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# Epidemiology of Coronary Microvascular Obstruction

Giampaolo Niccoli[1], Rocco A. Montone[2]

[1]INSTITUTE OF CARDIOLOGY, CATHOLIC UNIVERSITY OF THE SACRED HEART, ROME, ITALY
[2]CATHOLIC UNIVERSITY OF THE SACRED HEART, ROME, ITALY

## Introduction

ST-elevation myocardial infarction (STEMI) is caused by rupture or erosion of an atherosclerotic plaque, complicated by intraluminal thrombus formation that causes partial or complete occlusion of a coronary artery [1–3]. Primary percutaneous coronary intervention (PPCI) is nowadays the preferred reperfusion strategy for treating acute STEMI, aiming at restoring epicardial infarct-related artery patency, and achieving microvascular reperfusion as early as possible, thus limiting the extent of irreversibly injured myocardium [4]. Yet, in a sizeable proportion of patients, PPCI achieves epicardial coronary artery reperfusion but not myocardial reperfusion due to the occurrence of coronary microvascular obstruction (CMVO), a condition clinically known as no-reflow [5–7]. Originally, the existence of the no-reflow phenomenon was debated; however, a large amount of experimental and clinical data have now clearly shown that myocardial no-reflow can occur, with a variable prevalence, ranging from 5% up to 50%, according to the methods used to assess the phenomenon and to the population under study [6–9]. Indeed, CMVO can be assessed using different techniques and at different time points after STEMI. In the catheterization laboratory, after PPCI, it can be assessed with thrombolysis in myocardial infarction (TIMI) flow grade and myocardial blush grade (MBG) evaluation; in the coronary care unit, by assessing the electrocardiographic ST-segment elevation resolution (STR); and it can be better quantified, during in-hospital staying or later at follow-up, by noninvasive imaging techniques, such as myocardial contrast echocardiography (MCE) and contrast-enhanced cardiac magnetic resonance (CMR), which both allow direct visualization and quantification of the no-reflow areas [9] (Fig. 3–1).

In this chapter, we review the available data regarding the incidence of CMVO in STEMI patients according to different reperfusion strategies (PPCI, effective thrombolysis, and rescue PCI) and according to the different modalities of its detection. Finally, we analyzed data in the literature reporting the incidence of CMVO in different clinical subsets (diabetes, chronic kidney disease, women, and latecomers) and different subset of lesions (saphenous vein graft (SVG)).

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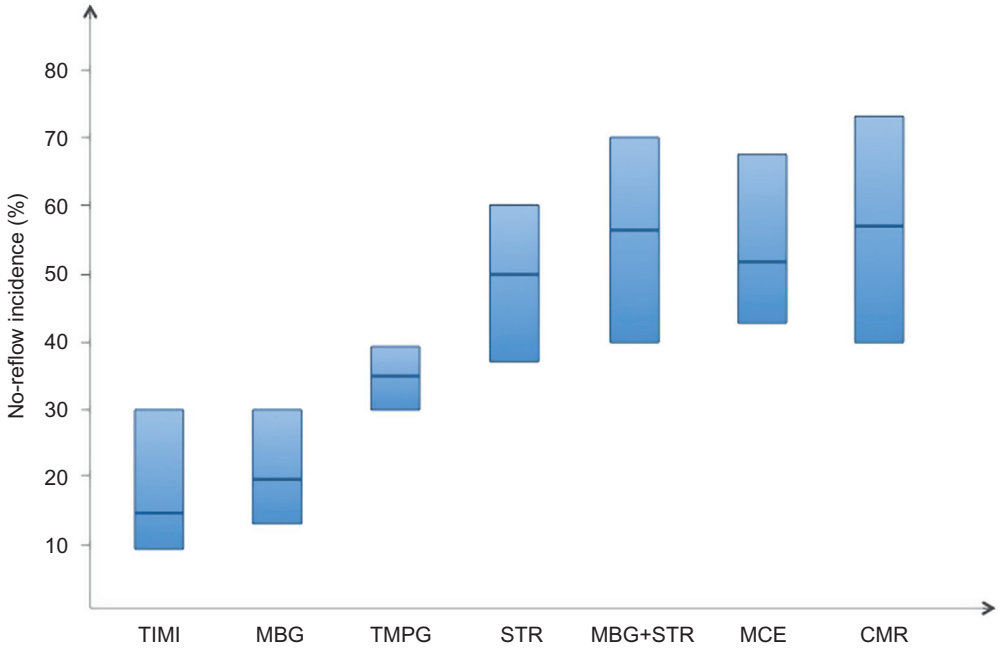


**FIGURE 3–1** Percentage of ST-elevation myocardial infarction patients, treated by primary percutaneous coronary intervention, showing no-reflow according to main no-reflow indexes (*TIMI*, thrombolysis in myocardial infarction flow grade;*TMPG*, TIMI myocardial perfusion grade; *MBG*, myocardial blush grade; *STR*, ST-segment resolution; *MCE*, myocardial contrast echocardiography; *CMR*, cardiac magnetic resonance).

