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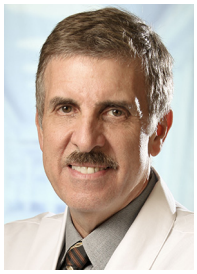
Editorials

Chilling Out With STEMI: Does Hypothermia Impact Microvascular Obstruction?



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Microvascular obstruction (MVO) remains a major unsolved clinical problem for optimal ST-elevation myocardial infarction (STEMI) therapy. Modern interventional STEMI therapy is both effective and efficient and rapidly restores epicardial flow to occluded coronary arteries. However, major adverse cardiac events (MACE) and other serious late complications are frequent after STEMI, most often resulting from distal MVO in dependent capillary beds [1–3]. MVO occurs in 50% to 70% of STEMI patients (including those with Thrombolysis in Myocardial Infarction [TIMI] 3 flow), is difficult to detect in the cath lab, and has proven elusive to treat [4].

MVO is strongly associated with both early and late MACE, recurrent ischemic events, negative ventricular remodeling, large residual infarct size, heart failure, and arrhythmias. MVO is a potent prognostic marker, superior to both infarct size and ejection fraction [3,5,6].

MVO histopathology comprises microvessels that are collapsed from low intraluminal pressure [7], with severe capillary injury, endothelial loss with intravascular protrusions and obstructing blebs [8,9], and embolic debris [10]. The resulting microvascular lumen instability causes congestion and, often, complete occlusion by normal erythrocytes and leukocytes trapped because of their large size and unable to traverse the compressed or obstructed capillaries.

MVO develops rapidly in both clinical and experimental STEMI. MVO mass triples between 2 minutes and 4 hours after coronary occlusion and increases continuously up to 8 hours after the acute event [11,12]. No therapies are effective against MVO despite many trials of both systemic and local drug infusion.

In this issue of *CRM,* Keeble et al. examined therapeutic hypothermia (TH) as a possible MVO therapy from the COOL AMI EU pilot study [13]. Several important findings emerged. First, MVO prevalence was remarkably high in both TH-treated patients (74%) and controls (77%), despite successful stenting and epicardial flow restoration. Second, MVO prevalence did not differ between TH-treated patients and controls, suggesting that TH does not limit MVO occurrence. Third, MVO mass also did not differ between TH-treated patients and controls, suggesting that TH has minimal effect on MVO mass. A final non-significant finding found extensive MVO mass (>3.9% of left ventricular mass) did not differ between TH-treated patients and controls.

The sole study result supporting TH efficacy occurred in the extensive MVO patient subset, which showed significantly higher 30-day ejection fraction (EF, 43% vs. 34%) in TH-treated patients vs. controls. In the literature, MVO prevalence and mass both correlate loosely with EF [6,14]. In patients with normal EF (>50%), MVO is a potent predictor of 5-year MACE [1,6,15]. Other studies show that MVO independently contributes to both MACE and prognosis, suggesting independent effects on ventricular function.

This study joins a growing list of essentially negative or minimally effective MVO therapies [16–19]. A common problem in all trials using intracoronary delivery may explain the poor therapeutic results. Therapeutic coronary infusion for MVO (pharmacologic, cooling, or others) requires therapy to reach obstructed microvasculature in appropriate concentration. This is a significant problem because the target capillary sites are partially or completely obstructed. This problem is compounded by myocardial microvascular anatomy. The microvascular coronary bed comprises richly parallel capillary networks, many of which remain patent at or near MVO-affected regions. Patent and occluded capillaries thus coexist in close proximity and are all supplied by the same coronary artery source. Quantitative hydrodynamic analysis in parallel flow systems estimates that only 2% or less of any intracoronary injection reaches the target MVO-occluded capillary system, depending on injection parameters. The patent, low-resistance parallel microvascular channels preferentially receive most injected therapy, with very little entering target MVO sites. Successful MVO therapy must address this inversely preferential infusion to overcome the severe hydrodynamic infusion bias toward open microvasculature.

MVO remains a major cause of late MACE and poor prognosis, and thus, it should be a top priority for cardiology investigation. Much key MVO literature resides in the cardiac magnetic resonance imaging realm, typically out of mainstream reading for general and

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interventional cardiologists. Publication of papers such as Keeble and colleagues' in interventional-related journals such as *CRM* may be changing this trend and so bringing well-deserved attention to a major clinical problem.

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