

# Comprehensive assessment of microcirculation after primary percutaneous intervention in ST-segment elevation myocardial infarction: insight from thermodilution-derived index of microcirculatory resistance and coronary flow reserve

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**Objectives** A pathophysiological mechanism of microvascular dysfunction in ST-segment elevation myocardial infarction (STEMI) is multifactorial; thus, multiple modalities were needed to precisely evaluate a microcirculation.

**Methods** We complementarily assessed microcirculation in STEMI by the index of microcirculatory resistance (IMR) and coronary flow reserve (CFR) immediately after a primary percutaneous intervention in 89 STEMI patients. Cardiovascular and cerebrovascular events (MACCE) including cardiovascular death, target vessel failure, heart failure, and stroke were assessed during a mean follow-up period of 3.0 years.

**Results** The microcirculation of enrolled patients was classified into four groups using cutoff CFR and IMR values (CFR > 2 and mean IMR): group-1 ( $n = 23$ , CFR > 2 and IMR ≤ 27); group-2 ( $n = 31$ , CFR ≤ 2 and IMR ≤ 27); group-3 ( $n = 9$ , CFR > 2 and IMR > 27); and group-4 ( $n = 26$ , CFR < 2 and IMR > 27). On echocardiography 3 months later, improvement in the wall motion score index was shown in group-1 ( $P < 0.01$ ), group-2 ( $P < 0.01$ ), and group-3 ( $P = 0.04$ ), whereas group-4 did not show improvement in

wall motion score index ( $P = 0.06$ ). During clinical follow-up, there were no MACCE in group-1 and the patients in group-2 and group-3 showed significantly lower MACCE compared with group-4 (group-1 = 0%, group-2, and group-3 = 10%, group-4 = 23.1%,  $P = 0.04$ ).

**Conclusion** Complimentary assessment of microcirculation by the IMR and CFR may be useful to evaluate myocardial viability and the long-term prognosis of STEMI patients. *Coron Artery Dis* 27:34–39 Copyright © 2015 Wolters Kluwer Health, Inc. All rights reserved.

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**Keywords:** left ventricular function, microcirculation, myocardial infarction

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## Introduction

Impaired microcirculation after reperfusion treatment is correlated strongly with a poor prognosis in patients with ST-segment elevation myocardial infarction (STEMI) [1–4]. However, despite its prognostic importance, precise assessment of impaired microcirculation is difficult especially in the acute phase of STEMI patients.

As an invasive parameter, index of microcirculatory resistance (IMR) and coronary flow reserve (CFR) have been used as robust assessment tools for impaired microcirculation in STEMI patients at the time of cardiac catheterization. The IMR, a parameter for the evaluation of microvascular resistance, has been accepted as a simple

and readily available method of coronary microcirculation assessment. In STEMI patients, the IMR was validated as a strong predictor of both acute and chronic microvascular damages [5,6]. In addition, the CFR has been used as a significant predictor for myocardial viability and left ventricular (LV) remodeling in damaged myocardium [7,8].

A pathophysiological mechanism of microvascular dysfunction (MVD) in STEMI is multifactorial; thus, multiple modalities could more precisely evaluate a microcirculation injury in STEMI patients. Therefore, we complementarily assessed the degree of impaired microcirculation in STEMI immediately after primary percutaneous coronary intervention (PCI) using IMR and CFR together. Then, we investigated the usefulness of overall microcirculation estimated using the IMR and CFR to predict LV functional recovery and long-term prognosis of STEMI patients.

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## Methods

### Study population

From March 2010 to June 2014, the STEMI patients who underwent a primary PCI and coronary physiologic study immediately after primary PCI were enrolled at the IMR cohort of INHA University Hospital. Reasons for exclusion were unprotected left main disease; culprit lesion at side branch; stent thrombosis; high-degree atrioventricular block; cardiogenic shock; contraindication to adenosine; history of cerebrovascular accident or myocardial infarction within 1 year; and final thrombolysis in myocardial infarction (TIMI) grade less than 3. Treatment of STEMI followed the contemporary guidelines [9]. Aspiration thrombectomy, direct stenting, and drugs were administered according to clinical judgment. Clinical follow-up was performed by clinic visit, medical record review, and telephone contact.