# Incidence of Coronary Microvascular Obstruction in Patients Treated With Primary Percutaneous Coronary Intervention According to Different Diagnostic Techniques

## Angiographic Indexes

TIMI flow grade was originally used for the diagnosis of no-reflow in the setting of acute myocardial infarction [10]. In 1996, Ito et al. [10] reviewed the cine-angiograms of 86 STEMI patients who achieved revascularization by PCI within 12 hours of symptoms onset and TIMI grade 2, defined as no-reflow, was observed in 18 patients (21%), while the other 68 (79%) patients showed TIMI grade 3 after recanalization. In 1998, with the introduction of MBG, Van't Hof et al. [11] studied 777 patients who underwent PPCI and they found that MBG 0 and 1, suggestive of no-reflow, were observed in 5.8% and 24.6% of patients, respectively. Of note, in this study population, MBG 0 to 1, was observed in as high as 50% of patients with TIMI flow grade 3 [236 (30%) with MBG 0 to 1 vs 87 (11%) with TIMI flow 0 to 2], highlighting the need of MBG assessment in order to avoid the underestimation of no-reflow incidence. More recently, in the Thrombus Aspiration during Percutaneous Coronary Intervention in Acute Myocardial Infarction Study (TAPAS) trial [12], where slightly more than a thousand of patients

were enrolled, the authors found that final TIMI flow was of 0, 1, or 2 in 72 of the 501 patients (14%) who underwent thrombus-aspiration and in 87 of the 496 patients (17.5%) who underwent conventional-PPCI. Post-procedural MBG 0 or 1 occurred in 84 of the 490 patients (17.1%) in the thrombus-aspiration group and in 129 of the 490 patients (26.3%) in the conventional-PPCI group. Similar results were also shown in the thrombectomy with export catheter in infarct-related artery during primary percutaneous coronary intervention (EXPIRA) [13] and Randomized Evaluation of the Effect of Mechanical Reduction of Distal Embolization by Thrombus Aspiration in Primary and Rescue Angioplasty (REMEDIA) trial [14], where the use of a manual thrombus-aspirating device translated in a significant reduction of no-reflow incidence. To this regard, De Vita et al. [15] pooled the single patients' baseline and post-PCI clinical and angiographic data from three randomized trials comparing thrombus-aspiration with PPCI in STEMI patients. The trials included were the REMEDIA trial [14], the Polish-Italian-Hungarian RAndomized ThrombEctomy (PIHRATE) trial [16], and the Export study by Noel et al. [17]. The whole study population was analyzed according to the time to treatment (time from symptom onset to catheter laboratory), which was categorized as $<3$ hours (short time to treatment subgroup), $>3$ hours to $\geq 6$ hours (intermediate time to treatment subgroup), and $>6$ hours to $\leq 12$ hours (long time to treatment subgroup). A total of 299 patients (150 in thrombus-aspiration group and 149 in standard PPCI group) entered the study. In the standard PPCI group, increasing time to treatment was associated with a decreased rate of optimal reperfusion (27.4% vs 17.9% vs 10%, $P$ for trend $= 0.06$), defined as the combination of MBG 2 or 3 at post-PCI angiography and STR $>70\%$ at post-PCI electrocardiogram, whereas in the thrombus-aspiration group, the same trend was not seen (40.9% vs 33.8% vs 50%, $P$ for trend $= 0.93$). TIMI flow was $<3$ in 13% patients in the thrombus-aspiration group and 23% in the placebo group, while MBG was $<2$ in 19% and 36% patients, respectively in the two groups. However, recent data from TOTAL and TASTE trials did not show a clinical benefit deriving from routine use of thrombus-aspiration in STEMI patients [18,19]. This study further demonstrated that the incidence of no-reflow may be variable according to the study population investigated, and, importantly, ischemic time and mechanical thrombus-aspiration may both play a crucial role in the occurrence of this detrimental phenomenon (Fig. 3−2).

