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Distribution and Determinants of Myocardial Perfusion Grade Following Late Mechanical Recanalization of Occluded Infarct-Related Arteries Postmyocardial Infarction: A Report From the Occluded Artery Trial

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Abstract

Objective—To evaluate the distribution and determinants of myocardial perfusion grade (MPG) following late recanalization of persistently occluded infarct-related arteries (IRA).

Background—MPG reflects microvascular integrity. It is an independent prognostic factor following myocardial infarction, but has been studied mainly in the setting of early reperfusion. The occluded artery trial (OAT) enrolled stable patients with persistently occluded IRAs beyond 24 hr and up to 28 days post-MI.

Methods—Myocardial blush was assessed using TIMI MPG grading in 261 patients with TIMI 3 epicardial flow following IRA PCI. Patients demonstrating impaired (0–1) versus preserved (2–3) MPG were compared with regard to baseline clinical and pre-PCI angiographic characteristics.

Results—Impaired MPG was observed in 60 of 261 patients (23%). By univariate analysis, impaired MPG was associated with failed fibrinolytic therapy, higher heart rate, lower systolic blood pressure, lower ejection fraction, LAD occlusion, absence of collaterals ($P < 0.01$) and ST elevation MI, lower diastolic blood pressure, and higher systolic sphericity index ($P < 0.05$). By multivariable analysis, higher heart rate, LAD occlusion, absence of collaterals and higher systolic sphericity index ($P < 0.01$), and lower systolic blood pressure ($P < 0.05$) were independently associated with impaired MPG.

Conclusion—Preserved microvascular integrity was present in a high proportion of patients following late recanalization of occluded IRAs post-MI. Presence of collaterals was independently associated with preserved MPG and likely accounted for the high frequency of preserved myocardial perfusion in this clinical setting. Impaired MPG was associated with baseline clinical and angiographic features consistent with larger infarct size.

Keywords

acute coronary syndrome; total occlusions; collaterals; percutaneous coronary intervention; coronary flow; no reflow

INTRODUCTION

Myocardial perfusion grade (MPG) is an angiographic indicator of microvascular integrity that provides independent prognostic information in patients with myocardial infarction (MI) [1, 2]. In patients treated with reperfusion therapy up to 6 hr following MI onset, MPG tends to be impaired when ischemic time is prolonged, infarct size is larger, and when distal embolization is evident [3–6].

In contrast, MPG following late recanalization of persistently occluded infarct-related arteries has not been studied. Thus, the clinical correlates and significance of MPG in this setting are unknown. The occluded artery trial (OAT) randomized 2,201 patients with persistently occluded infarct-related arteries after the first 24 hr and up to 28 days post-MI to percutaneous coronary intervention (PCI) or medical therapy alone [7,8]. Of these, MPG was assessed in 261 patients assigned to PCI, providing an ideal opportunity to evaluate the distribution and determinants of MPG following late recanalization of occluded infarct-related arteries.

METHODS

Study Population

The study design [7] and primary results [8] of OAT have been published. Briefly, OAT was a multicenter randomized controlled trial that compared a combination of optimal medical therapy and PCI with optimal medical therapy alone in high risk but stable patients with occluded infarct-related arteries after the first 24 hr (calendar day 3) and up to 28 days post-MI.

Inclusion criteria were documented index MI and an occluded infarct-related artery (TIMI Flow Grade 0 or 1) in addition to one of two high-risk criteria—proximal occlusion or ejection fraction less than 50%. Important exclusion criteria included a clinical indication for revascularization (significant angina, severe inducible ischemia, left main or triple vessel disease), serum creatinine > 2.5 mg/dl, severe valvular disease, New York Heart Association Class III or IV heart failure or cardiogenic shock at the time of screening.

MPG was assessed in 261 PCI assigned patients in the ancillary studies OAT cohort which had additional remodeling, viability, and electrophysiological measures obtained [7,9–11]. The source population for this analysis was derived from patients who met OAT inclusion and exclusion criteria, were enrolled at centers participating in the ancillary studies and had immediate post-PCI angiograms suitable for MPG analysis.

Data Collection

Baseline characteristics were recorded from the time of index MI (e.g., cardiac markers, electrocardiogram) to the time of randomization (e.g., history, physical examination). Qualifying coronary and left ventricular angiography was performed after the first 24 hr and

up to 28 days post-MI. Angiographic data were analyzed by experienced readers in a dedicated core angiographic laboratory. Angiographic grading of collateral filling and calculation of left ventricular volumes, ejection fraction, regional wall motion, and sphericity index were performed as described previously [12–15].

