Commentary

Therapeutic hypothermia in ST elevation myocardial infarction (STEMI): a long way to go

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Post-ischemic reperfusion injury is mediated by infiltration and activation of circulating inflammatory cell subsets (i.e., neutrophils) that early entered the area-at-risk and release proteases and reactive oxygen species (ROS) (1-3). A recent study demonstrated that during recovery neutrophil infiltration might be protective, thus favoring a proper scar formation and potentially preventing negative left ventricle remodeling (4). Given this pathophysiological complexity, some selective drugs targeting these cells failed to induce a clear benefit on mortality and post-ischemic heart failure development in experimental models (2,5). Treatment schedule and safety (i.e., risk of immunosuppression) were suggested as the key limiting issues, potentially weakening the relevance of pre-clinical studies. However, despite a promising pilot study (6), patients with acute ST-segment elevation myocardial infarction (STEMI), did not benefit of the acute administration of cyclosporine (an immunosuppressive drug) on post-infarction clinical outcomes (7,8). Therefore, evidence from both basic and clinical research raised some concerns on therapeutic approaches inhibiting inflammation in all phases of post-ischemic reperfusion. A clear need of more selective treatments transiently abrogating inflammation might be more effective and safe.

Since decades, therapeutic hypothermia (TH) is empirically considered as a useful physical approach abrogating inflammation and reducing cellular metabolism of ischemic cells (9).

This approach was first supposed to be neuroprotective in survivors of cardiac arrest (10) and then, investigated to reduce cardiac injury (11). More recently, a systematic review and meta-analysis of randomized controlled trials (RCTs) investigated if TH might significantly reduce major adverse cardiovascular events (MACEs) as compared to controls in patients with STEMI.

Villablanca and co-workers evaluated the clinical efficacy of this approach not only on MACEs (primary end point), but also on secondary end points, such as all-cause mortality, new myocardial infarction, heart failure/pulmonary oedema and infarct size (12). Finally, safety endpoints (i.e., all-bleeding, ventricular tachycardia and bradycardias) were also assessed. In the meta-analysis, 819 patients from six RCTs that met criteria (the study was a RCT, age >18, diagnosis of STEMI, assessment of MACEs and TH administered in the setting of acute disease) were included.

The meta-analysis failed to show a clear clinical benefit of TH on post-STEMI outcomes. Only a sub-analysis of 4 RCTs that specified site of infarction (13-16) suggested that patients with anterior wall infarct had a reduction in infarct size when submitted to TH as compared to controls. Despite preliminary, since this minor result came from only four RCTs, the article by Villablanca and co-workers suggests that TH might be useful in a selected population with cardiac arrest or some sub-groups of patients with STEMI. These results might be also explained by the fact that, differently from animal models of myocardial ischemia/reperfusion in which each 1 ℃ lowering of blood temperature cause a reduction in infarct size of 10% (17), the majority of STEMI patients

in these RTCs did not reach the target temperature (12). These results were potentially influenced by the method to induce HT that was different in the RCTs [five RCTs used endovascular inferior vena cava (IVC) catheters and one a peritoneal catheter] (12). The use of an IVC catheter was previously associated with the induction of a slow HT as compared to the infusion of chilled intravenous fluid, thus unappropriated for the time PCI procedure (18). On the other hand, a more rapid heart cooling was reported by the peritoneal HT (19). However, the target temperature by standard TH protocol might be hard to be reached also when using this second device.

This meta-analysis did not apparently raise major concerns on safety. Although the safety end points were not recorded in all six RCTs at the same time, TH induced similar adverse events (i.e., all-bleeding, ventricular arrhythmias and bradycardia) as compared to controls. We might speculate that future TH RCTs in selected STEMI population might not risk to be limited by safety issues.

As partially acknowledged by the authors, the limited sample size for efficacy suggests that a meta-analysis in the next five years might be reasonable. We believe that such study should take into the account of standardized definitions of MACEs, hypothermia and target temperatures. The meta-analysis by Villablanca and colleagues has to be considered as preliminary result that requires additional confirmation. In fact, we believe that reduction in ischemia/reperfusion injury is critical to improve sequelae after effective revascularization in patients with STEMI. A better pathophysiological knowledge of inflammatory processes related to reperfusion injury might help to develop more efficient and timely treatments.

TH was already beneficial in animal models of ischemia/reperfusion (17). However, as it often happens, the translation of basic research results into human disease might have some difficulties. As identified by Bolli and co-workers, multiple barriers are interposed between the animal model and the patient (20). The most relevant clinical barriers are comorbidities, pharmacological ongoing treatments, population bias and the inability to identify and pre-treat patient with STEMI. TH remains a promising strategy in patients with STEMI. Additional RCTs are needed to conclude and potentially provide recommendations on its efficacy against STEMI.

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Footnote

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