Moreover, microvascular resistance measured either by the use of a Doppler-tipped angioplasty guidewire or thermodilution can be assessed immediately after infarct-artery reperfusion in the catheterization laboratory. Microvascular integrity plays a pivotal role in myocardial viability assessment [20], which is crucial to predict prognosis in patients with acute myocardial infarction [21]. The thermodilution-derived index of microcirculatory resistance (IMR) has been proposed and validated for assessing the status of microcirculation. In the setting of STEMI patients, Fearon et al. [22] measured IMR in 29 patients undergoing PPCI and they reported that IMR only was an independent predictor of acute microvascular damage, as assessed by corrected TIMI frame count (TFC) and TIMI myocardial perfusion grade (TMPG), and of 3-month left ventricular functional recovery. Of note, IMR (cut off $\leq 32$U) correlated significantly with the peak creatinine kinase while other angiographic measures of microvascular dysfunction, such as TMPG and TFC, did not. However, it is worth noting that this study was not performed in homogenously selected patients with a

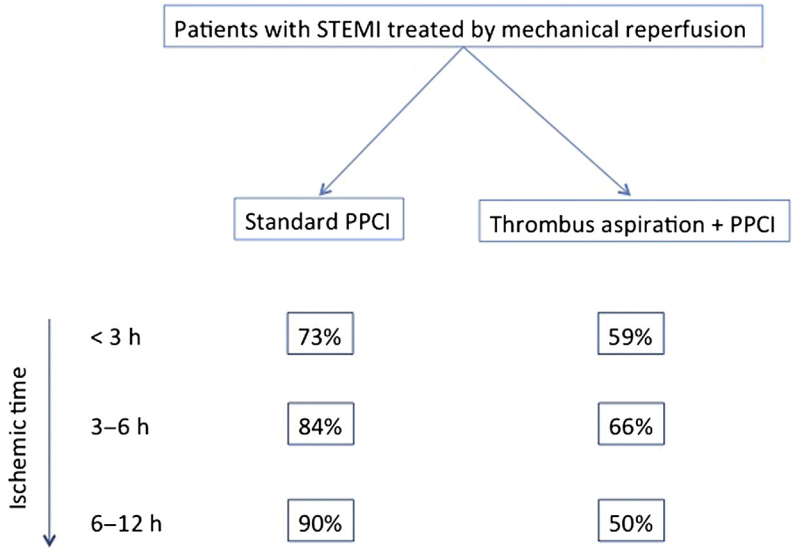


**FIGURE 3–2** Percentage of ST-elevation myocardial infarction (STEMI) patients showing no-reflow, defined as myocardial blush grade <2 and ST-segment resolution <70% post-revascularization, treated by primary percutaneous coronary intervention (PPCI), according to the use or not of thrombus-aspiration and different ischemic time. *Adapted from M. De Vita, F. Burzotta, I. Porto, et al., Thrombus aspiration in ST elevation myocardial infarction: comparative efficacy in patients treated early and late after onset of symptoms, Heart 96 (2010) 1287–1290.*

similar culprit vessel location. To overcome this limitation, Lim et al. [23] measured IMR immediately after PPCI in 40 patients with first anterior acute myocardial infarction. Among the study population, 21 patients showed IMR $\leq 33$ and 19 patients revealed IMR $>33$ and the authors demonstrated that IMR was a useful on-site measure for predicting myocardial viability in earlier recovery phase, as assessed by 18 fluorodeoxyglucose positron emission tomography, and left ventricular wall motion recovery at 6-month follow-up, as assessed by echocardiography [24,25]. Microvascular resistance assessment in the catheterization laboratory may represent a useful tool in order to study new therapies to improve myocardial salvage.

## Cardiac Magnetic Resonance

No-reflow is classically diagnosed during coronary angiography using the TIMI flow grade, MBG, and TFC [9]. CMR provides additional information on the effects of no-reflow at a myocardial level, enabling the measurement of CMVO and tissue edema [26,27]. In 1998, Wu et al. [27] evaluated 44 patients undergoing contrast-enhanced-CMR $10 \pm 6$ days after myocardial infarction and microvascular obstruction, defined as hypoenhancement seen 1 to 2 minutes after contrast injection, was observed in 25% of the study population. Interestingly, infarct-related artery status, as assessed by TIMI flow analysis, correlated with microvascular status, even if 5 out of the 11 patients with CMR microvascular obstruction had TIMI 3 flow.

