The Coronary Microcirculation in STEMI: The Next Frontier?

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This editorial refers to ‘How does coronary stent implantation impact on the status of the microcirculation during primary percutaneous coronary intervention in patients with ST-elevation myocardial infarction?’ by G.L. De Maria et al., on page 3165.

There have been significant reductions in the mortality associated with ST elevation myocardial infarction (STEMI) over the last several decades. On the background of declining coronary heart disease mortality in the USA and Western Europe, the use of prompt reperfusion strategies and adjunctive pharmacotherapy, mortality in STEMI patients has continued to improve. The 30-day mortality from four French registries over 15 years decreased from 11.3 to 4.4% between 1995 and 2010.1 Data from the American College of Cardiology National Cardiovascular Data Registry (ACC-NCDR) reveal a risk-adjusted in-hospital mortality of 5.5% among STEMI patients in 2009.2 A large registry of STEMI patients in Sweden demonstrated a reduction in 30-day and 1-year mortality from 15.0 to 8.6% (P < 0.001) and 21.0 to 13.3% (P < 0.001), respectively.3

The reperfusion era was ushered in during the 1980s with mortality reductions obtained using thrombolytic therapy.4 This was followed by the use of mechanical reperfusion with percutaneous coronary intervention (PCI). Subsequent meta-analyses of randomized trials comparing thrombolytic therapy and PCI documented PCI as the preferred strategy leading to reductions in mortality, stroke and re-infarction. In longer-term (>1 year) follow-up, PCI for STEMI patients was found to lower mortality and re-infarction rates.5 This has led to PCI as the preferred strategy in patients presenting with STEMI and is endorsed by guidelines internationally.6 Despite prompt restoration of epicardial coronary flow, however, normalization of flow at the myocardial or microcirculatory level is not always assured. Estimates of patients who achieve normal epicardial flow but have some sign of suboptimal myocardial perfusion [Thrombolysis in Myocardial Infarction (TIMI) flow <3, myocardial blush grade <3, <70% resolution of ST segments] range from 5 to 50%.7 This so-called ‘no-reflow phenomenon’ is strongly associated with worse outcomes and is manifest in the catheterization lab by slow contrast flow despite apparently successful treatment of the epicardial occlusion.

Mechanisms of coronary microvascular dysfunction after STEMI

The mechanisms responsible for no reflow are variable and likely different for each patient and are incompletely understood (Figure 1). These may include distal embolization, which has been shown experimentally to result in decreases in myocardial flow with obstruction of >50% of the coronary microvessels in the infarct-related region. Limited in vivo data suggest only a small number of emboli occur during PCI, making this mechanism less likely, but larger emboli (>200 μm diameter) and/or significant embolization pre-PCI remain a possibility.8 Depending on the duration of ischaemic injury, there may be changes in endothelial cells leading to protrusions and membrane-bound bodies. This may be accompanied by cell swelling and interstitial oedema that also contribute to coronary microvascular dysfunction. There is a complex interplay of inflammatory mediators from platelets, neutrophils and endothelium following restoration of epicardial flow that contributes to reperfusion injury. This can contribute to the post-infarction pro-inflammatory state and further compromise the coronary microcirculation. Reperfusion injury likely causes irreversible damage to cardiomyocytes, and despite attempts with multiple different agents to reduce its occurrence, none have been endorsed by guidelines. The no-reflow phenomenon may occur even during elective procedures. This likely represents a microvascular contribution from genetic or acquired patient factors such as diabetes or hypertension. There may also be a protective role of ischaemic preconditioning on microvascular function.

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Figure 1  Mechanisms responsible for the ‘no-reflow’ phenomenon. CFR, coronary flow reserve; DES, drug-eluting stent; FFR, fractional flow reserve; IMR, index of microcirculatory resistance; mTt, mean transit time; STEMI, ST elevation myocardial infarction; TIMI, Thrombolysis in Myocardial Infarction; VSM, vascular smooth muscle.
Knowledge gaps

Whether the choice of stent prosthesis actually contributes to coronary microvascular dysfunction in reperfused STEMI patients is unclear. There are concerns about defects to the polymer surface and the potential for microparticle embolization with the use of balloon expandable drug-eluting stent devices. Studies in our lab have shown disruption of some or all of the polymer coating when these stents are balloon expanded in a bath ex vivo. The extent to which these devices might contribute to the no-reflow phenomenon is unclear, but this remains a possibility. In addition to the possibility of particulate embolization, there may be an important reaction in the distal microvascular bed to the presence of anti-proliferative agents. An eosinophilic, hypersensitivity or other foreign body-type reaction has the potential to promote an abnormality of the coronary microvasculature and add to the likelihood of no reflow.