PCI

Protocol infarct-related artery PCI with routine stenting was performed within 24 hr of randomization according to standard clinical practice (Table I depicts intervals from index MI to baseline angiography, randomization, and PCI). Anticoagulation was achieved with heparin and all patients received aspirin and either ticlopidine or clopidogrel beginning the day of the procedure or earlier. Use of glycoprotein IIb/IIIa inhibitors was encouraged.

Myocardial Perfusion Grading

The MPG substudy was prospectively planned and participating centers were encouraged to obtain immediate post-PCI angiograms suitable for MPG analysis. Post-PCI angiograms were obtained in multiple projections with prolonged cine runs to visualize myocardial contrast perfusion, or blush. Myocardial blush was graded according to the TIMI MPG criteria [1] by two independent core lab readers (VJ, TS) blinded to clinical data. In case of discrepancies, angiograms were reread independently by both readers and any remaining discrepancies were resolved by a third reader (GBJM). Post-PCI angiograms were also evaluated for residual thrombus and evidence of distal embolization. The present analysis was limited to patients with post-PCI TIMI Flow Grade 3 since it is technically difficult to grade myocardial blush when the epicardial vessel is poorly opacified and moreover, MPG provides clinically relevant additive information over TIMI Flow Grade in patients with good epicardial flow [1].

Statistical Analysis

Categorical variables are expressed as frequencies and percentages and continuous variables as means and standard deviations. Baseline variables were compared between patients with MPG 0 to 1 versus MPG 2 to 3, as in prior studies [3,4]. Categorical variables were compared using Chi-square test or alternatively, Fisher's exact test if expected frequency for any cell in a 2×2 table was <5 . Wilcoxon two-sample test was used to compare time intervals from index MI to baseline angiography, randomization and PCI. Independent sample *t*-test was used to compare other continuous variables which were normally distributed. Correlates of impaired MPG (0 to 1) were examined in a multiple logistic regression model by the backward elimination method including variables with $P < 0.05$ on univariate analysis. The prespecified level of significance for all secondary analyses of OAT was $P < 0.01$, while $P < 0.05$ (but ≥ 0.01) was considered to indicate a strong trend toward statistical significance.

RESULTS

Distribution of MPG

Of 661 patients enrolled in OAT ancillary studies, 338 were assigned PCI and post-PCI TIMI Flow Grade was assessed in 336. The distribution of post-PCI TIMI Flow Grade in these 336 patients was as follows: Grade 0 in 24 (7.1%), Grade 1 in 13 (3.9%), Grade 2 in 19 (5.7%), and Grade 3 in 280 (83.3%). Of the 280 patients with TIMI Flow Grade 3 post-PCI, 261 had angiograms suitable for MPG analysis. The distribution of MPG grades in these 261 patients was as follows: 49 (18.8%) had MPG 0, 11 (4.2%) had MPG 1, 131 (50.2%) had MPG 2, and 70 (26.8%) had MPG 3.

Univariate Correlates of Impaired MPG (Table I and Table II)

Baseline characteristics significantly associated with MPG 0 to 1 were fibrinolytic therapy at presentation with index MI ($P = 0.005$), higher heart rate ($P = 0.001$), lower systolic blood pressure ($P = 0.003$), LAD occlusion ($P < 0.0001$), absence of collaterals ($P = 0.001$), and lower ejection fraction ($P < 0.0001$). There was a strong trend toward association between MPG 0 to 1 and ST elevation MI ($P = 0.02$), lower diastolic blood pressure ($P = 0.04$), higher pre-PCI CK-MB and Troponin T elevation ($P = 0.05$) and higher systolic sphericity index ($P = 0.03$). Absence of collaterals was noted more frequently when the infarct-related artery was the left anterior descending (14.5%) or left circumflex (23.5%) and less frequently with right coronary artery occlusions (3.4%, $P < 0.001$).

Age, sex, coronary artery disease risk factors, prior angina or MI, time from MI to randomization and PCI, Killip Class during index MI and New York Heart Association Class at randomization and pre-PCI ischemia on stress testing were similar between the two groups. Baseline angiographic data showed no difference in pre-PCI TIMI Flow Grade, extent of coronary artery disease, regional wall motion, or mitral regurgitation grade between the groups. In addition, there was no difference in use of glycoprotein IIB/IIIA inhibitors, mean post-PCI residual stenosis, minimal luminal diameter or in the proportion of patients with stent implantation, residual thrombus, distal embolization, or post-PCI CK-MB elevation between groups.

