


EDITORIAL COMMENT


Myocardial protection with postconditioning in cardiac surgery: the importance of the model

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In this issue of the European Journal of Cardio-Thoracic Surgery, Maruyama and Chambers [1] pose the question of whether postconditioning (POC) enhances the protection provided by normothermic St Thomas’ number 2 (ST2) cardioplegia solution. This is an excellent question, posed by a highly productive group, and whether POC provides protection in addition to that exerted by cardioplegia is a question that has been asked by others [2]. Maruyama and Chambers found that a POC algorithm applied after increasing durations of arrest induced by a single infusion of warm St Thomas’ number 2 (ST2) cardioplegia did not enhance the primary end points of recovery of contractile function or reduce infarct size relative to that observed after arrest and reperfusion alone. It is important that the intervention targets the end points or relevant mechanisms. POC has been shown to target mechanisms impacting these two end points; the improvement in global contractile function is likely through the reduction in infarct size since no effect has been demonstrated on contractile function per se. POC did not enhance the postcardioplegic outcomes at any duration of ischaemia, but was only effective when the magnesium concentration of ST2
cardioplegia solution was reduced to zero. Maruyama and Chambers conclude that POC has limited efficacy after arrest with ST2 cardioplegia solution, and there is likely a magnesium-sensitive component of POC protection.

POC is defined as reperfusion interrupted by brief periods of ischaemia applied during the opening minutes of reflow [3]. In cardiac surgery, POC can be applied by directly clamping and declamping the aorta, as performed by Luo et al. [4], or by iteratively infusing and halting the cardioplegia solution using a dedicated delivery system (Quest Medical Inc. MPS, Terumo Cardiovascular Systems System 1 Master/Follower, etc.). In contrast to cardioplegia solutions and adjunct strategies such as hypothermia that are designed to reduce the severity of ischaemia that, in part, also determines the severity of reperfusion injury, POC exclusively targets reperfusion injury. Conceptually, both cardioplegia and POC could reduce post-ischaemic injury. If the cardioplegia solution and related strategies successfully limit ischaemic injury, then there is little subsequent reperfusion injury on which POC may exert protection. If, on the other hand, the majority of injury occurs during ischaemia with or without cardioplegia, there may be little room for protection from reperfusion injury, and again POC may not play a role as in the 45 and 60 min ischaemia-only group (Figure 2).

It was important for the authors to show that the POC algorithm was effective in improving functional recovery and reducing infarct size, at least after 30 min of normothermic ischaemia alone (no cardioplegia). However, the observation that POC did not improve functional recovery or reduce infarct size does not necessarily represent a failure or loss of cardioprotection, but rather represents a limitation of that algorithm to stimulate the triggers and cardioprotective pathways [5] that impact the effectors of POC; this phenomenon has been called the ‘threshold’ of protection [6]. When a threshold is encountered, whereby protection is no longer observed after longer durations of ischaemia, increasing the number of postconditioning cycles has been shown to re-establish cardioprotection. The authors may have encountered such a threshold at the 45 and 60 min of index ischaemia in the present study. This should be determined in further studies.

The model often profoundly affects the outcomes of a study. In the Langendorff isolated perfused, non-working (not ejecting and performing external work) heart preparation, there may be fundamental species differences in biology, metabolic differences that effect the time course of ischaemic injury and efficacy of interventions. Whether the injury occurs primarily during ischaemia or during reperfusion is a fundamental question in this study. ST2 cardioplegia solution was used at 37°C, which differs from its use clinically, and is not consistent with clinical studies testing the efficacy of POC after hypothermic cardioplegia. Tables 2 and 3 show left ventricular end-diastolic pressures >30 mmHg at the end of ischaemia (0 min reperfusion), suggesting that contracture has already occurred to some extent during ischaemia with or without cardioplegia; contracture is associated with the onset of irreversible injury at the end of ischaemia that would not be amenable to reperfusion therapy such as POC. In addition, the isolated perfused heart preparation inherently lacks components of the inflammatory response, i.e. plasma-borne inflammatory cells, proteases and cytokines that contribute to reperfusion injury. POC has been shown to inhibit neutrophil accumulation, activation of the coronary vascular endothelium, adherence to the endothelium and cytokine release that may recruit inflammatory cells after reperfusion [3, 7]. Therefore, the absence of inflammatory cells, cytokines and the robust interaction with activated coronary endothelium constrains the effects of POC in isolated perfused models to non-inflammatory mechanisms such as improving calcium handling, triggering cardiomyocyte molecular pathways and local anti-oxidant effects, which limits the efficacy of POC in that model. In cardiac surgery, many surgical teams use blood cardioplegia, but all hearts are exposed to blood at reperfusion and, therefore, all hearts are vulnerable to some extent to inflammatory-related reperfusion injury, which would present a target for POC. Indeed, clinical studies have shown efficacy of POC when cardioplegia and other strategies were used [4, 8, 9].

The authors state that magnesium may have a role in POC protection, which is based on the appearance of improved post-ischaemic functional recovery and reduced infarct size when magnesium-free ST2 was combined with POC. Another interpretation of these data is that the high magnesium content (16 mM) masked a protective mechanism of POC in the isolated perfused heart model, and removal of magnesium unmasked the protection of POC; varying the magnesium concentration did not have an effect on functional recovery with ST2. Magnesium is a calcium channel blocker. Studies in models of simple ischaemia-reperfusion (or hypoxia-reoxygenation) have shown that POC attenuates the calcium dyshomoeostasis and accumulation in the cytosol and in mitochondria [10]. Magnesium in ST2 cardioplegia solution may have inhibited the calcium abnormalities that POC otherwise addresses, and it is only in the absence of magnesium that the calcium-related mechanisms of POC are unmasked. However, there was little if any difference in infarct size between 16 mM, 1.2 mM and 0 Mg ST2 at 45 min of arrest; at 60 min of arrest, infarct size was smaller with low Mg than 16 mM Mg ST2. The left ventricular developed pressure curves at 16, 1.2 and 0 mM magnesium are virtually superimposable. Therefore, the effects of Mg in ST2 as used in this model is not straightforward.

In conclusion, the study by Maruyama and Chambers did not necessarily show that ST2 ‘…abolished the window of POC protection’, but raises the question of whether other constituents and adjunct strategies (i.e. hypothermia) of cardioplegia solutions attenuate the pathophysiology of reperfusion injury, and whether this protection overlaps with that exerted by POC at the time of reperfusion. Overlapping protective mechanisms of POC may be unmasked when the efficacy of the cardioplegia strategy is challenged by antecedent warm ischaemia to mimic the failing heart, or when ST2 cardioplegia solution is used in clinically relevant fashion. Future studies should investigate hypothermic ST2 or other formulations (blood cardioplegia) in ischaemically injured hearts in which there is significant reperfusion injury, and in in vivo models where reperfusion with blood and the potential inflammatory response may present targets for a reperfusion therapy such as POC that may improve postcardioplegia endpoints such as functional recovery and morphological injury (troponin). The model is paramount.

REFERENCES


