Comparative Prognostic Utility of Indexes of Microvascular Function Alone or in Combination in Patients With an Acute ST-Segment–Elevation Myocardial Infarction

BACKGROUND: Primary percutaneous coronary intervention is frequently successful at restoring coronary artery blood flow in patients with acute ST-segment–elevation myocardial infarction; however, failed myocardial reperfusion commonly passes undetected in up to half of these patients. The index of microvascular resistance (IMR) is a novel invasive measure of coronary microvascular function. We aimed to investigate the pathological and prognostic significance of an IMR>40, alone or in combination with a coronary flow reserve (CFR≤2.0), in the culprit artery after emergency percutaneous coronary intervention for acute ST-segment–elevation myocardial infarction.

METHODS: Patients with acute ST-segment–elevation myocardial infarction were prospectively enrolled during emergency percutaneous coronary intervention and categorized according to IMR (≤40 or >40) and CFR (≤2.0 or >2.0). Cardiac magnetic resonance imaging was acquired 2 days and 6 months after myocardial infarction. All-cause death or first heart failure hospitalization was a prespecified outcome (median follow-up, 845 days).

RESULTS: IMR and CFR were measured in the culprit artery at the end of percutaneous coronary intervention in 283 patients with ST-segment–elevation myocardial infarction (mean±SD age, 60±12 years; 73% male). The median IMR and CFR were 25 (interquartile range, 15–48) and 1.6 (interquartile range, 1.1–2.1), respectively. An IMR>40 was a multivariable associate of myocardial hemorrhage (odds ratio, 2.10; 95% confidence interval, 1.03–4.27; P=0.042). An IMR>40 was closely associated with microvascular obstruction. Symptom-to-reperfusion time, TIMI (Thrombolysis in Myocardial Infarction) blush grade, and no (≤30%) ST-segment resolution were not associated with these pathologies. An IMR>40 was a multivariable associate of the changes in left ventricular ejection fraction (coefficient, −2.12; 95% confidence interval, −4.02 to −0.23; P=0.028) and left ventricular end-diastolic volume (coefficient, 7.85; 95% confidence interval, 0.41–15.29; P=0.039) at 6 months independently of infarct size. An IMR>40 (odds ratio, 4.36; 95% confidence interval, 2.10–9.06; P<0.001) was a multivariable associate of all-cause death or heart failure. Compared with an IMR>40, the combination of IMR>40 and CFR≤2.0 did not have incremental prognostic value.

CONCLUSIONS: An IMR>40 is a multivariable associate of left ventricular and clinical outcomes after ST-segment–elevation myocardial infarction independently of the infarction size. Compared with standard clinical measures of the efficacy of myocardial reperfusion, including the ischemic time, ST-segment elevation, angiographic blush grade, and CFR, IMR has superior clinical value for risk stratification and may be considered a reference test for failed myocardial reperfusion.

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Clinical Perspective

What Is New?

- The index of microvascular resistance (IMR) and coronary flow reserve were routinely measured in the culprit coronary artery of a reasonably large cohort of patients with acute ST-segment–elevation myocardial infarction treated by emergency percutaneous coronary intervention.
- Compared with ischemic time and angiographic and electrocardiographic measures of reperfusion, an IMR>40 was more consistently and strongly associated with microvascular pathology, changes in left ventricular function and volumes, and all-cause death and heart failure in the longer term.
- Compared with an IMR>40, the combination of IMR>40 and coronary flow reserve ≤2.0 did not have additional prognostic value.

What Are the Clinical Implications?

- Despite the routine success of primary percutaneous coronary intervention, failed myocardial reperfusion is common and usually passes undetected.
- IMR has emerging clinical utility as a routine test for the efficacy of myocardial reperfusion in invasively managed patients with acute ST-segment–elevation myocardial infarction.
- An IMR>40 represents a prognostically validated reference test for failed myocardial reperfusion at the end of primary percutaneous coronary intervention.
- Our results confirm previous investigations and support further research into IMR-based therapeutic strategies in patients with acute ST-segment–elevation myocardial infarction.

Despite the success of emergency percutaneous coronary intervention (PCI) in restoring coronary blood flow in patients with acute ST-segment–elevation myocardial infarction (STEMI), a failure of myocardial reperfusion, which manifests initially as microvascular obstruction and then subsequently as myocardial hemorrhage, affects approximately half of patients with acute STEMI.[1,2] Microvascular pathology (specifically, microvascular obstruction and myocardial hemorrhage) revealed by cardiac magnetic resonance (CMR) is prognostically important[3–5]; however, CMR is neither feasible acutely nor routinely recommended. Established tests for failed reperfusion such as the surface ECG, a test focused on ST-segment resolution and performed 60 to 90 minutes after reperfusion,[6] and the angiographic tissue myocardial perfusion grade[7,8] lack sensitivity and reproducibility in routine practice.[9] Failed myocardial reperfusion passes undetected in up to half of patients after acute STEMI.[3,4]

Invasive assessment of microcirculatory function at the end of emergency PCI before the patient is transferred to the ward presents an opportunity to identify STEMI patients with failed myocardial reperfusion with greater accuracy than the angiogram or the ECG. The index of microvascular resistance (IMR) is independently associated with left ventricular (LV) function[10] and infarct pathology,[11,12] and in a recent study, an IMR>40 was a multivariable associate of mortality after STEMI.[13] Coronary flow reserve (CFR) reflects epicardial and microvascular vasodilator capacity.[14] CFR is associated with composite cardiovascular outcomes, including revascularization, in patients with stable coronary disease[15] and after acute STEMI.[16] We have recently shown that IMR is more closely associated with severe microvascular pathology, LV remodeling, and health outcome than either the angiogram or CFR,[17] but whether the combination of IMR and CFR adds prognostic value is uncertain.

Different IMR cutoffs have been proposed,[10–13] but only an IMR>40 is associated with mortality.[13] The combination of an increased IMR and reduced CFR has been associated with enhanced detection of microvascular obstruction[18] and viability and prognosis.[16] However, in that study, only 10 major adverse cardiac and cerebrovascular events occurred, of which 5 were revascularizations. Changes in IMR and CFR within 24 hours after reperfusion have been associated with LV ejection fraction (LVEF).[19,20] However, prior studies are limited by sample size (n=27–45 subjects),[10,20–22] short follow-up (3–6 months),[10,18,20–22] lack of association with spontaneous hard outcomes,[16] and differences in cutoffs,[12,23] supporting the case for definitive research.

Building on prior literature, we hypothesized that in patients with an acute STEMI, an IMR>40 would be more closely associated with infarct pathology and clinical outcomes than established angiographic and ECG measures of myocardial reperfusion and that, compared with IMR alone, the combination of an IMR>40 and a CFR≤2.0 might be more closely associated with infarct pathologies and prognosis. We measured IMR and CFR simultaneously in the culprit coronary artery immediately after emergency PCI in a large, unselected population of patients with acute STEMI.

METHODS

Study Population and STEMI Management

We performed a prospective cohort study in a regional cardiac center between July 14, 2011, and November 22, 2012. Two hundred eighty-eight patients with STEMI were enrolled by 13 cardiologists. The patients provided written informed consent to undergo a diagnostic guidewire-based assessment after reperfusion and then CMR 2 days and 6 months later, as well as follow-up for health outcomes in the longer term.

Patients were eligible if they had an indication for primary PCI or thrombolysis for acute STEMI.[24,25] Exclusion criteria included standard contraindications to CMR, for example, a pacemaker. The study was approved by the National Research Ethics Service (reference 10-S0703-28). Acute STEMI management (Methods in the online-only Data Supplement) followed contemporary guidelines.[24,25] The ClinicalTrials.gov identifier is NCT02072850.

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Measurement of CFR and IMR in the Culprit Coronary Artery at the End of PCI

We adopted a thermodilution technique rather than Doppler because we wished to implement a method that is most transferable to routine clinical practice. In our experience, the Doppler measurements can be more time-consuming, require considerable experience, and may be less reproducible,[14] and the guidewire is typically more expensive.

A coronary pressure- and temperature-sensitive guide wire (St. Jude Medical, St. Paul, MN) was used to measure IMR and CFR in the culprit coronary artery at the end of primary or rescue PCI. The guidewire was calibrated outside the body, equalized with aortic pressure at the ostium of the guide catheter. and then advanced to the distal third of the culprit artery. This thermodilution method is based on the following basic relationship: flow=volume/mean transit time. CFR is defined as the ratio of peak hyperemic to resting flow (CFR=flow at hyperemia/flow at rest). Flow is the ratio of the volume (V) divided by the mean transit time (Tmn). Thus, CFR can be expressed as follows: CFR=(V/Tmn) at hyperemia/(V/Tmn) at rest. Assuming that the epicardial volume remains unchanged, CFR can be calculated as follows: CFR=Tmn at rest/Tmn at hyperemia. CFR and IMR are distinct physiological parameters. CFR reflects epicardial and microcirculatory function. In contrast, IMR is a direct invasive measure of microvascular resistance. IMR is defined as the distal coronary pressure multiplied by the mean transit time of a 3-mL bolus of saline at room temperature during maximal coronary hyperemia measured simultaneously (mm Hg·s or units).[10–12]

Hyperemia was induced by 140 $\mu g \cdot kg^{-1} \cdot min^{-1}$ of intravenous adenosine preceded by a 2-mL intracoronary bolus of 200 μg nitrate. The mean aortic and distal coronary pressures were recorded during maximal hyperemia. We have previously found IMR to be highly repeatable when assessed by duplicate measurements 5 minutes apart in 12 consecutive patients with STEMI at the end of PCI.[12]

On the basis of prior literature, we prespecified and examined an IMR>40 and the following classifications: (1) IMR≤40 and CFR>2.0, (2) IMR>40 and CFR>2.0, (3) IMR≤40 and CFR≤2.0, and (4) IMR>40 and CFR≤2.0.

CMR Imaging

We used CMR to provide reference data on LV function, pathology, and surrogate outcomes independently of the invasive tests (Figure 1). CMR was performed on a Siemens MAGNETOM Avanto (Erlangen, Germany) 1.5-T scanner with a 12-element phased-array cardiac surface coil.[26] The imaging protocol[5,27] (Methods in the online-only Data Supplement) included cine magnetic resonance imaging with steady-state free precession, T2 mapping,[28,29] T2* mapping, and delayed-enhancement phase-sensitive inversion-recovery pulse sequences.[30] The scan acquisitions were spatially coregistered and included different slice orientations to enhance diagnostic confidence.

Imaging Analyses

The CMR analyses are described in detail in Methods in the online-only Data Supplement.

Infarct Definition and Size

The presence of acute infarction was established on the basis of abnormalities in cine wall motion, rest first-pass myocardial perfusion, and delayed-enhancement imaging in 2 imaging planes. The myocardial mass of late gadolinium (grams) was quantified with computer-assisted planimetry, and the territory of infarction was delineated with the use of a signal intensity threshold of >5 SD above a remote reference region and expressed as a percentage of total LV mass.[31]

Microvascular Obstruction

Microvascular obstruction was defined as a dark zone on early gadolinium enhancement imaging 1, 3, 5, and 7 minutes after contrast injection that remained present within an area of late gadolinium enhancement at 15 minutes.

Myocardial Edema

The extent of myocardial edema was defined as LV myocardium with pixel values (T2) >2 SD from remote myocardium.[28,29,32–35]

Myocardial Salvage

Myocardial salvage was calculated by subtracting the percent infarct size from percent area at risk, as reflected by the extent of edema.[12,32,35] The myocardial salvage index was calculated by dividing the myocardial salvage area by the initial area at risk.