### Coronary physiologic parameter measurement

After successful PCI, intracoronary nitroglycerin (100–200 µg) was administered and a pressure sensor/thermistor-tipped guidewire (Radi Medical System, Uppsala, Sweden) was calibrated outside the body, equalized at the tip of a guiding catheter, and then advanced to the distal two-thirds of the culprit vessel. Three injections of room-temperature saline (3–5 ml) were administered to the culprit vessel and the mean transit time was determined using a thermodilution technique [10]. After intravenous adenosine 140 µg/kg per min was administered to induce maximal hyperemia, the hyperemic mean transit time (T<sub>mn</sub>) was measured again using the same method as described earlier. Simultaneously, the mean distal coronary pressure (Pd) was obtained in the resting and maximal hyperemic states. The IMR was calculated as Pd × hyperemic T<sub>mn</sub> [11]. Thermodilution CFR was calculated by dividing the resting T<sub>mn</sub> by the hyperemic T<sub>mn</sub> [12]. In addition, fractional flow reserve was derived from the ratio of Pd to the mean aortic pressure during maximal hyperemia [13].

### Echocardiographic analysis

A transthoracic echocardiogram (TTE) [14] was obtained within 24 h after primary PCI and 3 months later. LV ejection fraction was measured from apical four-chamber and two-chamber views using the modified Simpson method. As recommended by the American Society of Echocardiography, the wall motion score index (WMSI) was assessed in a 16-segment model [15]. An experienced cardiologist who was blinded to the IMR rated segmental wall motion as follows: normal or hyperkinesis = 1, hypokinesis = 2, akinesis = 3, and dyskinesis or aneurysmatic = 4. WMSI was calculated as the sum of all scores divided by the number of segments visualized.

### Angiographic analysis

TIMI flow grade and TIMI myocardial perfusion grade were rated using grades 0–3 on the basis of final cine

images obtained after reperfusion therapy, as described previously [2].

### Primary and secondary endpoints

The primary endpoint was WMSI at 3 months in pre-specified four IMR and CFR agreement groups. The secondary endpoint was the major adverse cardiovascular and cerebrovascular events (MACCE), which included the incidence of cardiovascular death or admission from congestive heart failure, target vessel failure, and stroke. Rehospitalization for congestive heart failure was defined as hospitalization because of signs and symptoms of heart failure in conjunction with noninvasive imaging findings.

### Statistical analysis

The study cohort included patients who had been enrolled TIME. Statistical analysis was carried out using the SPSS, 21.0 statistical software (SPSS Inc., Chicago, Illinois, USA). Variables are presented as percentage of the number of patients. Continuous variables were presented as mean ± SD. Normally distributed variables were tested using a two-tailed Student's *t*-test for paired or unpaired data, as appropriate. Analyses of categorical variables were carried out using the  $\chi^2$ -test or the Fisher exact test where appropriate. One-way analysis of variance was used to compare differences in the four groups according to the IMR and CFR. Univariate and multivariate logistic regression analyses were carried out to assess the independent predictors of WMSI improvement at 3 months. Kaplan–Meier analysis was used to compare the rate of MACE. A *P* value less than 0.05 was considered statically significant.