In 2003, Tarantini et al. [28] found, in 77 patients with PPCI-treated STEMI patients, a no-reflow incidence, defined as images of severe microvascular obstruction, in 25 (32%) patients. However, higher incidences of CMVO occurrence have been observed when using CMR indexes. Eitel et al. [29] examining 128 consecutive STEMI patients undergoing PPCI $<12$ hours after symptoms onset, found that 73 patients (57%) had signs of late CMVO at CMR, after a median time of 3 days from the index event. Accordingly, Jesel et al. [30], in 50 STEMI patients treated by PPCI that underwent scoring of contrast defects detected at CMR (from $0 =$ no hypoenhancement to $3 =$ strong hypoenhancement), found that score $1-3$ was observed in 90% of the patients and major microvascular obstruction (score $2-3$) in 54%. Similar results were shown by Nijveldt et al. [31] who found that CMVO was demonstrated on late gadolinium-enhanced-CMR images in 54% of the study population. In 2008, Bruder et al. [32] analyzed data from the Herzinfarktverbund Essen (HIVE) registry including 143 patients in whom early CMR imaging was performed and signs of microvascular obstruction occurrence were present in 61% of patients. A recent study of Durante et al. [33] enrolling 88 consecutive STEMI patients treated with PPCI within 12 hours from symptoms onset found that 31 patients (36%) had evidence of no-reflow, whereas 58 (67%) had CMVO. One no-reflow patient did not have CMVO. In contrast, no-reflow was present in 30 of 58 CMVO patients. The occurrence of no-reflow and CMVO is significantly different and might be explained by many factors, including the time of their assessment. Angiographic no-reflow varies between 5% and 10% using TIMI flow grade to around 30% using MBG, whereas CMVO at CMR can be observed in $>50\%$ of STEMI patients [9]. Thus, CMR should be considered a sensitive and reliable tool for CMVO detection and quantification. Moreover, using CMR it is possible to detect irreversible CMVO due to intra-myocardial hemorrhage. Of note, intra-myocardial hemorrhage occurs in $\sim 40\%$ of STEMI patients and is associated with larger infarct size, adverse left ventricular remodeling, and worse clinical outcome [34,35].

Of importance, CMR represents the most reliable technique in order to detect the incidence and the extent of CMVO, although other techniques such as MCE and electrocardiographic ST-resolution may be useful to monitor CMVO evolution [9].

## Myocardial Contrast Echocardiography

Ito et al. first described the significance of no-reflow detected by intracoronary MCE despite successful recanalization with thrombolysis or PPCI by studying 39 patients with STEMI [36]. They observed that 30 patients (77%) had significant contrast enhancement within the risk area, while the other 9 patients (23%) showed the residual contrast defect in the risk area. In particular, they showed for the first time that TIMI flow 3 is an unreliable index of good reperfusion, as no-reflow areas at MCE may be still present in case of final TIMI flow 3. A subsequent intracoronary MCE clinical study investigated 199 patients at a mean of 15 minutes following PPCI [37] and no-reflow within the risk area was observed in 79 patients (40%). Additionally, studying temporal evolution and functional outcomes of no-reflow in 24 STEMI patients undergoing successful coronary recanalization by thrombolysis or PPCI, Galiuto et al. [38] found that no-reflow detected at 24 hours may be sustained or spontaneously reversible

at 1 month, with such reversibility being associated with preserved left ventricular volumes and function. Finally, in the acute myocardial infarction contrast imaging (AMICI) study [39], that included 110 patients treated by successful PPCI, the authors showed myocardial no-reflow in 64% of patients in an early evaluation (within 24 hours from PPCI) and in 34% patients when evaluated at pre-discharge, confirming the dynamic nature of the phenomenon.

### Electrocardiographic ST-Resolution

Along with angiographic indexes of myocardial no-reflow, electrocardiographic STR assessed at 70 or 90 minutes after reperfusion has established utility for predicting both target vessel patency and prognosis in acute myocardial infarction, with lack of STR $<$50% or $<$70% at electrocardiogram being widely considered as a marker of microvascular obstruction [40]. In 1997, van't Hof showed that in 403 STEMI patients after PPCI, a normalized ST segment was seen in 51% of patients 1 hour after reperfusion therapy, a partially normalized ST segment in 34%, and 15% had no STR [41]. It is worth noting, however, that in this study, electrocardiogram did not predict infarct-vessel status in many patients, since 49% of patients had persistent ST-segment elevation despite an open epicardial vessel with TIMI 3 flow. In 2004, McLaughlin et al. analyzed 700 patients with technically adequate baseline and post-PCI electrocardiograms from the Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications (CADILLAC) trial [42] and STR in the single lead with maximum baseline ST-elevation $>$70% was observed in 63% of the whole population, STR between 30% and 70% was observed in 29%, while STR $<$30% was detected in 8% of the investigated population. Moreover, absolute maximum ST-segment elevation after intervention was $<$1 mm in 59% of the population, 1$-$2 mm in 25%, and $>$2 mm in 16% of the population only, thus demonstrating once more that the electrocardiographic incidence of no-reflow may be higher when compared to the angiographic definition of microvascular obstruction soon after reperfusion. More recently, Van der Zwaan et al., in 223 patients undergoing successful PPCI, defined as sustained patency of the occluded epicardial coronary artery with TIMI flow grade $\geq$2, found lack of STR in about 30% of patients [43], further suggesting the notion that no-reflow rate may be variable according to the study population investigated. Although easily available in the clinical arena, neither blush grade nor electrocardiographic STR provides a direct assessment of myocardial perfusion, which in turn may be determined by noninvasive imaging techniques such as MCE and CMR [44].