LV Remodeling

An increase in LV volume at 6 months from baseline was taken to reflect LV remodeling.[27,35,36] Adverse remodeling was defined as an increase in LV end-diastolic volume (LVEDV) ≥20% at 6 months from baseline.[27]

Myocardial Hemorrhage

On the T2* CMR maps, a region of reduced signal intensity within the infarcted area with a T2* value of <20 milliseconds[4,37–40] was considered to confirm the presence of myocardial hemorrhage.

Electrocardiography

A 12-lead ECG was obtained before coronary reperfusion and 60 minutes afterward. The extent of ST-segment resolution on the ECG assessed 60 minutes after reperfusion compared with the baseline ECG before reperfusion[41] was expressed as complete (≥70%), incomplete (30%–<70%), or none (≤30%).

Coronary Angiogram Acquisition and Analyses

Coronary angiograms were acquired during usual care with cardiac catheter laboratory x-ray (Innova, GE Healthcare) and information technology equipment (Centricity, GE Healthcare). The angiograms were analyzed by trained observers (J.C., V.T.Y.M) who were blinded to all other clinical and MRI data. The TIMI (Thrombolysis in Myocardial Infarction) coronary flow grade[42] and frame count[43] were assessed at initial angiography and at the end of the procedure. TIMI myocardial perfusion grade[44] was assessed at the end of the procedure (Methods in the online-only Data Supplement).

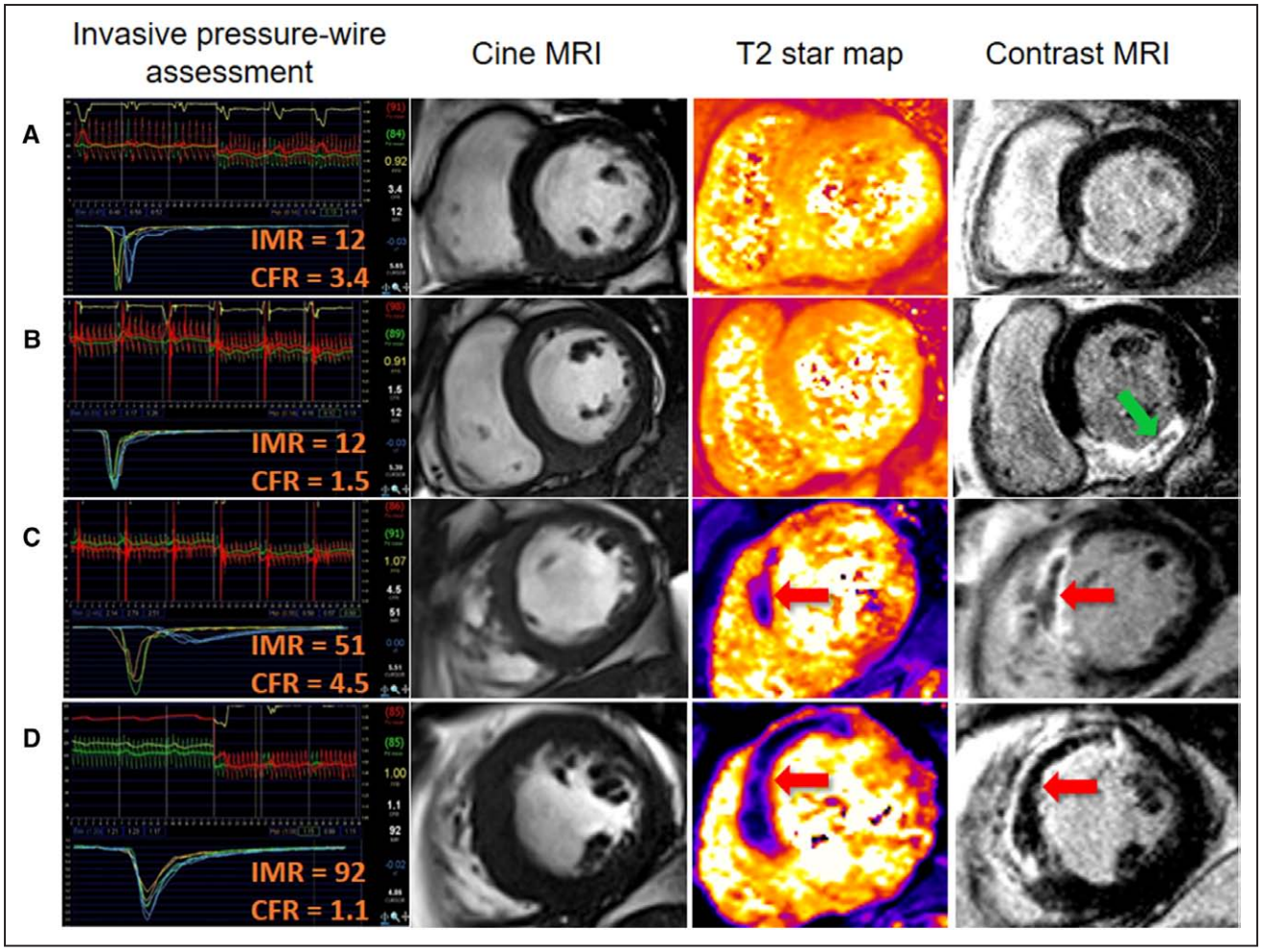

Figure 1. Four patients with acute ST-segment–elevation myocardial infarction treated by primary percutaneous coronary intervention (PCI).
Each patient had index of microvascular resistance (IMR) and coronary flow reserve (CFR) measured in the culprit coronary artery at the end of the procedure. The patients reflect the following categories: IMR≤40 and CFR>2.0; IMR≤40 and CFR≤2.0; IMR>40 and CFR>2.0; and IMR>40 and CFR≤2.0. The patients were treated with similar antithrombotic therapy, including aspirin, clopidogrel, heparin, and intravenous glycoprotein IIb/IIIa inhibitor therapy with tirofiban. Each patient had normal TIMI (Thrombolysis in Myocardial Infarction) grade 3 flow at the end of PCI. Cardiac magnetic resonance imaging (MRI) was performed for each patient 2 days later. **A**, A patient with a normal IMR and a normal CFR. Invasive assessment of microvascular function in the culprit coronary artery at the end of primary PCI indicated that microcirculatory function was preserved. Cardiac magnetic resonance (CMR) subsequently revealed nontransmural late gadolinium enhancement consistent with salvaged myocardium. There was no evidence of myocardial hemorrhage (**middle right**) or microvascular obstruction (**right**). **B**, A patient with a normal IMR and a low CFR. Late gadolinium contrast CMR revealed transmural inferior myocardial infarction with a small central zone of hypointense microvascular obstruction (**arrow**, **right**). T2*-CMR excluded myocardial hemorrhage within the infarct core (**middle right**). **C**, A patient with a high IMR and a normal CFR. Late gadolinium contrast-enhanced CMR revealed transmural anteroseptal myocardial infarction complicated by microvascular obstruction (**arrow, right**). T2*-CMR (**arrow, middle right**) revealed myocardial hemorrhage within the infarct core, and microvascular obstruction spatially corresponded with the myocardial hemorrhage. **D**, A patient with a high IMR and a low CFR. Invasive guidewire-based physiological testing at the end of primary PCI revealed severe microvascular dysfunction. Transmural myocardial infarction and microvascular obstruction are present, in association with abundant myocardial hemorrhage (**arrow**, **middle right**).

Laboratory Analyses

The acquisition of blood samples for biochemical and hematologic analyses is described in Methods in the online-only Data Supplement.

Prespecified Health Outcomes

We prespecified adverse health outcomes that are pathophysiologically linked with STEMI.[45,46] The primary composite outcome was all-cause death or first heart failure event after

the initial hospitalization (Methods in the online-only Data Supplement).

Statistical Analyses

The sample size calculation and statistical methods are described in the Methods in the online-only Data Supplement. Random-effects models were used to compute interrater and intrarater reliability measures (intraclass correlation coefficient) for the reliability of angiographic measures of myocardial reperfusion measured independently by 2 observers in 20 randomly selected patients from the cohort (Results in the online-only Data Supplement). All *P* values are 2-sided, and value of *P* >0.05 indicates the absence of a statistically significant effect. Statistical analyses were performed with R version 2.15.1, SAS version 9.3, or higher versions of these programs.

RESULTS

Patient Characteristics and IMR and CFR Measured Acutely in the Culprit Coronary Artery After Reperfusion

A total of 283 patients with STEMI had IMR and CFR measured in the culprit coronary artery at the end of emergency PCI (Table 1 and Figure 2). The median IMR and CFR were 25 (interquartile range, 15–48) and 1.6 (interquartile range, 1.1–2.1), respectively. A CFR≤2.0, an IMR>40, or both occurred in 210 (74%), 79 (28%) (Table 1), and 65 (23%) patients, respectively (Table I in the online-only Data Supplement).

CMR Findings

CMR imaging occurred 2.1±1.8 days later, and 264 patients (93%) had follow-up CMR at 6 months (Table 2 and Figure 2). Case examples are shown in Figure 1. Myocardial hemorrhage and microvascular obstruction occurred in 89 (42%) and 114 (54%) patients, respectively. An IMR>40 (Table 2) and the combination of an IMR>40 and a CFR≤2.0 (Table II in the online-only Data Supplement) were associated with LVEF and infarct pathology 2 days after MI and LVEF at 6 months.

Multivariable Associations for an IMR>40 With Microvascular Infarct Pathology Revealed by CMR

Myocardial Hemorrhage

In a binary logistic regression model with baseline characteristics, an IMR>40 was a multivariable associate of myocardial hemorrhage (odds ratio [OR], 2.86; 95% confidence interval [CI], 1.52–5.39; *P*=0.001; Table 3), whereas symptom-to-reperfusion time, TIMI blush grade, and no ST-segment resolution were not.

Microvascular Obstruction

An IMR>40 was a multivariable associate of microvascular obstruction (OR, 2.82; 95% CI, 1.62–4.93; *P*<0.001; Table III in the online-only Data Supplement). Symptom-to-reperfusion time, TIMI blush grade, and no ST-segment resolution were not multivariable associates of microvascular obstruction.

Microvascular Infarct Pathologies and Invasive Microvascular Parameters in Combination

The combination of IMR>40 and CFR≤2.0 was a multivariable associate with microvascular obstruction (OR, 2.28; 95% CI, 1.16–4.46; *P*=0.016) but not with myocardial hemorrhage (*P*=0.104).

Compared with IMR>40 and CFR≤2.0 (reference group), the group with the combination of IMR≤40 and CFR≤2.0 was associated with a reduced odds of microvascular obstruction (OR, 0.19; 95% CI, 0.05–0.76; *P*=0.019) and myocardial hemorrhage (OR, 0.17; 95% CI, 0.03–0.92; *P*=0.040).

Microvascular Dysfunction and Subsequent LV Outcomes

Changes in LVEDV

An IMR>40 was a univariable (regression coefficient, 11.43; 95% CI, 4.07–18.79; *P*=0.002) and a multivariable (regression coefficient, 7.85; 95% CI, 0.41–15.29; *P*=0.039) associate of the changes in LVEDV, including after adjustment for infarct size (n=264; Table 4).

Changes in LVEF

An IMR>40 was a univariable (regression coefficient, −2.89; 95% CI, −4.89 to −0.91; *P*=0.004, with adjustment for baseline LVEF) and a multivariable (regression coefficient, −2.12; 95% CI, −4.02 to −0.23; *P*=0.028) associate of the changes in LVEF at 6 months from baseline, including after adjustment for infarct size, as reflected by troponin or contrast-enhanced MRI (n=264; Table IV in the online-only Data Supplement).