## Results

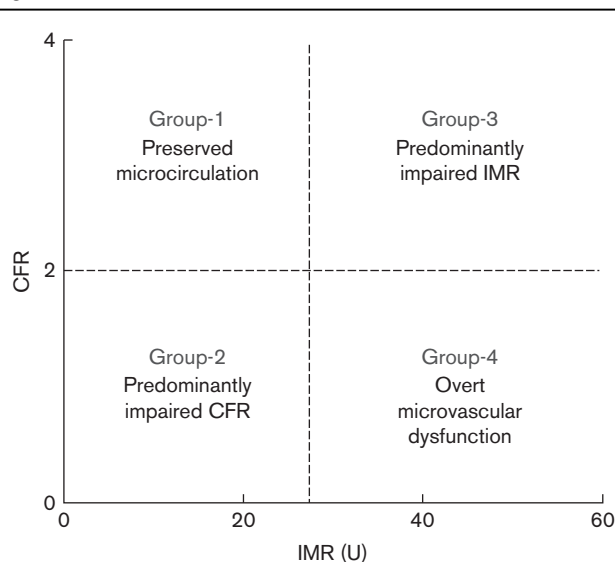
### Baseline characteristics

A total of 89 patients were enrolled in this study. The mean age of the study population was 54 ± 10 years. The mean fractional flow reserve immediately after PCI was 0.91 ± 0.05. The mean IMR was 26.5 ± 16.7 U (8.4–98 U). The mean CFR was 2.09 ± 1.09 (0.98–6.25).

### Classification of four IMR and CFR agreement groups

Then, enrolled patients were classified into four groups using cutoff CFR and IMR values on the basis of previous articles [8,16] (CFR > 2 and mean IMR): group-1 (CFR > 2 and IMR ≤ 27); group-2 (CFR ≤ 2 and IMR ≤ 27); group-3 (CFR > 2 and IMR > 27); and group-4 (CFR < 2 and IMR > 27) (Fig. 1). The demographic, laboratory, and echocardiographic parameters of the four groups are shown in Table 1. The patients in group-2 and group-3 were younger (52.8 ± 8.9 vs. 59.9 ± 11.3 years, *P* < 0.01) and had shorter symptom-to-balloon times (209 ± 117 vs. 328 ± 238 min, *P* = 0.02) than those in group-4.

Fig. 1



Conceptual classification of microcirculation according to IMR and CFR agreement. CFR, coronary flow reserve; IMR, index of microcirculatory resistance.

#### Infarct burden in four IMR and CFR agreement groups at baseline and 3 months later

On baseline TTE, group-1 showed a significantly lower WMSI compared with group-2 ( $1.33 \pm 0.25$  vs.  $1.51 \pm 0.28$ ,  $P=0.01$ ). Similarly, baseline WMSI was slightly lower in group-3 than group-4 ( $1.39 \pm 0.26$  vs.  $1.60 \pm 0.29$ ,  $P=0.06$ ).

On performing TTE 3 months later, a significant improvement in WMSI was found in group-1 ( $1.33 \pm 0.25$  vs.  $1.16 \pm 0.15$ ,  $P<0.01$ ), group-2 ( $1.51 \pm 0.28$  vs.  $1.40 \pm 0.32$ ,  $P<0.01$ ), and group-3 ( $1.39 \pm 0.26$  vs.  $1.18 \pm 0.23$ ,  $P=0.04$ ), whereas group-4 did not show an improvement in WMSI ( $1.60 \pm 0.29$  vs.  $1.56 \pm 0.34$ ,  $P=0.06$ ) (Fig. 2). In multivariate analysis, the IMR and CFR agreement groups included of group-1, group-2, and group-3 were strong independent predictors of WMSI improvement at 9 months (Table 2).

#### Outcome measures in the IMR and CFR agreement groups

During the median follow-up of 3.0 years, there were 10 MACCEs, including two cardiovascular deaths, five target vessel revascularizations, one hospitalization for heart failure, and two strokes. During the entire follow-up period, incidence of MACCE was none in group-1, four (10.0%) in patients of group-2 and group-3, and six (23.1%) in group-4 ( $P=0.04$ ). Incidences of MACCE in patients of group-2 and group-3 were lower than those in group-4 (hazard ratio 0.45,  $P=0.20$ , 95% confidence interval: 0.13–1.59). The Kaplan–Meier curves showing the relationship among the IMR and CFR agreement group and event-free survival from MACCE are shown in Fig. 3.