## Incidence of Coronary Microvascular Obstruction in Patients Treated With Thrombolysis

In 1993, at the climax of the thrombolytic era, Lincoff and Topol [45] wrote a provocative editorial wondering whether reperfusion was just an illusion. At that time, they estimated that, despite thrombolytic therapy had been unequivocally demonstrated to markedly improve the natural history of acute myocardial infarction with an approximate 30% reduction in mortality in randomized controlled trials [46$-$50], only "25% or less" of patients treated

by thrombolysis had an optimal reperfusion, defined as a rapid, complete, and sustained coronary recanalization with adequate myocardial tissue perfusion. Indeed, according to the authors, coronary patency rates as high as 85% assessed by angiography 90 minutes after initiation of treatment greatly overestimated the efficacy of thrombolytic regimens, as this conventional angiographic "snapshot" view did not satisfactorily reflect the dynamic processes of coronary artery recanalization and re-occlusion or the adequacy of myocardial perfusion. In fact, only the "unusual patient" appeared to achieve an optimal reperfusion for acute myocardial infarction, with a substantial deterioration of benefit in many patients due to insufficiently early or rapid recanalization, incomplete patency with TIMI grade 2 flow or critical residual coronary stenoses, absence of myocardial tissue reflow despite epicardial artery patency, intermittent coronary patency, subsequent re-occlusion, or reperfusion injury. In an analysis of studies performed in the thrombolytic era, after therapy with streptokinase in one large study [51], the patency rate (TIMI flow 2 or 3) at 60 minutes was only 48%, whereas in patients treated with conventional doses of tissue-type plasminogen activator (t-PA) during three randomized trials [52–54] 45%–62% (mean, 57%) of infarct arteries were open by 60 minutes. Accelerated dosage regimens of t-PA have been most efficacious, with a mean 60 minutes patency rate of 72% (range, 65%–76%) among 438 patients in four different reports [53–56]. Thus, rapid restoration of infarct-artery patency (TIMI flow 2 or 3), the first criterion of optimal reperfusion, is achieved in fewer than three-fourths of patients treated with even the most aggressive current regimen of thrombolytic therapy for acute myocardial infarction. Moreover, among 370 patients in three randomized trials undergoing angiography 60 minutes after therapy with accelerated dosages of t-PA, 57% (range, 54%–62%) and 17% (range, 15%–19%) were found to have TIMI 3 and TIMI 2 flow, respectively [44,46,47]. Thus, by the criteria of rapid and complete restoration of coronary patency (TIMI flow 3), less than 60% of patients appear to achieve optimal reperfusion, even with accelerated thrombolysis (Table 3–1). Finally, an electrocardiographic sub-study of 2352 patients from the Global

**Table 3–1** Coronary Flow After Thrombolysis for Acute Myocardial Infarction

| Study | *N* | Thrombolytic Regimen | Time to Angiography (min) | TIMI 3 Flow (%) | TIMI 2 Flow (%) |
|---|---|---|---|---|---|
| TAPS [56] | 210 | Accelerated t-PA | 60 | 54 | 19 |
| Neuhaus [55] | 73 | Accelerated t-PA | 60 | 59 | 14 |
| RAAMI [53] | 87 | Accelerated t-PA | 60 | 62 | 14 |
| RAAMI [53] | 86 | Standard t-PA | 60 | 40 | 23 |
| TAPS [56] | 211 | Anistreplase | 60 | 40 | 14 |
| TEAM-2 [49] | 359 | Anistreplase/streptokinase | 90–240 | 56 | 16 |
| Vogt [48] | 907 | Accelerated t-PA/anistreplase/urokinase/r-PA | 90 | 57 | 16 |

*TIMI*, thrombolysis in myocardial infarction; *t-PA*, tissue-type plasminogen activator; *r-PA*, recombinant plasminogen activator.
Adapted from A.M. Lincoff, E.J. Topol, Illusion of reperfusion. Does anyone achieve optimal reperfusion during acute myocardial infarction? Circulation 88 (3) (1993) 1361–1374.