LV Outcomes and the Combination of IMR>40 and CFR≤2.0

Results for the multivariable models for IMR>40 combined with CFR≤2.0 were not improved compared with the model with IMR>40 (Tables IV and V in the online-only Data Supplement, footnote).

Microvascular Dysfunction and Longer-Term Health Outcomes

All of the patients (n=283) had completed long-term follow-up data. The median duration of follow-up was of 845 days (range of postdischarge censor duration, 598–1098 days). Thirty patients (11%) died or experienced a first heart failure event during the index hospitalization or after discharge. These events included 5 cardiovascular

ORIGINAL RESEARCH ARTICLE

Table 1. Clinical and Angiographic Characteristics of 283 Patients With STEMI Categorized According to an IMR≤40 or >40 Measured in the Culprit Coronary Artery at the End of PCI

Characteristics*	All Patients (n=283)	IMR≤40 (n=204, 72%)	IMR>40 (n=79, 28%)	*P* Value
Age, y	60 (12)	59 (11)	62 (12)	0.093 (*t*)
Male sex, n (%)	206 (73)	147 (72)	59 (75)	0.766
BMI, kg/m^2	29 (5)	29 (5)	28 (5)	0.009 (*t*)
Medical history, n (%)				
Hypertension	91 (32)	60 (29)	31 (39)	0.120
Current smoking	175 (62)	130 (64)	45 (57)	0.340
Hypercholesterolemia	78 (28)	55 (27)	23 (29)	0.767
Diabetes mellitus†	30 (11)	21 (10)	9 (11)	0.830
Previous angina	32 (11)	22 (11)	10 (13)	0.678
Previous MI	20 (7)	15 (7)	5 (6)	1.000
Previous PCI	14 (5)	9 (4)	5 (6)	0.544
Presenting characteristics				
Heart rate, bpm	78 (17)	78 (17)	78 (16)	0.800 (*t*)
Systolic blood pressure, mm Hg	136 (24)	135 (25)	136 (24)	0.797 (*t*)
Diastolic blood pressure, mm Hg	79 (14)	79 (14)	80 (13)	0.358 (*t*)
Time from symptom onset to reperfusion, min	174 (120–316)	171 (119–300)	179 (129–364)	0.208 (MW)
Ventricular fibrillation,‡ n (%)	19 (7)	11 (5)	8 (10)	0.185
Heart failure, Killip class at presentation, n (%)	201 (71)	158 (80)	43 (54)	
I				
II	62 (22%)	40 (20)	22 (28)	<0.001
III/IV	20 (7)	6 (3)	14 (18)	
ECG				
ST-segment elevation resolution after PCI, n (%)				
Complete, ≥70%	128 (45)	23 (11)	17 (22)	
Incomplete, 30%–<70%	114 (40)	79 (39)	35 (44)	0.022
None, ≤30%	40 (14)	23 (11)	27 (34)	
Reperfusion strategy, n (%)				
Primary PCI	262 (93)	189 (93)	73 (92)	
Rescue PCI (failed thrombolysis)	14 (5)	10 (5)	4 (5)	1.000
Successful thrombolysis	7 (2)	5 (3)	2 (3)	
Coronary angiography				
No. of diseased arteries,§ n (%)				
1	158 (56)	112 (55)	46 (58)	
2	83 (29)	61 (30)	22 (28)	0.973
3	37 (13)	27 (13)	10 (13)	
Culprit artery, n (%)				
LM	5 (2)	4 (2)	1 (1)	
LAD	107 (38)	72 (35)	35 (44)	
LCx	51 (18)	39 (19)	12 (15)	0.371
RCA	125 (44)	93 (46)	32 (40)	

(*Continued*)

Table 1. Continued

Characteristics*	All Patients (n=283)	IMR≤40 (n=204, 72%)	IMR>40 (n=79, 28%)	*P* Value
TIMI coronary flow grade before PCI, n (%)				
0/1	204 (72)	141 (69)	63 (80)	
2/3	79 (28)	63 (31)	16 (20)	0.078
TIMI coronary flow grade after PCI, n (%)				
0/1	2 (1)	1 (1)	1 (1)	
2/3	281 (99)	203 (99)	78 (99)	0.481
TIMI frame count before PCI	29.4 (18.0–44.0)	28.0 (18.0–42.4)	35.9 (25.0–52.5)	0.129 (MW)
TIMI frame count after PCI	15.3 (10.0–24.7)	16.9 (8.2–22.6)	20.0 (14.6–29.1)	<0.001 (MW)
TIMI blush grade after PCI				
0/1	71 (26)	43 (22)	28 (38)	0.013
2/3	198 (74)	152 (78)	46 (62)	
Culprit lesion, residual stenosis, %	12.4 (5.5)	12.3 (5.6)	12.5 (5.4)	0.807 (*t*)
CFR	1.6 (1.1–2.1)	1.6 (1.2–2.2)	1.4 (1.0–1.8)	<0.001
IMR	25 (15–44)	18 (13–26)	56 (48–80)	<0.001
Fractional flow reserve	0.90 (0.10)	0.90 (0.09)	0.94 (0.06)	0.006
Resistive reserve ratio	1.8 (1.4–2.5)	1.9 (1.5–2.6)	1.8 (1.3–2.4)	0.093
Treatment in the catheter laboratory, n (%)				
Aspiration thrombectomy	203 (72)	143 (70)	60 (76)	0.379
Glycoprotein IIb/IIIa inhibitor	259 (92)	185 (91)	74 (94)	0.485
Medical therapy, n (%)				
ACE-I or ARB	279 (99)	200 (98)	79 (100)	0.579
β-Blocker	269 (95)	196 (96)	73 (92)	0.225
Initial blood results on admission				
C-reactive protein, mg/L	4 (2–7)	4 (2–7)	4 (2–7)	0.971 (MW)
Leukocyte cell count, $\times 10^9$ L	12.4 (3.6)	12.3 (3.4)	12.5 (4.0)	0.743 (*t*)
Platelet count, $\times 10^6$ L	246 (67)	249 (69)	238 (61)	0.193 (*t*)
Troponin T, ng/L	1566 (93–4411)	1500 (90–3911)	1967 (106–6465)	0.070 (MW)

ACE-I indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CFR, coronary flow reserve; IMR, index of microvascular resistance; LAD, left anterior descending coronary artery; LCx, left circumflex coronary artery; LM, left main coronary artery; MI, myocardial infarction; MW, Mann-Whitney; PCI, percutaneous coronary intervention; RCA, right coronary artery; STEMI, ST-segment–elevation myocardial infarction; and TIMI, Thrombolysis in Myocardial Infarction. Killip classification of heart failure after acute myocardial infarction: class I, no heart failure; class II, pulmonary rales or crepitations, a third heart sound, and elevated jugular venous pressure; class III, acute pulmonary edema; and class IV, cardiogenic shock.

*Data are reported as mean (SD), median (IQR), or n (%) as appropriate. *P* values have been obtained from a *t* test, MW test, or Fisher test. TIMI flow grades before and after PCI were grouped as 0/1 versus 2/3 for this analysis.

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

‡Successfully electrically cardioverted ventricular fibrillation at presentation or during emergency PCI procedure.

§Multivessel coronary artery disease was defined according to the number of stenoses of at least 50% of the reference vessel diameter by visual assessment and whether there was LM stem involvement.

deaths, 3 noncardiovascular deaths, and 22 episodes of heart failure (Killip class 3 or 4 heart failure [n=20] or defibrillator implantation [n=2]). Ten patients (3.5%) died or experienced a first heart failure hospitalization after discharge (Table V in the online-only Data Supplement).

IMR was a univariable associate of all-cause death or heart failure, whereas CFR was not (Table 5). Because of the number of events observed, 2 multivariable models were considered: 1 model with hypertension and smoking as covariates and 1 model with ST-segment resolution (none) and TIMI frame count (Table 5). In the model with smoking and hypertension, an IMR>40 (OR, 4.70; 95% CI, 2.10–10.53; *P*<0.001) was a multivariable associate of all-cause death or heart failure. In the model

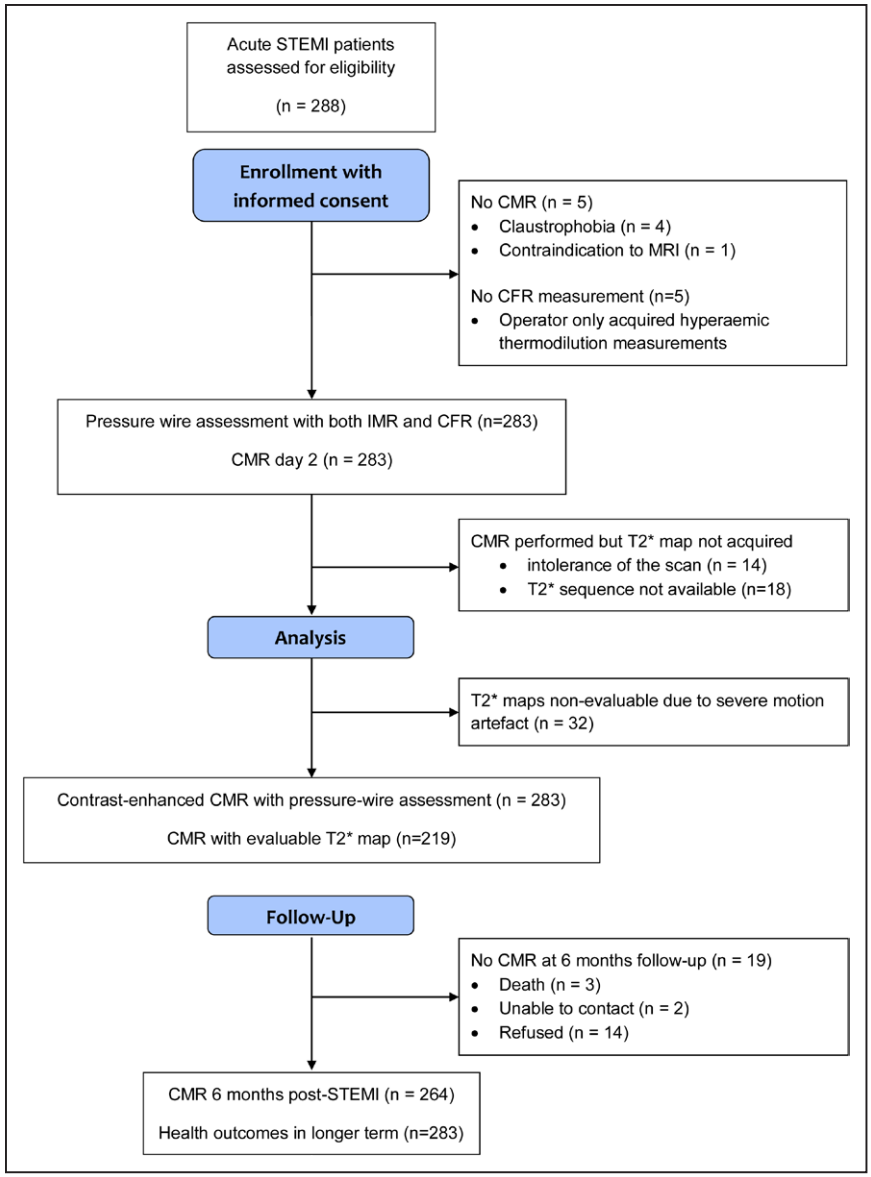

Figure 2. CONSORT (*Consolidated* Standards of Reporting Trials) flow diagram of the cohort study.
CFR indicates coronary flow reserve; CMR, cardiac magnetic resonance; IMR, index of microvascular resistance; and STEMI, ST-segment–elevation myocardial infarction.

with ST-segment resolution (none) and TIMI frame count, an IMR>40 was also a multivariable associate with this outcome (OR, 4.42; 95% CI, 1.93–10.10; $P<0.001$). The combination of IMR>40 and CFR≤2.0 did not enhance the magnitude of the prognostic significance of IMR>40 (Table 5).

