EDITORIAL

Infarct size reduction by targeting ischemic injury: back to square one

Short title: IS reduction by targeting ischemic injury

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Timely reperfusion is needed to salvage viable myocardium in ST-segment elevation myocardial infarction (STEMI) patients[1]. The concept that the fate of the ischemic myocardium depends on subsequent spontaneous or interventional coronary reperfusion was established in experimental large animal models more than 4 decades ago[2]. Further research identified that the process of restoring blood flow to the ischemic myocardium comes at a cost, as induces additional myocardial damage, known as "myocardial ischemia-reperfusion injury (IRI)"[2]. For a long time it has been assumed that, while ischemic injury can only be reduced by faster blood flow restoration, reperfusion-related myocardial injury can be ameliorated by interventions applied anytime before (or at the latest at) reperfusion. The possibility of reducing infarct size by a strategy applied soon before reperfusion (e.g. in the cath lab) is logistically very attractive and for this reason has gained lots of interest. Unlike reperfusion itself, whose translation is one of the most successful stories of medicine ever, cardioprotective therapies targeting reperfusion-related injury has not yet been successful and remain one of the top ten unmet clinical needs in cardiology[1,3].

One of the major determinants of (long-term) mortality and morbidity in STEMI patients is the extent of myocardial necrosis, known as infarct size (IS), resulting from both ischemic- and reperfusion-related injuries[4,5]. Therapies able to reduce IS have been historically tested under the hypothesis that smaller infarctions will result in fewer adverse clinical events in the long-term[4,6]. Amongst them, ischemic conditioning deserves special attention. In 1986, Murry *et al.* published a seminal study demonstrating that several brief (5 min) cycles of non-injurious ischemia and reperfusion render the myocardium significantly protection from a subsequent sustained ischemic insult. This phenomenon whereby the myocardium can endogenously be protected from lethal IRI was defined as "ischemic preconditioning" (IPC) and has been subsequently replicated in numerous pre-clinical studies[7], as well as in other organs[8]. Brief episodes of ischemia and reperfusion in one organ render remote tissues and organs resistant to ischemia/reperfusion injury, something known as remote ischemic conditioning (RIC)[8]. Interestingly, RIC has been shown to exert cardioprotection even when it is initiated during ongoing myocardial infarction[9], a maneuver known as remote ischemic per-conditioning (perRIC). All different variants of conditioning (pre, per, post, local or remote) are thought to reduce infarct size by targeting reperfusion-related injury.

In this issue of Circulation Research, Kleinbongard *et al.* studied the electrocardiographic (ECG) changes occurring during perRIC in a swine model of myocardial IRI[10]. Isoflurane-anesthetized Göttingen minipigs underwent open-chest temporary (60 min) coronary occlusion followed by reperfusion. At min 20 of ischemia pigs were randomized to perRIC (4 cycles of -5 min occlusion / 5 min reperfusion- of the hind limb) or control (no perRIC). ST-segment elevation was analyzed in a V2-like ECG-lead at baseline, 5 and 55 min coronary occlusion, and 10, 30, 60, and 120 min reperfusion. 180 min after reperfusion, animals were euthanized and hearts processed for pathology-based infarct size and no-reflow quantifications. perRIC was associated with significantly smaller infarct sizes. There was a non-significant trend for smaller areas of no-reflow in the perRIC group. perRIC increased phosphorylation of STAT3. These results are in agreement with many previous studies and validate the authors´ model of perRIC. The main novelty of the paper relates to the serial ECG findings: at 5 min ischemia (i.e. before perRIC was initiated), ST-segment deviations were not different, but ST-segment deviation at 55 min ischemia significantly recovered in perRIC pigs compared to matched controls. This observation has two main clinical implications: 1) ischemic-perconditioning has a clear impact on the ischemic bit of the overall ischemia/reperfusion injury; and 2) ECG can be used for real-time monitoring of the impact of cardioprotective therapies over myocardial ischemic injury and, maybe, can be used to roughly identify a subset of patients with a high underlying risk of developing large infarcts who can actually benefit from cardioprotective interventions.