Utilization of Streptokinase and t-PA for Occluded Coronary Arteries (GUSTO-III) trial found that complete STR occurred in 44.2% of patients at 90 minutes after thrombolysis while in 56.5% of patients at 180 minutes [57].

## Incidence of Coronary Microvascular Obstruction in Patients Treated With Rescue Primary Percutaneous Coronary Intervention

Patients undergoing a rescue PCI usually present a higher ischemic time compared with patients undergoing PPCI or effective thrombolysis, and a higher incidence of MVO.

A small study by Khan et al. [58] evaluated the incidence and extent of infarct size and CMVO in STEMI patients according to different reperfusion modalities. CMR infarct characteristics were measured in 94 STEMI patients (age 61.0 $\pm$ 13.1 years). Seventy-three received reperfusion therapy: PPCI in 47 patients, thrombolysis in 12 patients, rescue PCI in 8 patients, and late PCI ($>12$ hours from symptoms onset) in 6 patients. Twenty-one patients presenting late after symptoms onset ($>12$ hours) did not receive reperfusion therapy. Infarct size differed across the five study cohorts, being higher in rescue PCI and late PCI groups compared with PPCI and thrombolysed patients. When corrected for the ischemic time, the differences in infarct size in reperfused patients were no longer statistically significant. Of note, the prevalence of MVO showed a trend toward the extent (% of left ventricle (LV) mass) of MVO being greatest in the late PCI group, followed by nonreperfused and rescue PCI patients. When corrected for the ischemic time, the difference in MVO with the four reperfusion techniques was not statistically significant.

## Incidence of Coronary Microvascular Obstruction in Specific Subset of Patients

Several clinical conditions have been shown to be associated with an increased prevalence of CMVO after STEMI (Fig. 3—3). In particular, in this paragraph, we summarize relevant studies addressing this issue in specific subsets of patients.

### Diabetes

The effects of diabetes on both macro- and micro-vasculature are well known. The main microvascular complications are diabetic neuropathy, retinopathy, and nephropathy. Furthermore, diabetes has been associated with impaired microvascular reperfusion after primary PCI [59]. Even if uncomplicated, it causes a marked coronary microvascular dysfunction; both endothelium dependent and independent vasodilatation result impaired [60], causing an increase endothelial tendency to vasoconstriction and thrombosis. Blood glucose levels represent a risk factor for no-reflow not only by the chronic action of impairment of microvasculature. In fact, blood glucose levels at the time of admission for STEMI have been

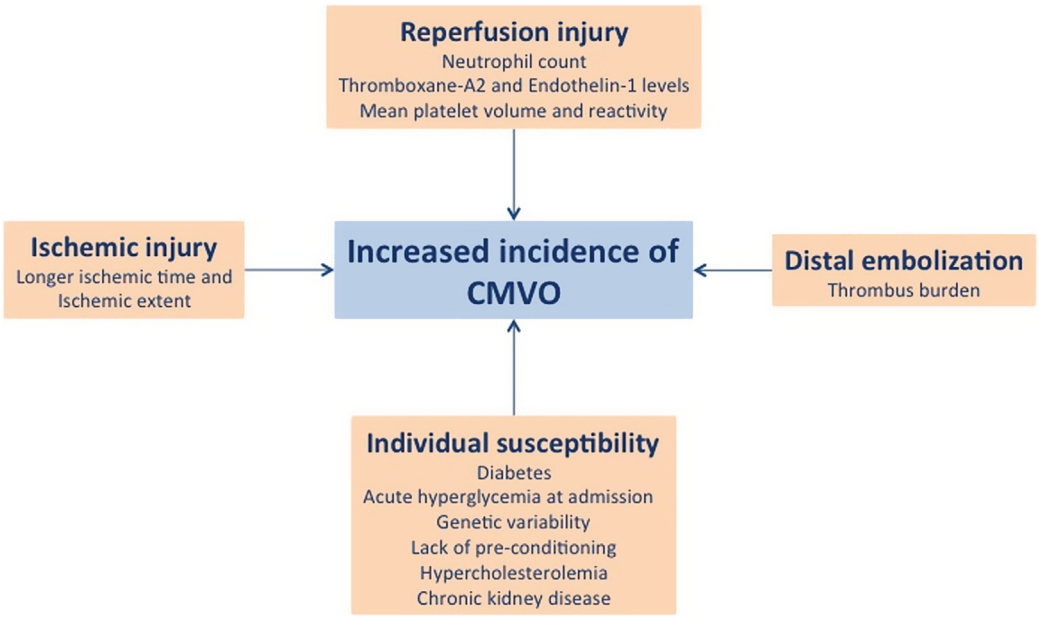


**FIGURE 3–3** Clinical and procedural factors influencing the incidence of coronary microvascular obstruction (CMVO). *Modified from G. Niccoli, G. Scalone, A. Lerman, F. Crea, Coronary microvascular obstruction in acute myocardial infarction, Eur Heart J 37 (13) (2016) 1024−1033.*

shown to predict the risk of development of no-reflow independently on the basal glycemic control, suggesting a direct effect of acute hyperglycemia on reperfusion injury [61].