Fractional Flow Reserve and the Ratio of CFR to Fractional Flow Reserve

Fractional flow reserve measured in the culprit coronary artery was not associated with myocardial hemorrhage status ($P=0.262$), nor was it associated with LVEDV or LVEF at baseline or at follow-up. Fractional flow reserve was not associated with health outcomes. Similar results were observed for the ratio of CFR to fractional flow reserve, which reflects true CFR (Results in the online-only Data Supplement).

DISCUSSION

We have undertaken the largest prospective study of invasive tests of microvascular function, infarct pathology revealed by serial CMR, and spontaneous adverse health outcomes in patients with acute STEMI.

The main findings are the following: (1) Microvascular dysfunction at the end of emergency PCI, as classified by an IMR>40 (without CFR), was more consistently associated with infarct pathology and prognosis than symptom-to-reperfusion time or angiographic and ECG measures of reperfusion; (2) an IMR>40 was more closely associated with myocardial hemorrhage and microvascular obstruction than the combination of an IMR>40 and CFR≤2.0; (3) an IMR>40 was a multivariable associate of the changes in LVEF and LVEDV independently of infarct size; and (4) an IMR>40 identifies patients who have a 4-fold increase in all-cause death

Table 2. CMR Findings at 2 Days and 6 Months After Reperfusion in 283 Patients With STEMI Categorized According to an IMR ≤40 or >40 in the Territory of the Culprit Artery at the End of Emergency PCI

Characteristics*	All Patients (n=283)	IMR≤40 (n=145, 51%)	IMR>40 (n=65, 23%)	*P* Value
CMR findings 2 d after MI				
LVEF, %	55 (10)	56 (9)	51 (10)	<0.001 (*t*)
LVEDV, mL				
Men	160 (32)	158 (32)	165 (34)	0.190 (*t*)
Women	124 (25)	126 (23)	120 (29)	0.418 (*t*)
LV end-systolic volume, mL				
Men	75 (26)	72 (24)	82 (30)	0.020 (MW)
Women	55 (18)	53 (18)	60 (17)	0.130 (MW)
LV mass, g				
Men	141 (123 to 160)	141 (123 to 161)	142 (127 to 152)	0.858 (MW)
Women	95 (85 to 105)	97 (87 to106)	88 (76 to 104)	0.211 (MW)
Edema and infarct characteristics				
Myocardial edema, % LV mass	32 (12)	30 (11)	37 (13)	<0.001 (*t*)
Infarct size, % LV mass	16 (7 to 27)	14 (4 to 24)	24 (11 to 34)	<0.001 (*t*)
Myocardial salvage index, % of LV mass	61 (44 to 85)	68 (50 to 87)	49 (39 to 72)	<0.001 (*t*)
Late microvascular obstruction, n (%)	142 (50)	88 (43)	54 (68)	<0.001
Late microvascular obstruction, % LV mass	0.1 (0.0 to 3.5)	0.0 (0.0 to 2.4)	2.1 (0.0 to 8.4)	<0.001 (*t*)
Myocardial hemorrhage, n (%)	89 (42)	51 (34)	38 (58)	0.0l
CMR findings 6 mo after MI (n=267)				
LVEF at 6 mo, %	62 (9)	64 (8)	58 (11)	<0.001 (*t*)
LV end-systolic volume at 6 mo, mL				
Men	61 (42 to 79)	60 (42, 72)	72 (52, 97)	0.004 (MW)
Women	41 (33 to 56)	39 (32, 53)	48 (42, 59)	0.060 (MW)
Change in LVEDV at 6 mo from baseline, mL				
Men	6 (–8 to 21)	4 (–8 to 16)	13 (–2 to 33)	0.024 (MW)
Women	1 (–11 to 10)	0 (–11 to 7)	3 (–13 to 19)	0.524 (MW)

CMR indicates cardiac magnetic resonance; IMR, index of microvascular resistance; LV; left ventricular; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; MI, myocardial infarction; MW, Mann-Whitney; and T1, myocardial longitudinal relaxation time. Area at risk was measured with T2 mapping. Data are given as n (%) or mean (SD). *P* values were obtained from a *t* test, Mann-Whitney test, or a Fisher test.

*Data are reported as mean (SD), median (IQR), or n (%) as appropriate. LVEF was missing in 24 subjects at follow-up. LVEDV at follow-up was missing in 16 men and 8 women.

or heart failure, whereas CFR (or true CFR) alone was not associated with this outcome and the combination of IMR and CFR had no incremental prognostic value. These results refute our hypothesis that the combination of IMR with CFR would have superior prognostic value.

Implications for Patient Management

Using IMR in patients with acute STEMI, the cardiologist can focus risk stratification with a simple index that has a single cutoff (IMR>40). This test of microvascular dysfunction provides incremental prognostic information over and above infarct size at an early time point before infarct size is disclosed by measurement of troponin or MRI. This result enhances the clinical relevance of measuring IMR in patients with acute STEMI. CFR, either alone or in combination with IMR, is not needed, and a more complicated combined approach with both measures is not necessary.

Our study adds to the literature on the invasive assessments of the efficacy of myocardial reperfusion in patients with acute STEMI.[11–13,20–22,47] Fearon et al[13] established that an IMR>40 was independently associated with all-cause mortality and heart failure; however, information on LV function and infarct pathology was not described, and the IMR threshold of 40 lacks validation against infarct pathology and LV outcomes. Our

Table 3. Multivariable Associations Between Clinical Characteristics, IMR>40 at the End of Emergency PCI, and the Occurrence of Myocardial Hemorrhage 2 Days Later (n=200) in Patients With Acute STEMI

Binary Logistic Regression	OR (95% CI)	*P* Value
IMR>40	2.86 (1.52–5.39)	0.001
Male sex	2.75 (1.32–5.72)	0.007
Smoker	2.08 (1.11–3.90)	0.023
Hypertension	1.98 (1.04–3.74)	0.037
Harrell C statistic	0.684	

CI indicates confidence interval; IMR, index of microvascular resistance; and OR, odds ratio. Manual backward selection was used with a *P* value threshold of 0.10 for inclusion. Previous percutaneous coronary intervention was excluded because numeric instability. The multivariable association for IMR>40 and coronary flow reserve ≤2.0 with myocardial hemorrhage was 2.51 (95% CI, 1.28–4.91; *P*=0.007; Harrell C statistic=0.671).

study includes new information with serial CMR. We have shown that an IMR>40 is independently associated with infarct pathology, changes in LV function and volume, and all-cause-death or heart failure. On the other hand, the prognostic significance of CFR was less than that of IMR, and CFR was not additive to IMR. CFR has greater hemodynamic dependence; it is subject to variations in resting flow, is not specific for the microvasculature, and has a narrower range of values.[14,48]

CFR reflects the functional (vasodilator) capacity of the coronary artery circulation,[48] whereas IMR reflects microvascular resistance. Park et al[16] undertook a prognostic study of IMR and CFR in 89 patients with acute STEMI. They found that the combination of an increased IMR and reduced CFR was associated with changes in LV wall motion score index at 3 months as revealed by echocardiography and major adverse cardiac and cerebrovascular events. The results of this study lend support to the theory that the combination of IMR and CFR might have additive prognostic value compared with either index alone. Compared with the study by Park et al,[16] our study included a population that was 3 times larger, advanced cardiac imaging with MRI, independent analysis of spontaneous adverse cardiac events, and a composite outcome that did not include revascularization. Furthermore, another small study (n=40)[18] in patients with acute STEMI showed that the combination of high IMR and low CFR enhanced the predictive accuracy of detecting microvascular obstruction compared with either index alone. The results from our study refute those of Park et al[16] and Ahn et al[18] and indicate that an IMR>40 is sufficient for prognostication.

In the acute clinical setting, failed myocardial reperfusion, as reflected by microvascular obstruction and myocardial hemorrhage, occurs in about half of all patients with STEMI and commonly passes undetected acutely. Microvascular obstruction is potentially reversible,[4] but without successful myocardial reperfusion, severe vascular damage progresses to irreversible myocardial hemorrhage in 40% of all patients.[3–5] When CMR is performed days later, it is too late for early intervention to prevent or treat severe microvascular damage, and CMR has limited availability in routine practice.

An IMR>40 was consistently associated with infarct pathology, changes in LV function and volumes independently of infarct size, and all-cause death or

Table 4. Multivariable Associations Between an IMR>40 and Changes in LVEDV at 6 Months From Baseline (n=264)

Linear Regression	Coefficient (95% CI)	*P* Value
Baseline LVEDV	−0.23 (−0.35 to −0.12)	<0.001
Infarct size	1.03 (0.75 to 1.30)	<0.001
BMI	1.16 (0.41 to 1.90)	0.003
Hypercholesterolemia	−10.55 (−18.13 to −2.97)	0.007
Male sex	11.27 (3.05 to 19.49)	0.007
IMR>40	7.85 (0.41 to 15.29)	0.039
Diabetes mellitus	−10.15 (−20.24 to −0.06)	0.049
TIMI blush grade 2/3 after PCI	−6.06 (−13.21 to 1.08)	0.096
Hypertension	5.13 (−1.99 to 12.25)	0.157
TIMI frame count after PCI	−0.16 (−0.42 to 0.11)	0.241
Heart rate	−0.10 (−0.30 to 0.09)	0.298
Previous PCI	−8.63 (−25.80 to 8.55)	0.323
Age	−0.14 (−0.47 to 0.19)	0.410
Smoker	3.00 (−4.22 to 10.23)	0.413
Culprit lesion, percentage residual stenosis	0.09 (−0.51 to 0.70)	0.758
Symptom-to-reperfusion time per 10 min	0.01 (−0.13 to 0.15)	0.894
Previous MI	−0.48 (−16.18 to 15.21)	0.952
Previous angina	−0.23 (−10.56 to 10.09)	0.965
SBP per 10 mm Hg	−0.01 (−1.35 to 1.32)	0.984
Bayesian information criterion	2137	

BMI indicates body mass index; CI, confidence interval; IMR, index of microvascular resistance; LVEDV, left ventricular end-diastolic volume; MI, myocardial infarction; PCI, percutaneous coronary intervention; SBP, systolic blood pressure; and TIMI, Thrombolysis in Myocardial Infarction. A combination of IMR>40 and CFR≤2.0 was not a multivariable associate of the change in LVEDV at 6 months from baseline when infarct size (percent LV mass) was included in the model (*P*=0.059). In a model that included peak troponin (μg/L), the multivariable association for IMR>40 and CFR≤2.0 with the change in LVEDV at 6 months from baseline was 10.68 (95% CI, 2.23–19.12; *P*=0.014; Bayesian information criterion=2080). According to the Bayesian information criteria, there was no improvement in the model that included IMR>40 and CFR≤2.0.