## Discussion

In this study, we complementarily assessed microcirculation in STEMI patients with combined IMR and CFR. The enrolled STEMI patients who underwent successful primary PCI were classified into group-1 ( $n=23$ ,  $\text{IMR} \leq 27$  U,  $\text{CFR} > 2$ ), group-2 ( $n=39$ ,  $\text{IMR} > 27$  U,  $\text{CFR} > 2$ ), group-3 ( $n=9$ ,  $\text{IMR} \leq 27$  U,  $\text{CFR} \leq 2$ ), and group-4 ( $n=26$ ,  $\text{IMR} > 27$  U,  $\text{CFR} \leq 2$ ). On performing TTE 3 months later, group-4 did not show LV functional improvement, whereas group-2 and group-3 showed significant LV functional improvement, reflecting the presence of viable myocardium. Finally, group-2 and group-3, who also had either impaired CFR or IMR, showed better long-term prognosis including cardiovascular death, heart failure, target vessel failure, and stroke compared with group-4 (group-1 = 0%, group-2, and group-3 = 10%, group-4 = 23.1%,  $P=0.04$ ). This finding indicates that comprehensive assessment of microcirculation using combined IMR and CFR may precisely discriminate the presence of myocardial viability and predict long-term prognosis of STEMI patients.

As a readily available method for assessing microcirculation after primary PCI, the IMR and CFR have been studied widely in STEMI patients. Fearon *et al.* [17] reported that STEMI patients with IMR more than 32 U did not show improvement in WMSI on TTE 3 months later ( $29.9 \pm 7.0$  vs.  $27.9 \pm 6.8$ ,  $P=0.44$ ). STEMI patients with elevated IMR defined with mean IMR ( $\text{IMR} > 40$  U) immediately after primary PCI showed higher cardiovascular death and heart failure admission than STEMI patients with IMR of 40 or less ( $17.1$  vs.  $6.6\%$ ,  $P=0.027$ ) [16]. Matthijs *et al.* [8] suggested that the CFR is also strongly correlated with LV functional recovery after myocardial infarction.

The IMR is calculated in a maximal hyperemic state; it shows superior reproducibility and less hemodynamic dependence [18]. Inversely, the IMR does not consider resting coronary blood flow; thus, vasodilatory reserve is not reflected in the IMR. In contrast, the CFR is formed by dividing the hyperemic coronary flow by the resting coronary flow. Although the CFR is variably affected by resting hemodynamic change and epicardial stenosis [18], it allows for direct measurement of vasodilatory flow reserve at the infarct-related artery. A previous study reported that there was only a modest correlation between IMR and CFR on acute myocardial infarction patients [19], which may support different characteristics of IMR and CFR in terms of estimating microcirculation. The pathophysiological mechanisms of MVD in the STEMI condition are multifactorial [20]; thus, a comprehensive assessment of microcirculation with multiple modalities that could reflect structural impairment and functional aspects could be better to determine the actual condition of microcirculation.

Table 1 Clinical, angiographic, and physiologic differences among the four microcirculation groups