Independent Correlates of Impaired MPG (Table III)

On multivariable analysis, there was a significant independent association between MPG 0 to 1 and higher heart rate ($P = 0.004$), LAD occlusion ($P < 0.001$), absence of collaterals ($P < 0.001$) and higher systolic sphericity index ($P = 0.009$). There was a strong trend toward independent association between MPG 0 to 1 and lower systolic blood pressure ($P = 0.018$).

DISCUSSION

We have demonstrated for the first time that the majority of stable MI survivors with TIMI 3 epicardial flow after successful PCI of a persistently occluded IRA in the days to weeks after the event also have preserved MPG. In addition, we demonstrate an association between absence of angiographically visible collaterals and impaired MPG.

In the context of early reperfusion for MI, MPG is thought to reflect microvascular integrity and is closely associated with infarct size. The present population provided an opportunity to study the relationship between clinical characteristics at the time of index MI and the status of the microvasculature following epicardial artery recanalization after the first 24 hr and up to 28 days following MI.

Distribution of MPG

A high proportion of patients (83.3%) achieved post-PCI TIMI Flow grade 3, and of these, a high proportion (77%) had MPG 2 to 3. Good epicardial and microvascular flow as defined by TIMI Flow grade 3 with myocardial blush grade 2 to 3 was seen in 59.8% of patients following late recanalization in the present study, compared to 76.9% following early reperfusion by primary PCI [16]. Several factors may be responsible for the high rates of epicardial patency and preserved MPG following late IRA recanalization by PCI in the present study. By mandating clinical stability without significant ischemic symptoms despite an occluded IRA, OAT may have favored selection of patients with collateral-perfused viable myocardium. The presence of viable myocardium in turn may be associated with an intact microvasculature and preserved MPG. In addition, stents were implanted in nearly all patients, achieving low post-PCI residual stenosis. Angiographic evidence of residual thrombus and distal embolization

was uncommon after PCI, likely reflecting the use of aspirin, thienopyridines, and glycoprotein IIb/IIIa inhibitors.

Infarct Size and MPG

Patients with baseline clinical and angiographic features suggesting larger initial infarct size (LAD occlusion, higher heart rate, lower blood pressure, higher pre-PCI CK-MB and Troponin T elevation, lower ejection fraction, and higher systolic sphericity index) subsequently demonstrated impaired MPG following PCI. This is in agreement with previous studies suggesting that infarct size is an important determinant of microvascular obstruction [17–19]. Microvascular obstruction leading to impaired regional myocardial perfusion despite restoration of epicardial patency is believed to be the pathophysiologic basis for impaired MPG. Kloner et al. in an experimental coronary occlusion model showed that ultrastructural evidence of microvascular damage was always preceded by myocardial cell injury, implying that microvascular disruption is a consequence of progressive cell necrosis during the infarction process [17]. Infarct size was shown to be a major determinant of reflow following release of coronary occlusion in an experimental model of coronary occlusion and reperfusion [18]. In patients with acute MI, contrast-enhanced magnetic resonance imaging after successful primary PCI showed that microvascular obstruction occurred in conjunction with severe transmural necrosis and was associated with longer ischemic time and higher troponin elevation (consistent with larger infarct size) compared to transmural necrosis without microvascular obstruction or non-transmural necrosis [19]. Moreover, contrast-enhanced magnetic resonance imaging and multidetector computed tomography have shown that microvascular obstruction is located within the necrotic core of large infarcts [20,21].

Infarct size was measured by technetium-99m sestamibi imaging in a pooled patient-level analysis of four recent trials of primary or rescue PCI [22]. Important independent predictors of larger infarct size in that study included LAD occlusion, pre and post-PCI TIMI Flow Grade and failed fibrinolytic therapy prior to PCI [22]. Other studies have shown that failed fibrinolytic therapy prior to rescue or facilitated PCI is associated with larger infarct size and greater extent of infarct transmural extent [23] and have suggested that myocardial salvage by PCI is attenuated when performed after failed fibrinolytic therapy [24]. However, microvascular perfusion was not assessed in these studies of PCI following failed fibrinolytic therapy. We found that failed fibrinolytic therapy was significantly associated with impaired MPG following late recanalization of occluded IRAs by PCI. The association was no longer significant when adjusted for multiple variables that correlate with infarct size. This suggests that impaired post-PCI MPG in patients with failed fibrinolytic therapy is related to larger infarct size in these patients, an observation that is consistent with that of Ito et al. who found microvascular obstruction following infarct-related artery recanalization by fibrinolytic therapy to be associated with poor functional recovery, suggesting that microvascular disruption resulted from extensive myocardial necrosis [25].