Table 5. Relationships Between IMR and CFR and All-Cause Death or First Hospitalization for Heart Failure During or After the Index Hospitalization Obtained With Logistic Regression

Associations	OR (95% CI)	*P* Value
Univariable associations		
IMR>40	4.36 (2.10–9.06)	<0.001
IMR (for a 5-unit change)	1.08 (1.05–1.12)	<0.001
IMR>median	2.16 (1.01–4.61)	0.047
CFR≤2.0, IMR>40	4.37 (2.13–8.97)	<0.001
CFR≤median, IMR>median	2.96 (1.24–7.08)	0.015
CFR (for a 0.2-unit change)	0.92 (0.82–1.02)	0.124
CFR≤median	1.74 (0.81–3.72)	0.153
CFR≤2.0	1.17 (0.50–2.72)	0.721
Multivariable associations		
Model A (n=283)		
IMR>40	4.70 (2.10–10.53)	<0.001
Cigarette smoker	2.49 (1.01–6.14)	0.048
Hypertension	2.84 (1.26–6.42)	0.012
IMR>40, CFR ≤2.0	5.01 (2.22–11.33)	<0.001
Cigarette smoker	2.69 (1.08–6.69)	0.033
Hypertension	2.84 (1.26–6.42)	0.12
Model B (n=282)		
IMR >40	4.42 (1.93–10.10)	<0.001
No ST-segment resolution	2.49 (1.01–6.15)	0.049
TIMI frame count after PCI	1.00 (0.97–1.03)	0.823
IMR>40, CFR≤2.0	4.46 (1.96–10.15)	<0.001
No ST-segment resolution	2.58 (1.04–6.38)	0.041
TIMI frame count after PCI	1.00 (0.97–1.03)	0.866

CFR indicates coronary flow reserve; CI, confidence interval; IMR, index of microvascular resistance; OR, odds ratio; PCI, percutaneous coronary intervention; and TIMI, Thrombolysis in Myocardial Infarction. The median duration of follow-up was 845 days (postdischarge censor duration range, 598–1098 days). Thirty patients (10.4%) died or experienced an index heart failure event.

heart failure compared with other standard measures of reperfusion injury, including TIMI frame count, TIMI myocardial perfusion grade, and ST-segment resolution.[24,49] In our population, a minority of patients (14%) had no evidence of ST-segment resolution 60 minutes after reperfusion, yet microvascular obstruction and myocardial hemorrhage occurred in 50% and 42% of patients, respectively. TIMI myocardial perfusion grade was not associated with clinical outcomes (Table 5) and is difficult to reliably measure in clinical practice. Reliable measurement of failed reperfusion at the end of the PCI procedure is therefore a difficult clinical conundrum, not least because coronary reperfusion is successfully achieved in the majority of all patients.

Our results have important clinical implications. Failed myocardial reperfusion in patients with acute STEMI is common, is associated with adverse outcome, and often goes unnoticed, largely because current assessment methods lack sensitivity and routine CMR, usually performed days after the acute event, is often not practical or cost-efficient. Immediate detection of failed myocardial reperfusion becomes feasible with IMR, is safe,[50] and allows direct stratification of the highest-risk patients at the time of emergency reperfusion, when early therapeutic interventions may yield the greatest clinical benefit. Conversely, the possibility remains that an IMR>40 may represent an unmodifiable marker of elevated risk.

Implications for Therapy and Clinical Trials

Further research is warranted to investigate preventive or therapeutic interventions in patients stratified by IMR to assess whether IMR-guided strategies might improve prognosis compared with standard care.

Our results provide evidence both for and against IMR as identifying modifiable risk (hence a target for treatment) as opposed to being only an unmodifiable marker of elevated risk (and hence not a target for treatment). The modifiable associations include myocardial salvage index, microvascular obstruction, and myocardial hemorrhage (all of which are linked to the pathophysiology of LV remodeling), and nonmodifiable associations (eg, body mass index, Killip class at presentation, area at risk [myocardial edema] which are essentially markers for increased myocardial mass at risk). Although IMR might offer an opportunity to guide therapy, it may mostly reflect a larger area at risk and thus be unmodifiable. Only an outcomes-based, randomized, controlled trial will decide the issue.

There is some evidence that IMR is responsive to the effects of treatments known to have favorable cardiovascular effects, including vasodilators[51] and anti-ischemic[52] therapies. During PCI, compared with a direct stenting approach without initial balloon angioplasty, a predilatation step to disrupt and modify the plaque before stenting is associated with a higher IMR at the end of the PCI procedure.[53] In the setting of acute STEMI, a randomized trial of initial antiplatelet therapy in 76 patients undergoing primary PCI disclosed that, compared with an oral loading dose of 600 mg clopidogrel, an oral loading dose of 180 mg ticagrelor was associated with a lower IMR at the end of the procedure (22.2±18.0 versus 34.4±18.8 U; *P*=0.005).[54] In other randomized, controlled trials in acute MI, IMR is being used to assess the comparative efficacy of antiplatelet therapies[55] (NCT0273334), vasodilator therapy,[56] and low-dose intracoronary thrombolysis (T-TIME [A Trial of Low-Dose Adjunctive alteplase During Primary PCI]; NCT02257294).

Sample Size Calculation and Clinical Trials

In addition to the study design, estimated treatment effect, and power, the key factor that will influence the sample size in a clinical trial in which IMR is used as measure of treatment effect is the variance in IMR for the population studied. T-TIME is a randomized, placebo-controlled trial of 2 reduced doses of alteplase (10 and 20 mg) administered directly into the culprit coronary artery after reperfusion but before stent implantation. In that trial, we have estimated that if the median IMR is 33.9 (SD, 25.2) and the IMR values are 27.2 and 20.5 in the 10- and 20-mg dose groups, respectively, then 80 subjects per group would be needed. This calculation is based on an average difference in IMR between treatment and placebo of 10, assuming that there is a linear trend with dose. If the average difference in IMR between treatment and placebo is 13, then 48 subjects per group would be needed.

Limitations

We performed a single-center, natural-history study. The median IMR in our population was 25, which is comparable to previous IMR values in some[12,23] but not all[11,13] cohorts of patients with STEMI. IMR is associated with infarct size[11] and potentially the duration of ischemia. The ischemic time in our population was relatively short (Table 1), which potentially explains IMR distribution in our population. There was a comparatively lower proportion of patients with an anterior STEMI in our cohort (37% of patients) compared with, for example, 49% of cases in the study by McGeoch et al[11] (median IMR, 35) and 55% of cases in the study by Fearon et al[13] (median IMR, 31). These studies involved fewer patients, and enrollment may have been more selective. IMR measurement involves a diagnostic guidewire and use of intravenous adenosine and may prolong the procedure by ≈5 minutes. In 2013, the US Food and Drug Administration issued a safety announcement on the risk of MI and death in patients receiving Adenoscan (adenosine) for stress testing. However, a subsequent prospective, multicenter study has shown that intravenous adenosine when administered briefly for invasive physiology testing is safe and well tolerated in patients with acute or recent MI.[50] IMR was measured routinely in our catheter laboratories, with measurements obtained by all of the cardiologists (n=13) without complication and in the setting of routine emergency care.

Most of the adverse events occurred initially during the index hospitalization. The limited number of adverse events constrained the statistical power of the multivariable models of adverse health outcomes. The study population included 21 patients initially treated with thrombolysis, and 14 of these patients had rescue PCI. The main results of our study were unchanged when these patients were removed (data not shown). The limited number of adverse events constrained the number of variables and related statistical power in the prognostic models. Our analysis does not permit inference on causality, and further studies are warranted.

Conclusions

Compared with the angiographic and ECG measures of reperfusion, the combination of IMR>40 and CFR≤2.0, and CFR alone, an IMR>40 is consistently and strongly associated with microvascular pathology, changes in LV function and volumes, and all-cause death and heart failure in the longer term. Our results validate previous investigations and support further research into IMR-based therapeutic strategies.

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FOOTNOTES

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Comparative Prognostic Utility of Indexes of Microvascular Function Alone or in Combination in Patients With an Acute ST-Segment–Elevation Myocardial Infarction

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Supplementary Material

Supplementary Methods

Comparative prognostic utility of indices of microvascular function alone or in combination in patients with an acute ST-segment elevation myocardial infarction.

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Setting and study populations

STEMI patients

Screening, enrolment, and data collection were prospectively performed by cardiologists in the cardiac catheterization laboratories of the Golden Jubilee National Hospital, Glasgow, United Kingdom. This hospital is a regional referral centre for primary and rescue percutaneous coronary intervention (PCI). The hospital provides clinical services for a population of 2.2 million. A screening log was recorded, including patients who did not participate in the cohort study. Patients were invited to undergo cardiac magnetic resonance imaging (CMR) 2 days and 6 months after hospital admission (1)(2).

Coronary angiogram acquisition

Coronary angiograms were acquired during usual care with cardiac catheter laboratory X-ray (Innova®) and IT equipment (Centricity®) made by GE Healthcare.

Percutaneous coronary intervention

Consecutive admissions with acute STEMI referred for emergency percutaneous coronary intervention (PCI) were screened for the inclusion and exclusion criteria. During ambulance transfer to the hospital, the patients received 300 mg of aspirin, 600 mg of clopidogrel and 5000 IU of unfractionated heparin (3, 4). The initial primary PCI procedure was performed using radial artery access. A conventional approach to primary PCI was adopted in line with usual care in our hospital (3, 4). Conventional bare metal and drug eluting stents were used in line with guideline recommendations and clinical judgement. The standard transcatheter approach for reperfusion involves minimal intervention with aspiration thrombectomy only or minimal balloon angioplasty (e.g. a compliant balloon sized according to the reference vessel

diameter and inflated at 4-6 atmospheres 1-2 times). During PCI, glycoprotein IIbIIIa inhibitor therapy was initiated with high dose tirofiban (25 μg/kg/bolus) followed by an intravenous infusion of 0.15 μg/kg/min for 12 hours, according to clinical judgement and indications for bail-out therapy (3, 4). No reflow was treated according to contemporary standards of care with intra-coronary nitrate (i.e. 200 μg) and adenosine (i.e. 30 – 60 μg) (3, 4), as clinically appropriate. In patients with multivessel coronary disease, multivessel PCI was not recommended, in line with clinical guidelines (3, 4). The subsequent management of these patients was symptom-guided.

Measurement of IMR and CFR at the end of PCI

We adopted a thermodilution technique rather than Doppler, in order to implement a method that is potentially transferable to routine clinical practice. The Doppler measurements are more time-consuming, require considerable experience, may be less reproducible (14), and the guidewire is typically more expensive. The Doppler method less transferrable to every-day practice than the thermodilution method.

A coronary pressure- and temperature-sensitive guidewire (St Jude Medical, Uppsala, Sweden) was used to measure coronary flow reserve (CFR) and the index of microvascular resistance (IMR) in the culprit coronary artery at the end of primary or rescue PCI. The guidewire was calibrated outside the body, equalized with aortic pressure at the ostium of the guide catheter and then advanced to the distal third of the culprit artery. Coronary flow reserve is defined as the mean transit time at rest divided by the mean transit time during hyperemia.

IMR is defined as the distal coronary pressure multiplied by the mean transit time of a 3 ml bolus of saline at room temperature during maximal coronary hyperemia, measured simultaneously (mmHg x s, or units) (5-7).

Hyperemia was induced by 140 μ/kg/min of intravenous adenosine preceded by a 2 ml intracoronary bolus of 200 μg of nitrate. The mean aortic and distal coronary pressures were recorded during maximal hyperemia. We have previously assessed the repeatability of IMR using duplicate measurements 5 minutes apart in a subset of 12 consecutive patients (7).

A priori, based on the prior literature, we pre-specified and examined an IMR>40 and also the following classifications: 1) IMR≤40 and CFR>2.0, 2) IMR>40 and CFR>2.0), 3) IMR≤40 and CFR≤2.0, 4) IMR>40 and CFR≤2.0.