	Group-1 (N=23) (IMR ≤ 27, CFR > 2)	Group-2 (N=31) (IMR ≤ 27, CFR ≤ 2)	Group-3 (N=9) (IMR > 27, CFR > 2)	Group-4 (N=26) (IMR > 27, CFR ≤ 2)	P value
Age (years)	51.7 ± 9.7	52.1 ± 9.0	55.0 ± 9.0	59.9 ± 11.3	0.01
Male [n (%)]	23 (100)	28 (90.3)	8 (88.9)	19 (73.1)	0.04
Door-to-balloon time (min)	69.8 ± 18.0	70.2 ± 46.6	96.9 ± 44.5	79.3 ± 30.7	0.21
Symptom-to-balloon time (min)	201 ± 86	200 ± 122	240 ± 99	329 ± 238	0.01
Hypertension [n (%)]	10 (43.5)	13 (41.9)	3 (33.3)	14 (53.8)	0.69
Diabetes [n (%)]	8 (34.8)	10 (32.3)	1 (11.1)	9 (34.6)	0.58
Dyslipidemia [n (%)]	10 (43.5)	14 (45.2)	3 (33.3)	10 (38.5)	0.90
Smoker [n (%)]	17 (73.9)	26 (83.9)	7 (77.8)	16 (61.5)	0.29
CK peak (IU/l)	2092 ± 1760	3311 ± 3098	2054 ± 1538	3971 ± 2302	0.03
CK-MB peak (ng/ml)	177 ± 136	305 ± 256	236 ± 171	365 ± 270	0.03
Trop I peak (ng/ml)	45.1 ± 45.1	94.2 ± 101.8	53.0 ± 53.8	121.4 ± 90.4	0.03
Stent diameter (mm)	3.2 ± 0.3	3.0 ± 0.3	3.1 ± 0.3	3.1 ± 0.3	0.13
Stent length (mm)	24.4 ± 7.3	24.6 ± 9.4	25.6 ± 9.8	27.3 ± 10.0	0.66
Coronary territory [n (%)]					0.91
LAD	14 (60.9)	23 (74.2)	7 (77.8)	18 (69.2)	
LCX	3 (13.0)	4 (12.9)	1 (11.1)	3 (11.5)	
RCA	6 (26.1)	4 (12.9)	1 (11.1)	5 (19.2)	
Multivessel	29 (76.3)	23 (63.9)	11 (64.7)	21 (67.7)	0.67
Thrombus aspiration	16 (42.1)	15 (41.7)	11 (64.7)	19 (61.3)	0.17
G IIb/IIIa inhibitors	7 (18.4)	6 (16.7)	1 (5.9)	7 (22.6)	0.53
Initial TIMI [n (%)]					0.10
0/1	9 (39.1)	21 (67.7)	6 (66.7)	21 (80.8)	
2	8 (34.8)	4 (12.9)	2 (22.2)	3 (11.5)	
3	6 (26.1)	6 (19.4)	1 (11.1)	2 (7.7)	
Final TMPG [n (%)]					0.01
1	0 (0)	1 (3.2)	1 (11.1)	7 (26.9)	
2	9 (39.1)	10 (32.3)	5 (55.6)	11 (31.4)	
3	14 (60.9)	20 (64.5)	3 (33.3)	8 (30.8)	
Baseline LVEF (%)	48.7 ± 5.5	45.4 ± 6.0	46.1 ± 3.4	46.6 ± 5.5	0.02
Baseline WMSI	1.33 ± 0.25	1.51 ± 0.28	1.39 ± 0.26	1.60 ± 0.29	< 0.01
3-month LVEF (%)	53.8 ± 5.3	49.5 ± 7.8	52.7 ± 5.7	45.8 ± 7.3	< 0.01
3-month WMSI	1.16 ± 0.15	1.40 ± 0.32	1.18 ± 0.23	1.56 ± 0.34	< 0.01
Physiological parameters					
Pa (hyp) (mmHg)	88.0 ± 13.9	86.0 ± 16.2	92.2 ± 19.1	87.2 ± 17.8	0.79
Pd (hyp) (mmHg)	80.2 ± 12.3	77.8 ± 16.7	87.2 ± 16.0	82.5 ± 16.8	0.46
FFR	0.91 ± 0.05	0.90 ± 0.08	0.92 ± 0.06	0.94 ± 0.11	0.80
Rest Tmn	0.64 ± 0.31	0.29 ± 0.13	1.55 ± 0.66	0.75 ± 0.25	< 0.001
Hyper Tmn	0.20 ± 0.06	0.22 ± 0.07	0.51 ± 0.24	0.53 ± 0.24	< 0.001
CFR	3.20 ± 1.12	1.45 ± 0.32	3.17 ± 1.18	1.49 ± 0.32	< 0.001
IMR (U)	15.7 ± 4.8	16.7 ± 5.1	41.4 ± 13.0	42.1 ± 17.7	< 0.001

