals of pressure and flow for its calculation, and cannot be calculated using thermodilution systems that estimate mean flow from transit time across the entire cardiac cycle. It is likely that the benefit of Pzf is the exclusion of the systolic portion from the calculation where resistance is recognized to be highly variable due to ongoing wave activity and the pressure-flow relations are nonlinear.

We analyzed how these invasive parameters predicted transmurality of infarction, ST-segment resolution and 6-month EF. In each case, Pzf outperformed hMR and IMR as demonstrated by the greater area under the ROC curve. In our study, the main endpoint was final infarct size ≥24% of LV mass on CMR. This value of infarct size has been shown to be predictive of short-term mortality (9) and therefore offers a clinically relevant cutoff to test physiological parameters. Additionally, it is the mean percentage of LV infarction in our cohort. Pzf again outperformed hMR and IMR in prediction of this percentage infarct size.

A value of 42 mm Hg for Pzf was the optimal cutoff for predicting ≥24% LV infarction. This categorical approach selected a group with no significant difference in the portion of left anterior descending coronary artery infarctions, but lower ST-segment resolution, larger troponin release, a larger area at risk, lower 6-month EF, and significantly lower myocardial salvage index. The latter observation is particularly relevant because it is clear that a larger area at risk is associated with larger final infarct size, but the salvage index adjusts for this. Our data show that Pzf can provide a measure at the time of PPCI, that relates to salvage.

STUDY LIMITATIONS. This was a small, single-center study, but it is the first study to directly examine and compare the relationship and effects of acute myocardial infarction on thermodilution *and* Doppler/pressure-derived indices following PPCI. The studied cohort may represent a selective group of PPCI patients, but patients with TIMI flow grade 0 were recruited, and the area at risk and APPROACH (Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease) score both confirmed that the IRA subtended substantial myocardium, suggesting that the study did not exclude those with large myocardial infarctions. The results presented in the preceding text are based on coronary pressure and Doppler measurements taken after PPCI, and maximal hyperemia may not be obtained. The use of a fully automated technique to measure Pzf is straightforward and independent of operator influences. However, these analysis techniques are not available for immediate results. As a consequence of the small sample size, there is potential for a type 1 error affecting the results. However, the consistency of the relationships and highly significant p values between Pzf and multiple important clinical outcome measures suggest that these findings are of clinical relevance. However, further investigation is justified in order to define the clinical utility of Pzf and improve our understanding of the microcirculation after STEMI.

CONCLUSIONS

Microvascular reperfusion is only present in <50% of patients, making it a potential therapeutic target. Our study has shown that Pzf is a more sensitive measure of microvascular function compared with IMR and hMR, and therefore, may offer a means to identify patients, at the time of PPCI, that would benefit from therapies directed at the microcirculation. Furthermore, this technique may allow objective measurement of response to such future therapies that may improve myocardial salvage and long-term LV function.

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PERSPECTIVES

WHAT IS KNOWN? Following primary percutaneous coronary intervention for STEMI more than one-half of patients have impaired microcirculatory flow, which is associated with larger infarction and poorer outcomes. Several invasive indices have been described to assess the microcirculation, and we compared these measures.

WHAT IS NEW? Our study demonstrates that Pzf is significantly better at predicting infarct size following PPCI than hyperemic microvascular resistance or the index of microcirculatory resistance. Assessment of microcirculatory function following PPCI using Pzf allows identification of patients with adverse myocardial recovery.

WHAT IS NEXT? Future investigations are needed to fully understand its clinical utility in relationship to longer term outcomes and as a technique to identify high risk patients who may benefit from alternative treatments.

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