The higher frequency of impaired MPG in patients with LAD occlusion may be related to larger infarct size in these patients. In addition, absence of collaterals, noted more frequently with LAD occlusion, may have further contributed to the higher frequency of impaired MPG in this subset.

MPG in the Context of OAT Results

The high rates of epicardial patency and preserved microvascular integrity following late recanalization in this subset of OAT needs to be placed in the context of the lack of clinical benefit with PCI in the overall OAT population. In the setting of early reperfusion, shorter time to reperfusion is associated with smaller infarct size, preserved microvascular integrity, and better MPG [3]. The lack of association between time to reperfusion and MPG in the present

study suggests that extent of infarct and microvascular obstruction likely stabilized before the time window for inclusion in OAT. Moreover, presence of collaterals was an important independent correlate of better MPG. This further suggests that in this population with stabilized infarcts, collateral flow may contribute to preserved viability and microvascular integrity within the occluded infarct-related artery territory. With regard to the overall OAT population, a significant proportion had collaterals (88%) and these were equally distributed in the PCI and medical therapy arms [8]. The presence of stabilized infarcts with collateral-dependent viable myocardium may portend less potential for myocardial salvage and moreover, clinical benefit from PCI may be potentially offset by adverse consequences of procedure-related distal embolization or reocclusion.

Implications

The association between collateral flow and preserved MPG is an important observation and adds to the literature on the significance of collaterals in the setting of occluded infarct-related arteries post-MI. These observations also revisit the question of viability testing post-MI to guide intervention. Our results suggest that in patients with collateral flow and viable myocardium, late recanalization of occluded infarct-related arteries may not necessarily achieve myocardial salvage. The prognostic significance of MPG was not directly addressed in this study. However, given the association of impaired MPG with markers of larger infarct size in the present study and the independent prognostic significance of MPG in the setting of early reperfusion, MPG may be expected to provide clinically relevant information in the setting of late recanalization of infarct-related arteries.

Limitations

The study population was relevant to examining the benefit of routine late PCI compared to medical therapy alone in patients with occluded infarct-related arteries post-MI and the results cannot be extrapolated to all patients undergoing late PCI after MI. Assessment of myocardial blush is semiquantitative and provides an estimate of the severity but not the spatial extent of microvascular obstruction. Moreover, MPG provides a “snapshot” of the microvasculature immediately after restoration of epicardial flow. A strength of the MPG technique is that it can be readily integrated into clinical studies involving PCI in patients with MI, obviating the need for additional procedures to assess the microvasculature.

CONCLUSION

Preserved microvascular integrity as assessed by MPG was present in a high proportion of this group of high risk but stable patients following late PCI of occluded infarct-related arteries post-MI. Presence of angiographically visible collaterals was independently associated with preserved MPG and likely accounted for the high frequency of preserved myocardial perfusion in this clinical setting. Impaired MPG was associated with baseline clinical and angiographic features consistent with larger infarct size.

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TABLE I**Baseline Clinical Characteristics by Post-PCI MPG**

	Post-PCI MPG 0 to 1, <i>N</i> = 60	Post-PCI MPG 2 to 3, <i>N</i> = 201	<i>P</i> value
Male, %	81.7	78.1	0.55
Age yrs, mean (SD)	54.6 (9.1)	57.3 (10.8)	0.08
Diabetes, %	18.3	16.9	0.80
Hypertension, %	48.3	51.2	0.69
Hyperlipidemia, %	43.3	60.2	0.02
Family history of CAD, %	40.0	43.3	0.65
Current smoker, %	45.0	36.3	0.22
Prior angina, %	18.3	17.4	0.87
Prior MI, %	8.3	9.4	0.79
Interval from MI to baseline angiogram (days), median (IQR)	5 (4, 9.5)	6 (3, 11)	0.50
Interval from MI to randomization (days), median (IQR)	9 (5, 17)	10 (6, 20)	0.25
Interval from MI to PCI (days), median (IQR)	10 (6, 19.5)	11 (7, 21)	0.25
Interval from baseline angiogram to PCI (days), median (IQR)	2 (1, 7)	2 (0, 7)	0.92
Heart rate beats/min, mean (SD)	74.3 (12.6)	68.3 (10.4)	0.001
Systolic blood pressure mm Hg, mean (SD)	112.4 (16.6)	119.1 (15.1)	0.003
Diastolic blood pressure mm Hg, mean (SD)	69.3 (11.8)	72.5 (10.1)	0.04
Fibrinolytic therapy during first 24 hr of index MI (%)	31.7	15.4	0.005
ST elevation >0.1mV, %	78.3	61.4	0.02
ST depression > 0.1 mV, %	73.3	71.4	0.77
Maximum pre-PCI Total CK divided by ULN, mean (SD)	9.2 (6.0)	7.0 (7.6)	0.07
Maximum pre-PCI CK MB divided by ULN, mean (SD)	18.3 (22.0)	10.6 (13.4)	0.05
Maximum pre-PCI TNI divided by ULN, mean (SD)	284.0 (493.5)	241.2 (605.7)	0.71
Maximum pre-PCI TNT divided by ULN, mean (SD)	159.6 (160.8)	51.4 (68.0)	0.05
Killip Class > 1 during index MI,%	10.0	14.4	0.38
NYHA Class > 1 at randomization,%	8.3	11.0	0.56
Presence of ischemia in IRA territory on pre-PCI stress testing, <i>N</i> (%)	8/19 (42.1%)	23/62 (37.1%)	0.69