A study by Iwakura et al. [61] enrolled 146 consecutive patients with a first acute myocardial infarction studied by intracoronary MCE after successful reperfusion within 24 hours after symptom onset. The no-reflow phenomenon was found on MCE in 49 (33.6%) of 146 patients; their glucose level on hospital admission was significantly higher than that of patients who did not exhibit this phenomenon ($209 \pm 79$ vs $159 \pm 56$ mg/dL; $P < 0.0001$). There was no difference in glycosylated hemoglobin or in the incidence of diabetes mellitus between the two subsets. The no-reflow phenomenon was more often observed in the 75 patients with hyperglycemia ($\geq$160 mg/dL) than in those without hyperglycemia (52.0% vs 14.1%; $P < 0.0001$). Moreover, the blood glucose level was an independent prognostic factor for no-reflow, along with age, gender, absence of pre-infarction angina, complete occlusion of the culprit lesion, and anterior acute myocardial infarction. A study by Eitel et al. [62] enrolling 411 consecutive STEMI patients undergoing PPCI and subsequent CMR imaging (1−4 days after index event) demonstrated that CMVO was identified in 243 patients (59%) with similar occurrence and extent in patients without known diabetes versus those with diabetes (66% vs 57%). However, patients with known diabetes had a significantly higher CMVO/infarct size ratio as compared with nondiabetic patients ($P = 0.03$). Of note, in the overall study cohort, there was a graded relationship between glycemic status on admission

and infarct size, more reduced left ventricle ejection fraction and the presence and extent of CMVO. In particular, CMVO occurred in more than 70% of patients with severe hyperglycemia at admission both in patients with known diabetes and without known diabetes. Finally, a recent paper of Zhao et al. [63] enrolling 154 consecutive diabetic patients who underwent primary PPCI for a first STEMI demonstrated that angiographic no-reflow (defined as a final TIMI flow of $\leq 2$ or final TIMI flow of 3 with a MBG of $<2$) occurred in 53 of 154 (34%) patients.

## Women

Compared with men, women who present with STEMI have a higher unadjusted rate of early mortality [64,65]. The basis for this disparity is not fully understood and likely complex. In prior analyses, adverse outcomes in women have been attributed to differences in patient risk factor profile and treatment. Women with STEMI tend to be older with more comorbid illness such as hypertension, renal insufficiency, and anemia [65–67]. There is conflicting evidence on the impact of gender on reperfusion after PPCI. A study by Canali et al. [68] evaluated 283 (238 males and 45 females) consecutive STEMI patients, treated with PPCI within 12 hours from symptoms onset undergoing CMR $3 \pm 2$ days after STEMI and at 4-month follow-up. By CMR, the area at risk, infarct size, CMVO, and myocardial salvage index (MSI) were assessed. Women were older than men ($P = 0.014$), more hypertensive ($P < 0.001$), and more frequently presented with pre-infarct angina ($P = 0.018$). An MSI extent was significantly higher ($P = 0.013$), infarct size was significantly smaller at both time points (acute $P < 0.001$, follow-up $P < 0.001$), and the CMVO extent was significantly smaller ($P < 0.001$) in women. At multivariate analysis, Killip class and female sex were independently associated with a higher MSI ($P = 0.02$, $P = 0.05$, respectively). Another study by Tomey et al. [69] enrolling 118 women and 334 men with anterior STEMI in the Intracoronary abciximab and aspiration thrombectomy in patients with large anterior myocardial infarction (INFUSE-AMI) randomized trial assessed infarct size by CMR imaging at 5 days for CMVO assessment and at 30 days for infarct size assessment. Women were older, were more commonly affected by hypertension and renal impairment, and had a 50.5-minute longer delay to reperfusion. However, there were no differences in infarct size at 30 days, microvascular obstruction at 5 days, or reperfusion success in terms of angiographic no-reflow. At 30 days, major adverse cardiac events (MACE), defined as death, re-infarction, new-onset severe heart failure, or re-hospitalization for heart failure, were more common in women (11.1% vs 5.4%, hazard ratio 2.09, 95% CI 1.03–4.27, $P = 0.04$). After multivariable adjustment, age, but not sex or time to reperfusion, was an independent predictor of MACE.