CFR, coronary flow reserve; CK, creatine kinase; FFR, fractional flow reserve; hyp, hyperemia; IMR, index of microcirculatory resistance; LAD, left anterior descending artery; LCX, left circumflex artery; LVEF, left ventricular ejection fraction; Pa, aortic pressure; Pd, distal coronary artery pressure; RCA, right coronary artery; TIMI, thrombolysis in myocardial infarction; Tmn, mean transit time; TMPG, thrombolysis myocardial perfusion grade; WMSI, wall motion score index.

Thus, we addressed pilot groups of patients testing an overarching concept of whether microcirculation can be more accurately estimated by a combination of CFR and IMR. In our study, the patients in group-2 and group-3 had an impaired IMR (group-3 vs. group-4,  $41.4 \pm 13.0$  vs.  $42.1 \pm 17.7$  U,  $P=0.91$ ) or CFR (group-2 vs. group-4,  $1.45 \pm 0.32$  vs.  $1.49 \pm 0.32$ ,  $P=0.63$ ) comparable with group-4; nevertheless, they showed a significant improvement in WMSI 3 months later, which would imply the presence of viable myocardium despite a high IMR or a low CFR value. In terms of clinical characteristics, they were younger and had shorter symptom-to-balloon times than group-4. The result of this study showed that the patients having either only impaired IMR (group-3) or CFR (group-2) may have different clinical characteristics and better long-term prognosis compared with the overt MVD group (group-4).

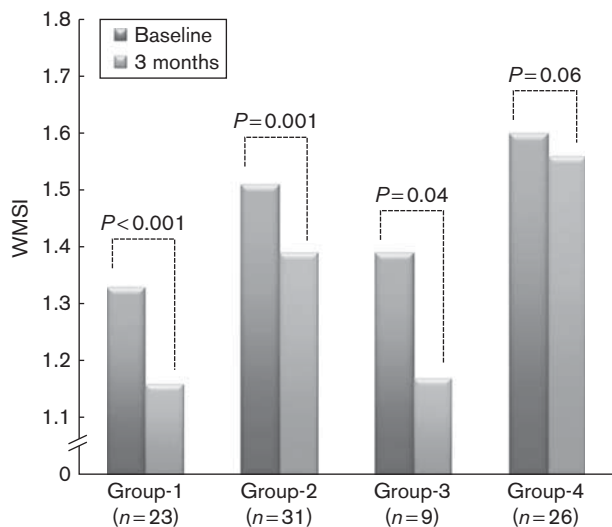
In a cardiac catheterization laboratory, microcirculation of STEMI patients can be complementarily estimated

through IMR and CFR, calculated using the thermodilution method. The main clinical application of this finding is that by assessing microcirculation of STEMI patients with combined IMR and CFR, individual risk stratification from low to very high could be available immediately after reperfusion therapy. Finally, following to clinical risk factors, intensive care including addition medication and advanced treatment such as stem cell therapy could be adapted to high-risk patients at an early stage of MVD [21].

### Study limitations

First, we did not measure the coronary wedge pressure. Simple IMR was assessed in our study as a parameter of microvascular resistance. Functionally severe stenotic lesions were excluded from our study. Consequently, simple IMR could be a reliable parameter of microvascular resistance irrespective of coronary wedge pressure. Second, the IMR and CFR values could differ according to the lesion location and size of myocardium,

Fig. 2



WMSI of four groups at baseline and 3 months later on TTE. When left ventricular functional recovery was estimated as change in WMSI from baseline to 3-month TTE, group-1 ( $1.33 \pm 0.25$  vs.  $1.16 \pm 0.15$ ;  $P < 0.001$ ), group-2 ( $1.51 \pm 0.28$  vs.  $1.40 \pm 0.32$ ;  $P < 0.001$ ), and group-3 ( $1.39 \pm 0.26$  vs.  $1.18 \pm 0.22$ ;  $P = 0.04$ ) showed a significant improvement in left ventricular function, whereas group-4 ( $1.60 \pm 0.29$  vs.  $1.56 \pm 0.34$ ;  $P = 0.06$ ) did not. TTE, transthoracic echocardiography; WMSI, wall motion score index.