PCI, percutaneous coronary intervention; MPG, myocardial perfusion grade; SD, standard deviation; CAD, coronary artery disease; MI, myocardial infarction; IQR, interquartile range; ULN, upper limit of the local laboratory normal; CK, creatine kinase; TNI, troponin I; TNT, troponin T.

TABLE II
Angiographic and Procedural Characteristics by Post-PCI MPG

	Post-PCI MPG 0 to 1, N = 60	Post-PCI MPG 2 to 3, N = 201	P value
Pre-PCI coronary angiography			
IRA–LAD, %	53.3	22.4	<0.0001
IRA–Circ, %	25.0	9.4	
IRA–RCA, %	21.7	68.2	
IRA TIMI Flow Grade 0 to 1, %	100	99	1.00
Collaterals absent, %	20	6	0.001
Multivessel disease (>70% stenosis), %	15.0	16.4	0.79
Pre-PCI left ventricular angiography			
LVEF, mean(SD)	43.8, (10.5)	50.8 (8.8)	<0.0001
Infarct Segment Regional Wall Motion SD/Chord, mean (StdDev)	−3.2 (0.7)	−2.9 (1.0)	0.06
Diastolic Sphericity Index, mean (SD)	30.6 (6.6)	30.1 (6.4)	0.63
Systolic Sphericity Index, mean (SD)	24.6 (6.8)	22.6 (5.7)	0.03
Mitral Regurgitation present, %	21.6	33.9	0.09
Procedural characteristics and post-PCI angiography			
Glycoprotein IIB/IIIa inhibitor use during PCI (%)	70.0	69.2	0.90
Residual thrombus (%)	8.3	4.0	0.18
Distal embolization (%)	5.0	7.5	0.77
Post-PCI in-stent residual % diameter stenosis, mean, SD	14.8 (14.0)	14.0 (12.3)	0.69
Post-PCI in-lesion residual % diameter stenosis, mean, SD	32.1 (18.7)	29.6 (14.5)	0.34
Post-PCI Minimal Luminal Diameter mm, mean, SD	2.1 (0.7)	2.2 (0.5)	0.13
Stent implanted, %	96.7	99.5	0.13
Occurrence of post-PCI CK-MB elevation ^a (>ULN), %	4.8	6.5	1.00

IRA, infarct-related artery; LAD, left anterior descending coronary artery; RCA, right coronary artery; Circ, left circumflex coronary artery; TIMI, thrombolysis in Myocardial infarction; LVEF, left ventricular ejection fraction, other abbreviations as in Table 1.

^aPost-PCI CK-MB elevation was present in 2/42 patients with MPG 0 to 1 and in 10/153 patients with MPG 2 to 3.

TABLE III

Multivariable Correlates of Post-PCI MPG 0 to 1 (N = 224)

Covariates	<i>P</i> value	Odds ratio	95% Confidence interval for odds ratio	
Heart rate	0.004	1.652	1.176	2.319
Systolic blood pressure	0.018	1.349	1.054	1.726
LAD occlusion	<0.001	4.120	1.919	8.846
Absence of collaterals	<0.001	6.303	2.277	17.452
Systolic sphericity index	0.009	2.228	1.218	4.074

Odds ratios are for 10 unit increase in heart rate and systolic sphericity index and for 10 unit decrease in systolic blood pressure.