Angiographic analysis

Coronary artery anatomy

The coronary anatomy and disease characteristics of the study participants were described based on the clinical reports of the attending cardiologist. Coronary dominance were assigned as left, right or balanced according to the origin of the posterior descending coronary artery.

Coronary artery disease severity

Quantitative coronary analysis (QCA) of the culprit vessel was performed by two trained observers (J.C., V.Y.T.M) using standard methods (Centricity®, GE Healthcare, Pollards Wood, UK). All coronary angiograms were analysed on a single image analysis software platform using de-identified images. Automatic edge detection algorithms were used to determine the vessel contours by assessing brightness along scan lines perpendicular to the vessel center. Image analysis was performed by two experienced observers supervised by an

expert physician, all of whom were blinded to the other study data. End-diastolic frames were used to assess disease severity using angulations reveal the stenosis at its most severe degree with minimal foreshortening and branch overlap. The coronary artery segments in the culprit artery included all those with a reference diameter ≥1.5 mm.

Definitions

TIMI flow grade

Coronary blood flow can be described based on the visual assessment of coronary blood flow revealed by contrast injection into the coronary arteries (3, 4, 8).

TIMI Coronary Flow Grade	
0	No flow
1	Minimal flow past obstruction
2	Slow (but complete) filling and slow clearance
3	Normal flow and clearance

Myocardial perfusion

Angiographic evidence of myocardial perfusion will be evaluated using the TIMI myocardial perfusion grade (TMP) at the end of the PCI procedure (9).

Grade	
0	No myocardial blush
1	Minimal blush and very slow clearing (e.g. present at

	beginning of next cine)
2	Good blush with slow clearing of myocardial contrast (present at end of cine but gone at beginning of next)
3	Good blush and normal clearing (ie. gone by end of cine)

Assessment by corrected Thrombolysis In Myocardial Infarction Frame Count

Corrected TIMI frame count (cTFC) was calculated as the number of frames for dye to reach a standardised distal landmark in each angiographic territory. The first frame taken for the measurement was the frame in which dye touched both borders of the coronary artery in question and moved forward with at least 70% of the vessel lumen opacified. The standardised distal landmarks were taken as the first branch of the postero-lateral artery for the right coronary artery, the most distal branch of the obtuse marginal for the circumflex, and the distal bifurcation of the left anterior descending (LAD) coronary artery. The number of frames from the first frame to the last frame when the dye entered the standardised distal landmark was counted. A standard image acquisition speed of 30 frames per second was used. The correction factor used to account for the increased length of the LAD compared to the right and circumflex arteries was 1.7 thereby giving a "corrected TIMI frame count".

CMR acquisition and analyses

We used CMR to provide reference data on LV function, pathology and surrogate outcomes, independent of the invasive tests.

CMR acquisition

CMR was performed on a Siemens MAGNETOM Avanto (Erlangen, Germany) 1.5-Tesla scanner with a 12-element phased array cardiac surface coil. T2 maps were acquired in contiguous short axis slices covering the whole ventricle, using an investigational prototype T2-prepared (T2P) TrueFisp sequence (10, 11). Typical imaging parameters were: bandwidth ~947 Hz/pixel; flip angle 70°; T2 preparations: 0 ms, 24 ms, and 55 ms respectively; matrix 160 x 105 pixels; spatial resolution 2.6 x 2.1 x 8.0 mm; slice thickness 8 mm.

T2*-maps were obtained using an investigational prototype T2* map sequence acquired in 3 short-axis slices (basal, mid and apical). Typical imaging parameters were: bandwidth ~814 (x8) Hz/pixel; flip angle 18°; matrix 256x115; spatial resolution 2.6 x 1.6 x 10 mm; slice thickness 8 mm.

In order to assess early microvascular obstruction, early gadolinium enhancement imaging was acquired 1, 3, 5 and 7 minutes post-contrast injection using a TrueFISP readout and fixed inversion time (TI) of 440 ms. Late gadolinium enhancement images covering the entire LV were acquired 10-15 minutes after intravenous injection of 0.15 mmol/kg of gadoterate meglumine (Gd^{2+}-DOTA, Dotarem, Guebert S.A.) using segmented phase-sensitive inversion recovery (PSIR) turbo fast low-angle shot (12). Microvascular obstruction was defined as a dark zone on early delayed enhancement imaging 1, 3, 5 and 7 minutes post-contrast injection and within an area of late gadolinium enhancement. Typical imaging parameters were: matrix = 192 x 256, flip angle = 25°, TE = 3.36 ms, bandwidth = 130 Hz/pixel, echo spacing = 8.7ms and trigger pulse = 2. The voxel size was 1.8 x 1.3 x 8 mm^3. Inversion times were individually adjusted to optimize nulling of apparently normal myocardium (typical values, 200 to 300 ms).

MR image analyses

The images were analysed on a Siemens work-station by observers with at least 3 years CMR experience (N.A., D.C., I.M). All of the images were reviewed by experienced CMR cardiologists (C.B., N.T.). LV dimensions, volumes and ejection fraction were quantified using computer assisted planimetry (syngo MR®, Siemens Healthcare, Erlangen, Germany). All scan acquisitions were spatially co-registered.

T2 and T2 – standardized measurements in myocardial regions of interest*

LV contours were delineated with computer assisted planimetry on the raw T2* image and the last corresponding T2 raw image, with echo time of 55 ms (13). Contours were then copied onto the colour-encoded spatially co-registered maps and corrected when necessary by consulting the SSFP cine images. Apical segments were not included because of partial volume effects. Particular care was taken to delineate regions of interest with adequate margins of separation from tissue interfaces prone to partial volume averaging such as between myocardium and blood. Each T2/ T2* map image was visually assessed for the presence of artefacts relating to susceptibility effects or cardio-respiratory motion. Each map was evaluated against the original images. When artefacts occurred, the affected segments were not included in the analysis.

T2/ T2* values were segmented spatially and regions of interest were defined as (1) remote myocardium, (2) injured myocardium and (3) infarct core. The regions-of-interest were planimetered to include the entire area of interest with distinct margins of separation from tissue interfaces to exclude partial volume averaging. The remote myocardial region-of-interest was defined as myocardium 180º from the affected zone with no visible evidence of infarction, edema or wall motion abnormalities (assessed by inspecting corresponding contrast enhanced T1-weighted, T2-weighted and cine images, respectively). The infarct zone

region-of-interest was defined as myocardium with pixel values (T2) >2 SD from remote myocardium on T2-weighted CMR (10, 11). The infarct core was defined as an area in the center of the infarct territory having a mean T2/ T2* value of at least 2 standard deviations (SDs) below the T2/ T2* value of the periphery of the area-at-risk.

In healthy volunteers, the mid-ventricular T2/T2* map was segmented into 6 equal segments, using the anterior right ventricular-LV insertion point as the reference point (2). T2/T2* was measured in each of these segments, and regions-of-interest were planimetered distinct and separate from blood-pool and tissue interfaces. These segmental values were also averaged to provide one value per subject. Results are presented as average values for segments and slices.

Infarct definition and size

The presence of acute infarction was established based on abnormalities in cine wall motion, rest first-pass myocardial perfusion, and delayed-enhancement imaging. In addition, supporting changes on the ECG and coronary angiogram were also required. Acute infarction was considered present only if late gadolinium enhancement was confirmed on both the axial and long axis acquisitions. The myocardial mass of late gadolinium (grams) was quantified using computer assisted planimetry and the territory of infarction was delineated using a signal intensity threshold of >5 standard deviations above a remote reference region and expressed as a percentage of total LV mass (14). Infarct regions with evidence of microvascular obstruction were included within the infarct area and the area of microvascular obstruction was assessed separately and also expressed as a percentage of total LV mass. The measurements of infarct size were performed by I.M. and N.A.

Microvascular obstruction

Microvascular obstruction was defined as a dark zone on EGE imaging 1, 3, 5 and 7 minutes post-contrast injection that remained present within an area of late gadolinium enhancement at 15 minutes. Identification of microvascular obstruction was performed independently by I.M. and N.A.

Myocardial hemorrhage

Myocardial hemorrhage was scored visually. On the T2* maps, a region of reduced signal intensity within the infarcted area, with a T2* value of <20 ms (15-18), was considered to confirm the presence of myocardial hemorrhage.

Myocardial edema

The extent of myocardial edema was defined as LV myocardium with pixel values (T1/T2) >2 standard deviations from remote myocardium (10, 11, 19-22).

Myocardial salvage

Myocardial salvage was calculated by subtraction of percent infarct size from percent area-at-risk (7, 19, 22). The myocardial salvage index was calculated by dividing the myocardial salvage area by the initial area-at-risk.

Adverse remodeling

Adverse remodeling was defined as an increase in LV end-diastolic volume ≥ 20% at 6 months from baseline (23).

Reference ranges

Reference ranges used in the laboratory were 105 – 215 g for LV mass in men, 70 – 170 g for LV mass in women, 77 – 195 ml for LV end-diastolic volume in men, 52 – 141 ml for LV end-diastolic volume in women, 19 – 72 ml for LV end-systolic volume in men and 13 – 51 ml for LV end-systolic volume in women.

Electrocardiogram

A 12 lead electrocardiogram (ECG) was obtained before coronary reperfusion and 60 minutes afterwards with Mac-Lab® technology (GE Healthcare) in the catheter laboratory and a MAC 5500 HD recorder (GE Healthcare) in the Coronary Care Unit. The ECGs were acquired by trained cardiology staff. The ECGs were de-identified and transferred to the local ECG management system. The ECGs were then analysed by the University of Glasgow ECG Core Laboratory which is certified to ISO 9001: 2008 standards as a UKAS Accredited Organization.

The extent of ST-segment resolution on the ECG assessed 60 minutes after reperfusion compared to the baseline ECG before reperfusion (3) was expressed as complete (≥70%), incomplete (30% to < 70%) or none (≤30%). ECG evidence of reperfusion injury was taken as persistence of ST segment elevation resolution post-procedure, and specifically ≤30% ST-segment resolution post-PCI.

Biochemical and hematologic measurements

Blood samples were obtained immediately after reperfusion in the cardiac catheterization laboratory, and subsequently between 0600 - 0700 hrs each day during the initial in-patient stay in the Coronary Care Unit.

Biochemical assessment of infarct size

Troponin T was measured (Elecsys Troponin T, Roche) as a biochemical measure of infarct size. The high sensitive assay reaches a level of detection of 5 pg/ml and achieves less than 10% variation at 14 pg/ml corresponding to the 99th percentile of a reference population. The peak troponin T value for each patient was recorded in the study database.

Biochemical assessment of inflammation

C-reactive protein (CRP) was measured in an NHS hospital biochemistry laboratory using a particle enhanced immunoturbimetric assay method (Cobras C501, Roche) and the manufacturers calibrators and quality control material, as a biochemical measure of inflammation. The high sensitive assay CRP measuring range is 0.1-250 mg/L. The expected CRP values in a healthy adult are < 5 mg/L, and the reference range in our hospital is 0 - 10 mg/L.