Table 2 Univariate and multivariate predictors of WMSI improvement at 3 months

	Hazard ratio	P value	95% CI
<b>Univariate</b>			
Age > 65 years	0.36	0.14	0.095–1.411
Male sex	0.44	0.20	0.123–1.579
Hypertension	0.46	0.09	0.190–1.138
Diabetes mellitus	0.18	< 0.01	0.057–0.594
TMPG 3	1.70	0.13	0.855–3.398
Dyslipidemia	1.05	0.90	0.442–2.528
IMR < 27 U	2.31	0.07	0.913–5.851
Groups 1–3	4.69	0.01	1.449–15.18
<b>Multivariate</b>			
Diabetes mellitus	0.22	0.02	0.062–0.812
Groups 1–3	9.190	0.02	1.250–67.57

The WMSI improvement was defined as a decrease in WMSI > 0.06 at 3 months compared with baseline WMSI.

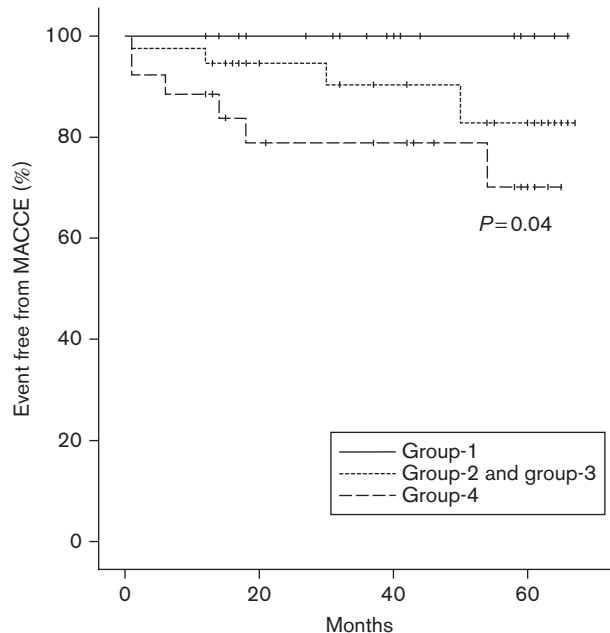
CI, confidence interval; IMR, index of microcirculatory resistance; TMPG 3, thrombolysis myocardial perfusion grade 3; WMSI, wall motion score index.

but the key concept of assessing microcirculation using CFR and IMR agreement could be consistently adapted to other coronary arteries. Finally, we did not subtract the actual central venous pressure. As a significantly elevated central venous pressure could affect the calculation of the physiologic parameters by pressure wire, this could be a confounding parameter for the value of IMR.

**Conclusion**

STEMI patients with either only impaired IMR or CFR showed different clinical characteristics comparable with

Fig. 3



Kaplan–Meier curve presenting the relationship between IMR and CFR agreement groups and event-free survival from MACCE. There was no incidence of MACCE (cardiovascular death, target vessel failure, heart failure, and stroke) in group-1, 10.0% in patients of group-2 and group-3, and 23.1% in group-4 ( $P = 0.04$ ). CFR, coronary flow reserve; IMR, index of microcirculatory resistance; MACCE, major adverse cardiovascular and cerebrovascular events.

patients with overt MVD. They showed a significant improvement in WMSI, reflecting the presence of viable myocardium on performing TTE 3 months later and a lower MACCE rate than the overt MVD group during a 3-year follow-up period. Complimentary assessment of microcirculation by the IMR and CFR may be useful to evaluate myocardial viability and predict the long-term prognosis of STEMI patients.

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**Conflicts of interest**

There are no conflicts of interest.

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