The study by Prof Heusch´s group challenges the paradigm that perRIC mostly attenuates reperfusion-related injury, as the reduction in ST-segment elevation observed during ongoing ischemia points towards an impact on ischemic injury[10]. The mechanism by which

perRIC can ameliorate ischemic damage is unknown and was beyond of the scope of this paper. Given the virtual absence of residual blood flow into the ischemic region, it seems implausible that a humoral signal released from the distant organ undergoing brief episodes of I/R is the source of ischemic injury attenuation. It is intuitive to argue that a neural pathway is involved in this protection but we are far from understanding the actual mechanism. This study is landmark not just from the conditioning perspective, but also for the entire cardioprotection field since it places ischemic injury back in the arena of relevant targets for infarct size reduction, something ignored for many years. This study also provides explanation for a finding identified in the CONDI trial[9], where perRIC seemed to offer stronger protection when applied long before reperfusion[11]. In this line, another strategy which has been shown to reduce infarct size (i.e. intravenous metoprolol) exerts stronger cardioprotection when applied long before reperfusion[12]. Altogether, these evidences suggest that therapies effectively reducing infarct size exert an important effect on ischemic injury. Beyond the conceptual change of this finding, there is a very practical consequence: these therapies should be applied as soon as possible upon myocardial infarction diagnosis, and this is many times in the out-of-hospital setting. The identification of the anti-ischemic effect of perRIC and metoprolol (and probably other strategies) does not mean that they do not ameliorate reperfusion-related injury as well. In this sense, recently it has been shown that metoprolol has a direct effect on neutrophils and this results in a potent effect against reperfusion-related injury[13]. In fact, ischemic- and reperfusion-related injuries are indissoluble from each other and thus any therapy reducing ischemic-related injury will also impact reperfusion-related injury.

The ECG is a tool routinely used in patients with suspected AMI to establish a diagnosis[1]. The identification of ST segment elevation in two or more contiguous leads provides information about the affected location, the need for reperfusion and even about its prognosis. Taking into account recent disappointing results in randomized clinical trials assessing cardioprotective therapies, there is a need to find early markers which can provide valuable information to identify patients at high risk, who can actually benefit from cardioprotective therapies, as well as patients already protected, who cannot benefit at all of them. Despite being used worldwide for more than 100 years, ECG is still the cornerstone of the diagnosis of AMI and can emerge as a "new" test to select which patients should and should not be included in randomized clinical trials evaluating cardioprotective interventions.

In the past decades, ST segment, T wave and QRS changes have been incorporated into ECG scoring systems to assess the severity and acuteness of ischemia. For instance, Birnbaum *et al*. demonstrated that the distortion in the terminal portion of the QRS complex in admission ECG in patients presenting with ST-segment elevation myocardial infarction was associated with poor prognosis when present in two or more contiguous leads. More recently, this ECG pattern has been independently associated with larger myocardium at risk and infarct size in patients with anterior AMI[14]. Therefore, QRS distortion might be used to select those patients with larger myocardial at risk, who can greatly benefit from a cardioprotective intervention.

There is currently great expectation for the outcome of the combination of two large ongoing randomized, controlled, clinical trials, namely the CONDI2 (NCT01857414) and ERIC-PPCI (NCT02342522) studies[15], which is a European endeavor (Denmark, Spain, Serbia, and UK respectively) involving together >5300 STEMI patients undergoing primary percutaneous coronary intervention. These trials aim to evaluate the effect of perRIC on long-term clinical outcomes. These trials enroll patients at a wide range of time to reperfusion (i.e. some patients are recruited and put on perRIC long before reperfusion (in the ambulance), while others are recruited in the cath lab soon before reperfusion). According to the results from Heusch´s group motivating this editorial[10], it seems imperative to design a secondary analysis of the trials in which only patients recruited in the out-of-hospital setting are analyzed. If ischemic injury reduction was the main driver of protection upon perRIC, applying this intervention soon before reperfusion (i.e in the cath lab or emergency department), when ischemic damage is almost ended, would significantly reduce the infarct-limiting effects of this maneuver.

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