Hematological measurement of inflammation

Leucocyte count and leucocyte sub-populations were measured as a hematologic measure of inflammation using sheath flow technology incorporating semi-conductor laser beam, forward and side scattered light (Sysmex XT200i and XT1800i for white blood cell and differential white blood cell counts, respectively). The linearity ranges for white blood cells was 0.00-440.0 x10(9) /L. The following are the normal ranges for full blood count parameters:

	MALE	**FEMALE**
WBC x 10^9/L	4.0 - 11.0	4.0 - 11.0
RBC x 10^12/L	4.50 - 6.50	3.80 - 5.80
Hgb g/L	130 – 180	115 - 165
HCT L/L	0.400 - 0.540	0.370 - 0.470
MCV fL	78 – 99	78 - 99
MCH Pg	27.0 - 32.0	27.0 - 32.0

MCHC g/L	310 – 360	310 - 360
PLATELETS x 10^9/L	150 – 400	150 - 400
NEUTROPHILS x 10^9/L	2.5 - 7.5	2.5 - 7.5
LYMPHOCYTES x 10^9/L	1.5 - 4.0	1.5 - 4.0
MONOCYTES x 10^9/L	0.2 - 0.8	0.2 - 0.8
EOSINOPHILS x 10^9/L	0.0 - 0.4	0.0 - 0.4
BASOPHILS x 10^9/L	0.01 - 0.10	0.01 - 0.10

A blood sample was routinely obtained in the cardiac catheter laboratory, immediately following revascularization and then again at 0700 on the first and second days after admission to hospital.

Pre-specified health outcomes

We pre-specified adverse health outcomes that are pathophysiologically linked with STEMI (43, 44). The primary composite outcome was (1) all-cause death or first heart failure event following the initial hospitalization (Supplementary Methods).

Research staff screened for events from enrolment by checking the medical records and by contacting patients and their primary and secondary care physicians, as appropriate with no loss to follow-up (Figure 2). Each serious adverse event (SAE) was reviewed by a cardiologist who was independent of the research team and blinded to all of the clinical and CMR data. The SAEs were defined according to standard guidelines (43, 44) (Supplementary Methods) and categorized as having occurred either during the index admission or post-discharge. All study participants were followed-up for a minimum of 18 months after discharge. The median duration of follow-up was of 845 days (post-discharge censor duration (range) 598 - 1098 days).

Statistics

Sample size calculation for the whole cohort

With an estimated hemorrhage incidence of 33% at 48 h post-STEMI, 100 subjects would have evidence of myocardial hemorrhage and 200 subjects would not. The study would have 90% power at a 5% level of significance using a two sided two sample t-test to detect a between-group difference in a baseline variable of interest e.g. index of microvascular resistance equivalent to three eighths of a common standard deviation. We also estimated that at least 30 major adverse cardiac events (MACE) would occur based on a conservative estimate of the event rate (10-12%) at 18 months. The sample size calculation was performed using nQuery version 7.0.

Statistical analysis

Categorical variables are expressed as the number and percentage of patients. Most continuous variables followed a normal distribution and are therefore presented as means together with standard deviation. Those variables that did not follow a normal distribution are presented as medians with interquartile range. Differences in continuous variables between groups were assessed by the Student's t-test or ANOVA for continuous data with normal distribution, otherwise the nonparametric Mann-Whitney test or Kruskal-Wallis H test. Differences in categorical variables between groups were assessed using a Fisher's test.

Two raters assessed the angiograms of 30 subjects randomly selected from the whole cohort. Inter-rater reliability for angiographic parameters was assessed using weighted Cohen's kappa and the intra-class correlation coefficient (ICC) with random effects models (Supplementary Results).

Univariable and multivariable associations are assessed using binary logistic regression or linear regression where appropriate. Binary logistic models are compared using

Harrel's C-statistic. Linear regression models are compared using the Bayesian Information Criterion (BIC). The likelihood ratio test was used to compare the binary logistic and linear regression models with IMR, or an IMR>40 and CFR≤2.0. A p-value <0.05 favors including the variable in the model.

Logistic regression (odds ratio, 95% confidence interval) was used to identify potential clinical predictors of all-cause death/heart failure events, including patient characteristics, CMR findings, and IMR and CFR.

All p-values are 2-sided and a p-value > 0.05 indicates the absence of a statistically significant effect. Statistical analyses were performed using R version 2.15.1 or SAS v 9.3, or higher versions of these programs.

Trial Management

The study was conducted in line with Guidelines for Good Clinical Practice (GCP) in Clinical Trials. http://www.mrc.ac.uk/documents/pdf/good-clinical-practice-in-clinical-trials/

Trial management included a Trial Management Group, and an independent Clinical Trials Unit. Day to day study activity was coordinated by the Trial Management Group who was responsible to the Sponsor which was responsible for overall governance and that the trial was conducted according to GCP standards.

Clinical events were assessed and validated by an independent cardiologist (A.M.) who had access to relevant source clinical data. This cardiologist followed an agreed charter and he was blinded to all of the other clinical data.

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Supplementary Results

Comparative prognostic utility of indices of microvascular function alone or in combination in patients with an acute ST-segment elevation myocardial infarction.

ClinicalTrials.gov identifier: NCT02072850.

Reproducibility

Inter-rate reliability

Two raters assessed the angiograms of 25 randomly selected participants. The weighted Cohen's kappa for initial TIMI flow was 0.84 (0.92, 0.99) and the Cohen's kappa for final TIMI flow was 0.62 (0.87, 1.0). The weighted Cohen's kappa for TIMI myocardial blush grade was 0.10 (0.35, 0.61).The intra-class correlation coefficient for TIMI frame count was 0.75 (0.54, 0.87).

CFR/FFR ratio, a measure of true CFR

In a multivariable model for predictors of the changes in LV ejection fraction at baseline, the ratio of CFR/FFR was associated with LVEF, independent of other parameters (coefficient (95% CI) 0.96 (0.04, 1.88); p=0.041), however, when IMR was included in this model, the relationship for CFR/FFR was no longer statistically significant (0.77 (-0.17, 1.71); p=1.08).

CFR/FFR was not a multivariable predictor of LVEDV when included alone (p=0.33) or in combination with IMR (p=0.661) whereas IMR was a multivariable associate of LV EDV (0.71 (0.02, 1.40); p=0.043).

Table 1. Clinical and angiographic characteristics of 283 STEMI patients with culprit artery microvascular function at the end of emergency PCI categorized as follows 1) IMR ≤40 and CFR >2.0, 2) IMR >40 and CFR >2.0), 3) IMR ≤40 and CFR ≤2.0, 4) IMR >40 and CFR ≤2.0.

Characteristics*	All patients	CFR>2.0, IMR≤40	CFR>2.0, IMR>40	CFR≤2.0, IMR≤40	CFR≤2.0, IMR>40	P-value
	n = 283	n = 59 (21%)	n = 14 (5%)	n = 145 (51%)	n = 65 (23%)	
Age, years	60 (12)	57 (12)	56 (10)	60 (11)	63 (12)	0.002
Male sex, n (%)	206 (73)	46 (78)	8 (57)	101 (70)	51 (79)	0.230
BMI, (kg/m^2)	29 (5)	30 (5)	27 (6)	29 (5)	28 (4)	0.024
Medical history						
Hypertension, n (%)	91 (32)	16 (27)	5 (36)	44 (30)	26 (40)	0.407
Current smoking, n (%)	175 (62)	37 (63)	11 (79)	93 (64)	34 (52)	0.225
Hypercholesterolemia, n (%)	78 (28)	18 (31)	6 (43)	37 (26)	17 (26)	0.509
Diabetes mellitus‡, n (%)	30 (11)	3 (5)	1 (7)	18 (12)	8 (12)	0.438
Previous angina, n (%)	32 (11)	4 (7)	2 (14)	18 (12)	8 (12)	0.634
Previous myocardial infarction, n (%)	20 (7)	4 (7)	0 (0)	11 (8)	5 (8)	0.944

Previous PCI, n (%)		14 (5)	2 (3)	0 (0)	7 (5)	5 (8)	0.681
Presenting characteristics							
Heart rate, bpm		78 (17)	77 (19)	78 (15)	78 (16)	78 (17)	0.853
Systolic blood pressure, mmHg		136 (24)	138 (27)	137 (23)	134 (24)	136 (24)	0.524
Diastolic blood pressure, mmHg		79 (14)	80 (12)	82 (10)	78 (15)	80 (14)	0.580
Time from symptom onset to reperfusion, min		174 (120, 316)	163 (112, 281)	240 (149, 454)	183 (120, 304)	175 (129, 336)	0.384
Ventricular fibrillation†, n (%)		19 (7)	3 (5)	2 (14)	8 (6)	6 (9)	0.360
Heart failure, Killip class at presentation, n (%)	I	201 (71%)	57 (80)	10 (71)	111 (76)	33 (51)	
	II	62 (22%)	10 (17)	4 (29)	30 (21)	18 (28)	<0.001
	III/IV	20 (7)	2 (3)	0 (0)	4 (3)	14 (21)	
ECG							
ST segment elevation resolution post PCI, n (%)							
Complete, ≥70 %		128 (45)	32 (54)	6 (43)	69 (48)	21 (32)	
Incomplete, 30% to < 70%		114 (40)	20 (34)	5 (36)	59 (41)	30 (46)	0.148

None, ≤30%		40 (14)	7 (12)	3 (21)	16 (11)	14 (22)	
Reperfusion strategy, n (%)							
Primary PCI		262 (93)	55 (93)	14 (100)	134 (92)	59 (91)	
Rescue PCI (failed thrombolysis)		14 (5)	3 (5)	0 (0)	7 (5)	6 (6)	0.995
Successful thrombolysis		7 (2)	1 (2)	0 (0)	4 (3)	2 (3)	
Coronary angiography							
Number of diseased arteries¥, n (%)	1	158 (56)	34 (58)	7 (50)	78 (54)	39 (60)	
	2	83 (29)	16 (27)	6 (43)	45 (31)	16 (25)	0.979
	3	37 (13)	8 (14)	1 (7)	19 (13)	9 (14)	
	LM	5 (2)	1 (2)	0 (0)	3 (2)	1 (2)	
Culprit artery, n (%)	LAD	107 (38)	23 (39)	5 (36)	49 (34)	30 (46)	
	LCX	51 (18)	10 (17)	2 (14)	29 (20)	10 (15)	0.791
	RCA	125 (44)	26 (44)	7 (50)	67 (46)	25 (39)	
TIMI coronary flow grade pre-PCI, n (%)	0/1	204 (72)	37 (62)	10 (71)	104 (72)	53 (82)	
	2	51 (18)	11 (19)	3 (21)	28 (19)	9 (14)	0.190
	3	28 (10)	11 (19)	1 (7)	13 (9)	3 (5)	