Whether other patient factors play a role in coronary microvascular abnormalities identified at the time of STEMI and contribute to adverse outcomes remains speculative. The presence of coronary microvascular dysfunction is well described and associated with symptoms of ischaemic heart disease, more commonly in women than in men. Could baseline abnormalities in coronary microvascular function predispose patients to worse outcomes in the setting of STEMI? Could patients with diabetes or hypertension have pre-existing dysfunction of the coronary microvessels that would increase their risk of a poor outcome following STEMI despite adequate macrovascular reperfusion? What about the coronary microvessels in the increasing numbers of patients presenting with non-STEMI?

Contributions and limitations

In the current issue, De Maria et al. present a detailed analysis of coronary reactivity in 85 patients undergoing PCI for STEMI. For the first time, fractional flow reserve (FFR), coronary flow reserve (CFR) and the index of microcirculatory resistance (IMR) were measured both before and after successful restoration of epicardial coronary flow with stent prostheses in the same patients. The authors demonstrated that all measures of coronary microvascular assessment improved following stent implantation. However, in about one-third of patients (n = 28), the IMR either remained elevated or only partially improved (IMR > 40). This was more likely among the ‘late presenters’, as well as in patients with more thrombus. In multivariate analysis, the amount of jeopardized myocardium and pre-stenting IMR predicted improvement in the post-PCI IMR, while the degree of thrombus and overall stent volume correlated with a deleterious increase in post-PCI IMR.

The authors have shown that following stent implantation, overall there is improvement in both measures of macro- and microvascular function. Statistically significant improvements occurred in the mean distal pressure and FFR consistent with treatment of the epicardial stenosis. There was also improvement in CFR, mean transit time (mTT) and IMR after stenting (P < 0.001), suggesting better microcirculatory function, although only in about two-thirds of patients. It appears that those patients with worse microvascular dysfunction before stenting (pre-stenting IMR > 40) had the most to gain. When the cohort was dichotomized according to pre-stent IMR < 40 vs. > 40, most of the improvement in microvascular function indices concentrated in the latter group. Patients who had more severe abnormalities in microvascular function before stenting had greater improvements in CFR, mTT and IMR following stenting (Figure 3 in De Maria et al.). The questions remain, why was there not a more universal improvement in microvascular function and what if anything could have been done to improve it?

Due to the nature of the methodology required to measure microvascular function when treating STEMI patients, all those in the current study underwent balloon pre-dilatation. While this is required in many patients for stent delivery, ‘wiring’ the occlusion and pre-dilatation does have the potential to cause distal embolization and could contribute to microvascular plugging and affect baseline microvascular function. What is less clear is the contribution of other factors to the poor outcomes in one-third of patients. It is interesting to note that in the group with a high residual IMR, all patients received a drug-eluting stent (DES) (P = 0.02 when compared with the group with post-stent IMR < 40). While the numbers are small, this could reflect an effect of using a DES due to microparticle shedding (stent coating and/or platelet and white cell microthrombi) and/or a possible response of the microvasculature to the anti-proliferative agents used to coat the stents.

In addition, at least half of the enrolled patients had hypertension, diabetes or both. These conditions are well known to be associated with coronary microvascular dysfunction. The extent to which a patients’ pre-existing microvascular abnormalities contributed to their outcome following stenting for STEMI also remains unknown. Finally, it is unclear how IMR, when used as an index of microcirculatory function, is affected by the presence of collateral flow, particularly at the microvasculature level, and whether this technique can assess dishomogeneities in flow that may be present.

The authors have provided valuable information on assessment of coronary microvascular circulation both before and after the treatment of STEMI. Yet, despite adequate restoration of epicardial flow, about one-third of patients remain with markers suggesting poor microcirculatory function, and this has been associated with poor outcomes. While the exact mechanism(s) responsible for these residual defects remains unclear, it is clear that there is a critical need for further investigation of this knowledge gap. Information is needed about the cause/mechanism(s) and, even more so, novel diagnostic and treatment options to address this important issue. Despite important successes in the macrovascular domain, the coronary microcirculation remains a challenge.

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References