## Chronic Kidney Disease

The presence of renal impairment is associated with a poor reperfusion in STEMI patients treated with PPCI. In particular, a study by Kurtul et al. [70] evaluated consecutive patients ($n = 673$; $59 \pm 13$ years; 77.1% men) stratified into three groups according to estimated

glomerular filtration rate (eGFR) at admission: normal renal function (eGFR $\geq$ 90 mL/min/1.73 $m^2$), mild renal impairment (eGFR 60−89 mL/min/1.73 $m^2$), and moderate renal impairment (eGFR 30−59 mL/min/1.73 $m^2$). No-reflow phenomenon was defined as TIMI flow <3 after PPCI. The rate of no-reflow gradually increased from the normal renal function group to the moderate impaired renal function group ($P < 0.001$). Multivariate analysis showed that eGFR [odds ratio (OR) 0.942, $P < 0.001$], Killip $\geq$2 class (OR 3.968, $P = 0.008$), left ventricular ejection fraction (OR 0.959, $P = 0.034$), and early patency of infarct-vessel (OR 0.186, $P < 0.001$) were independent predictors of no-reflow phenomenon. Mild to moderate renal impairment at admission is independently associated with no-reflow phenomenon after PPCI.

## Saphenous Vein Graft

PPCI for STEMI due to SVG occlusion is associated with a high risk of distal embolization and no-reflow. A study by Brodie et al. [71] enrolled 2.240 consecutive patients with STEMI treated with primary PCI from 1984 to 2003. Patients with primary PCI for SVG occlusion ($n = 57$) versus native artery occlusion had more prior MI, advanced Killip class, and three-vessel coronary disease and lower acute ejection fraction. Patients with SVG occlusion had lower rates of TIMI 3 flow post-PCI (80.7% vs 93.6%; $P = 0.0001$), higher in-hospital mortality (21.1% vs 8.0%; $P = 0.0004$), and lower follow-up ejection fraction (49.3% vs 54.7%; $P = 0.055$). Moreover, culprit SVG were patent in 64% of patients at 1 year and 56% at 5 years. Another study by Stone et al. [72] evaluated 1.100 STEMI patients undergoing PPCI, with 58 (5.3%) patients with a previous coronary artery bypass (CABG). The infarct-related vessel in these patients was a bypass graft in 32 patients (55%) and a native coronary artery in 26 patients. Compared with patients without previous CABG, patients with previous CABG were older and more frequently had a previous myocardial infarction and triple-vessel disease. Moreover, PCI was less likely to be performed when the infarct-related vessel was a bypass graft rather than a native coronary artery (71.9% vs 89.8%, $P = 0.001$). Of importance, TIMI flow grade 3 was less frequently achieved (70.2% vs 94.3%, $P < 0.0001$) when the culprit was a bypass graft compared with native vessels.

## Latecomers

A recent study of our group [73] evaluated the incidence and prognostic value of angiographic CMVO in latecomers STEMI patients. We prospectively enrolled 78 consecutive patients that were latecomers after STEMI (symptoms onset >12 hours) undergoing PCI. We performed an angiographic analysis to assess the occurrence of CMVO (defined as TIMI flow grade $\leq$2 or 3 with a MBG <2). Mean time of symptom onset was 23.14 ± 16.06 hours and mean follow-up time was 29.7 ± 14.1 months. Of interest, angiographic CMVO occurred in 39 (50%) patients. Importantly, patients with CMVO had a higher rate of MACE [18 (46%) vs 3 (8%), $P < 0.001$] and LV remodeling [25 (64%) vs 6 (15%), $P < 0.001$] compared with patients without CMVO. By multivariable Cox regression CMVO and left anterior descending artery were independent predictors of MACE.

## Conclusions

A sizeable proportion of patients undergoing PPCI achieve epicardial coronary artery reperfusion but not myocardial reperfusion due to the occurrence of CMVO. Prevalence of CMVO is variable, ranging from 5% up to 50%, according to the methods used to assess the phenomenon and to the population under study. CMR represents the most reliable technique in order to detect the incidence and the extent of CMVO, although other techniques such as MCE and electrocardiographic ST-resolution may be useful to monitor CMVO evolution. Moreover, specific clinical factors (hyperglycemia at admission, chronic kidney disease, and SVG as culprit lesion) are associated to a higher incidence of CMVO.

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