TIMI coronary flow grade post-PCI, n (%)	0/1	2 (1)	0 (0)	0 (0)	1 (1)	1 (2)	
	2	13 (5)	1 (2)	2 (14)	3 (2)	7 (11)	0.017
	3	268 (95)	58 (98)	12 (86)	141 (97)	57 (88)	
TIMI frame count pre-PCI		29.4 (18.0, 44.0)	27.1 (16.0, 42.4)	28.0 (18.9, 34.0)	28.0 (19.5, 38.5)	41.0 (25.7, 55.0)	0.182
TIMI frame count post-PCI		15.3 (10.0, 24.7)	16.0 (10.0, 24.0)	22.6 (17.0, 26.0)	12.9 (8.0, 22.0)	20.0 (14.0, 30.0)	<0.001
TIMI blush grade post-PCI	0/1	71 (26.4%)	20 (35.1%)	3 (23.1%)	23 (16.7%)	25 (41.0%)	0.001
	2/3	198 (73.6%)	37 (64.9%)	10 (76.9%)	115 (83.3%)	36 (59.0%)	
Culprit lesion, percentage residual stenosis		12.4 (5.5)	12.12 (5.67)	14.05 (4.12)	12.42 (5.62)	12.18 (5.57)	0.948
Aspiration thrombectomy, n (%)		203 (72)	43 (73)	13 (93)	100 (69)	47 (72)	0.307
Coronary flow reserve		1.8 (0.9)	3.1 (1.0)	2.7 (0.7)	1.4 (0.3)	1.3 (0.4)	<0.001
Index of microvascular resistance		24 (15, 44)	19 (13, 25)	49 (43, 53)	18 (13, 27)	63 (49, 93)	<0.001
Fractional flow reserve		0.90 (0.10)	0.92 (0.08)	0.96 (0.07)	0.90 (0.09)	0.93 (0.06)	0.027
Resistive reserve ratio		1.8 (1.4, 2.5)	3.3 (2.8, 4.0)	2.8 (2.6, 3.5)	1.7 (1.3, 1.9)	1.5 (1.2, 2.0)	<0.001
Treatment in the catheter laboratory							
Thrombus aspiration		203 (71.7%)	43 (72.9%)	13 (92.9%)	100 (69.0%)	47 (72.3%)	0.307
Glycoprotein IIbIIIa inhibitor		259 (91.5%)	52 (88.1%)	14 (100.0%)	133 (91.7%)	60 (92.3%)	0.631

Medical therapy						
ACE-I or ARB	279 (99)	58 (98)	14 (100)	143 (98)	65 (100)	0.723
Beta-blocker	269 (95)	55 (93)	12 (86)	141 (97)	61 (94)	0.132
Initial blood results on admission						
C-reactive protein, (mg/L)	8 (21)	6 (6)	11 (24)	7 (11)	13 (38)	0.774
Leucocyte cell count ($x10^9$L)	12.4 (3.6)	12.2 (3.7)	12.9 (4.2)	12.4 (3.3)	12.4 (4.0)	0.731
Neutrophil count ($x10^9$L)	9.6 (3.3)	9.2 (3.4)	10.3 (4.3)	9.7 (3.1)	9.8 (3.6)	0.278
Monocytes ($x10^9$L)	0.9 (0.4)	0.9 (0.3)	0.9 (0.4)	0.8 (0.3)	0.9 (0.5)	0.602
Platelet count ($x10^6$L)	246 (67)	239 (66)	245 (58)	253 (70)	237 (62)	0.883
Troponin T (ng/L)	1566 (93, 4411)	1272 (106, 2675)	1727 (1727, 1727)	1731 (85, 4302)	2717 (111, 7419)	0.023

Footnote: ACE-I or ARB = angiotensin converting enzyme inhibitor or angiotensin receptor blocker; LAD = Left anterior descending coronary artery; LCX = Left circumflex coronary artery; LM = left main coronary artery; RCA = right coronary artery; TIMI = Thrombolysis in Myocardial Infarction grade, PCI = percutaneous coronary intervention. Killip classification of heart failure after acute myocardial infarction: class I - no heart failure, class II - pulmonary rales or crepitations, a third heart sound, and elevated jugular venous pressure, class III - acute pulmonary edema, class IV - cardiogenic shock. * Data are reported as mean (SD), median (IQR), or N (%) as appropriate. P-values have been obtained from a one-way ANOVA, Kruskal-Wallis test or Fisher test. TIMI flow grades pre- and post-PCI were grouped 0/1 vs. 2/3 for this analysis. ‡ Diabetes mellitus was defined as a history of diet-controlled or treated diabetes. † Successfully electrically cardioverted ventricular fibrillation at presentation or during emergency PCI procedure. ¥ Multivessel coronary artery disease was defined according to the number of stenoses of at least 50% of the reference vessel diameter, by visual assessment and whether or not there was left main stem involvement.

Table 2. Cardiac magnetic resonance imaging findings at 2 days and 6 months post-reperfusion in 283 STEMI patients with culprit artery microvascular function categorized as follows 1) IMR ≤40 and CFR >2.0, 2) IMR >40 and CFR >2.0), 3) IMR ≤40 and CFR ≤2.0, 4) IMR >40 and CFR ≤2.0.

Characteristics*	All patients	CFR>2.0, IMR≤40	CFR>2.0, IMR>40	CFR≤2.0, IMR≤40	CFR≤2.0, IMR>40	P-value
	n = 283	n = 59 (21%)	n = 14 (5%)	n = 145 (51%)	n = 65 (23%)	
CMR findings 2 days post-MI						
LV ejection fraction, %	55 (10)	56 (9)	54 (9)	57 (9)	51 (10)	0.027
LV end-diastolic volume, ml						
Men	160 (32)	160 (30)	167 (29)	158 (33)	165 (35)	0.628
Women	124 (25)	124 (25)	130 (38)	126 (23)	116 (24)	0.461
LV end-systolic volume, ml						
Men	74 (54, 92)	70 (54, 89)	74 (69, 78)	73 (50, 86)	81 (59, 104)	0.106
Women	53 (41, 67)	46 (43, 59)	73 (54, 78)	51 (40, 68)	61 (51, 65)	0.338

LV mass, g						
Men	141 (123, 160)	140 (120, 157)	144 (130, 152)	141 (123, 163)	142 (127, 153)	0.994
Women	95 (85, 105)	101 (85, 116)	105 (97, 123)	97 (87, 104)	85 (76, 90)	0.088
Edema and infarct characteristics						
Myocardial edema, % LV mass	32 (12)	28 (11)	33 (6)	31 (11)	38 (14)	<0.001
Infarct size, % LV mass	16 (7, 27)	11 (4, 21)	14 (7, 24)	11 (3, 22)	24 (12, 33)	<0.001
Myocardial salvage index, % of LV mass	61 (44, 85)	71 (56, 90)	60 (47, 91)	67 (47, 86)	46 (39, 67)	<0.001
Late microvascular obstruction, n (%)	142 (50)	17 (29)	9 (64)	71 (49)	45 (69)	<0.001
Late microvascular obstruction, % LV mass	0.1 (0.0, 3.5)	0.0 (0.0, 0.5)	1.7 (0.0, 4.5)	0.0 (0.0, 2.7)	2.1 (0.0, 9.4)	<0.001
Myocardial hemorrhage, n (%)	89 (42)	8 (21)	10 (48)	22 (31)	48 (60)	<0.001
CMR findings 6 months post-MI (n=267)						
LV ejection fraction at 6 months, %	62 (9)	65 (7)	61 (10)	64 (9)	57 (11)	<0.001
LV end-diastolic volume at 6 months, ml						

Men	165 (136, 192)	161 (135, 189)	192 (172, 209)	165 (132, 187)	170 (141, 212)	0.113
Women	121 (109, 136)	118 (102, 130)	124 (99, 146)	122 (111, 135)	130 (110, 135)	0.877
Change in LV end-diastolic volume at 6 months from baseline, ml						
Men	6 (-8, 21)	4 (-8, 14)	13 (4, 19)	5 (-9, 18)	13 (-6, 33)	0.145
Women	1 (-11, 10)	-1 (-5, 11)	-13 (-16, 2)	0 (-11, 7)	9 (-3, 19)	0.242

Footnote: Abbreviations: LV = left ventricle, T1 = myocardial longitudinal relaxation time. Area-at-risk was measured with T2-mapping. Data are given as n (%) or mean (SD). P-values were obtained from one-way ANOVA, Kruskal-Wallis test, or a Fisher test. * Data are reported as mean (SD), median (IQR), or n (%) as appropriate. LV ejection fraction was missing in 24 subjects at follow-up. LV end-diastolic volume at follow-up was missing in 16 men and 8 women.

Table 3. Multivariable associations between clinical characteristics, an increased IMR>40 at the end of emergency PCI, and myocardial obstruction revealed by contrast-enhanced MRI two days later (n=262) in patients with acute STEMI.*

Binary logistic regression	Odds ratio (95% CI)	p value
Index of microvascular resistance >40	2.82 (1.62, 4.93)	<0.001
Male gender	1.78 (1.03, 3.09)	0.039
Hypertension	1.31 (0.77, 2.23)	0.311
Cigarette smoker	1.23 (0.74, 2.04)	0.429
Harrel's C-statistic	0.634	

* Manual backwards selection using a p-value threshold of 0.10 for inclusion. Previous PCI was excluded due to numerical instability. Likelihood ratio test, p=0.005, favouring inclusion of IMR>40 in the model. The multivariable association for IMR>40, CFR≤2.0 in this model was 2.75 (1.51, 5.02); p=0.001; Harrel's C-statistic = 0.626).

Table 4. Multivariable associations between an IMR>40 and the changes in left ventricular ejection fraction at 6 months from baseline.

Linear regression	Coefficient (95% CI)	p value
Baseline LV ejection fraction, %	-0.64 (-0.74, -0.53)	<0.001
Infarct size, % LV mass	-0.31 (-0.39, -0.23)	<0.001
Previous MI	-5.44 (-9.40, -1.48)	0.007
TIMI blush grade post-PCI (2 or 3 vs. 1)	2.10 (0.30, 3.91)	0.022
Index of microvascular resistance >40	-2.12 (-4.02, -0.23)	0.028
No-resolution of ST-elevation	2.31 (-0.03, 4.64)	0.053
Previous PCI	4.09 (-0.23, 8.42)	0.064
BMI, kg/m^2	-0.14 (-0.32, 0.04)	0.116
Hypercholesterolemia	1.05 (-0.86, 2.97)	0.279
Male sex	-1.03 (-2.91, 0.85)	0.283
TIMI frame count post PCI	0.03 (-0.04, 0.09)	0.412
Culprit lesion, percentage residual stenosis	-0.05 (-0.21, 0.10)	0.476
Diabetes mellitus	0.90 (-1.66, 3.47)	0.487
Smoker	-0.54 (-2.36, 1.29)	0.560
Symptom to reperfusion time per 10 minutes	0.01 (-0.03, 0.05)	0.572
Age (years)	0.02 (-0.07, 0.10)	0.682
Previous angina	0.48 (-2.13, 3.10)	0.716
Hypertension	-0.18 (-2.01, 1.64)	0.844
SBP per 10 mmHg	0.02 (-0.31, 0.36)	0.892
Heart rate (bpm)	0.00 (-0.05, 0.05)	0.894

Bayesian Information Criterion	1520.33

The Bayesian Information Criterion (BIC) reflects the goodness of fit of a multivariable model, where a smaller criterion indicates a preferable model. Likelihood ratio test, p=0.005, favors inclusion of IMR>40 in the model.

An IMR>40 was a multivariable associate of the change in left ventricular ejection fraction at 6 months from baseline in a different model that included infarct size as reflected by troponin concentration (co-efficient (95% CI) -2.73 (-4.76, -0.69); p=0.001; BIC 1489).

In a model that included infarct size (% LV mass) as revealed by MRI, the multivariable association for IMR>40, CFR≤2.0 with the change in left ventricular ejection fraction at 6 months from baseline was -1.91 (-3.94, 0.12); p=0.066 (BIC 1521.91). In a model that included peak troponin (μg/L), the multivariable association for IMR>40, CFR≤2.0 with the change in left ventricular ejection fraction at 6 months from baseline was -2.38 (-4.58, -0.19); p=0.034; BIC 1491). According to the BICs, there was no improvement in the model including for IMR>40, CFR≤2.0.

Table 5.

Breakdown of all cause death or heart failure events (n=30)	
Breakdown of all cause death or heart failure events during index hospital admission	
Death	n = 1
Heart failure (requiring IV furosemide)	n = 19
Breakdown of all cause death or heart failure events post-discharge	
Death	n = 7
Heart failure (requiring IV furosemide)	n = 3