Letter to the Editor

Cardioplegia and myocardial protection: time for a reassessment?

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Since the beginnings of open cardiac surgery many different strategies have been introduced to clinical practice in order to provide a motion- and bloodless operation field. Arresting the heart with cardioplegic solutions was described by Melrose and colleagues for the first time (1). Since then cardioplegic solutions have been widely accepted as feasible and safe for the majority of cardiac operations (2). In 1981 Hearse formulated the axioms of myocardial protection during cardiac surgery: firstly cardiac arrest for the conservation of cellular energy storages; secondly hypothermia for the reduction of cellular energy demands; and thirdly application of substances to prevent or reduce ischemia-reperfusion injury (3). These axioms form the foundation for most cardioplegic solutions today. However warm cardioplegia was successfully introduced in 1995 by Calafiore and colleagues. It seems to offer equivalent myocardial protection under the critical condition that the solution must be applied repetitively or continuously to avoid oxygen deficit of the heart (4). The convenience of most cardioplegic solutions lies in the good myocardial protection—even for long arrest times—and the ease of application. Although these solutions have been studied extensively, evidence on the perfect preservation strategy during cardiac surgery is still disputed. This debatable evidence might in part be due to different patient cohorts, various solutions and miscellaneous preservation strategies. Additionally, many different definitions of myocardial injury or low-output syndrome following cardiac procedures have been used to describe study endpoints. These definitions range from laboratory parameters in the form of elevated serum levels of CK-MB or troponin to mostly indirect clinical signs such as the occurrence of arrhythmias or ECG changes (2).

The explanation for this lack of evidence in the face of a thorough clinical and laboratory investigation is complex. Complicating the comparison of various cardioplegic solutions is the great variety of commercially available cardioplegic solutions such as Custodiol or homemade blood cardioplegia as initially described by Calafiore, as well as the various options of application (warm *vs.* tepid *vs.* cold, antegrade *vs.* retrograde, single-shot or intermittent application). Furthermore the underlying cardiac pathology is of crucial importance. This is not only reflected by the pathoanatomy of the treated heart with possibly disturbed uniform distribution of the cardioplegic solution due to atherosclerosis, but also by the pathophysiology. In this context it seems obvious that ischemic myocardium due to coronary artery disease has fundamentally different metabolic demands compared to a hypertrophied ventricle as seen in aortic valve stenosis (5). Considering these fundamentals the surgeon's preference as a result of his training or the availability of a certain cardioplegic solution at his or her institution almost seems to be of secondary importance.

So far few randomized clinical trials (RCT) have been conducted in order to find the best cardioplegic solution. The largest RCT to date has been presented by Øvrum and colleagues. In their trial a homemade blood cardioplegia composition was compared to a self-manufactured crystalloid cardioplegic solution—mainly consisting of Ringer's lactate combined with potassium and other substances like procaine—which were tested on

patients undergoing primarily aortic valve replacement (AVR). Yet many of the test subjects in this trial received additional coronary bypass surgery. This inhomogeneity of the study population might give rise to selection bias, even if no significant difference has been found in the subgroup analysis. Nevertheless the authors admit that the study might have been underpowered to detect any significant differences (6). In contrast to the solutions tested in the trial by Øvrum *et al.*, HTK solution is characterized as intracellular. This attribute requires a precise dosage to ensure optimal myocardial protection. Accordingly a low dosage could decrease the protective capabilities of the solution. The manufacturer of HTK recommends a dosage of 1 mL/min/g of the estimated heart weight within a perfusion time of 6–8 min. Heart weight can be estimated to be about 0.5% of the average body-weight of adults. Considering all these specifications an adequate dosage for an adult weighing 80 kg would result in a minimum of 2,400 mL of the HTK-solution. With an adequate dosage and application of HTK arrest times up to three hours and more are reported to be safe (7). However, ischemia-tolerance time of the heart is directly dependent on the circulatory temperature during cardiopulmonary bypass (8). Cardiac surgery nowadays is most commonly conducted during mild hypothermia, demanding a further reassessment of cardioplegic strategies. Even though HTK is postulated to be a cardioplegic solution making repeating doses unnecessary, some have raised concerns about this strategy in clinical practice.

First, temperature of the arrested heart over time approximates the body or circulation temperature as has been discovered in our laboratory during in vivo experiments on juvenile pigs (data not published). Thus hypothermia is diminished as one of the main protecting factors of cold cardioplegia over time.

Second, insufficient venous drainage for extracorporeal circulation can occur during cardiac operations. Venous backflow into the coronary sinus or through the Thebesian veins as well as non-coronary collateral flow could produce a washout of the cardioplegic solution in these particular areas, annihilating the protective effect of any cardioplegic solution. This is peculiarly relevant for single-shot cardioplegic solutions which are claimed to make cardioplegia repeating dosing unnecessary (7). A washout can be avoided by cardioplegia reperfusion. And when repetitive cardioplegia is administered why not dispense oxygen with blood-cardioplegia if possible to circumvent any myocardial ischemia?

However, there is a lack of clinical evidence proving blood-cardioplegia to be advantageous compared to crystalloid cardioplegic solutions. In coronary artery bypass grafting (CABG) a meta-analysis from Guru *et al.* suggests that blood-cardioplegia might be beneficial for this particular patient cohort (9). At our institution CABG is routinely accomplished with BCP when performed on-pump, and we find that repetitive administration does not hinder the surgical procedure. Concerning valve surgery, the only available data comes from two RCT's conducted by the working group of Braathen and colleagues. During their trials they found no relevant difference in clinical outcome between the BCP and the HTK group (10,11). Yet they found a relationship between arrest time and CK-MB release postoperatively in the HTK group, which was not seen in the BCP group (11). A greater myocardial injury in the HTK group without any clinical impact could be a hint that these trials were not powered to detect a clinical difference.

Since there is always a basal energy demand of the myocardium to preserve basal cellular functions, myocardial damage occurs over time also during cardioplegia. In our opinion, cardioplegic arrest with HTK is safe for most cardiac procedures and particularly for AVR. Yet there is uncertainty about complex procedures in which the arrest time might be unknown. At our institution, HTK is repeated after 90 minutes of ischemia. There is no evidence which strategy might be the best for these particular scenarios. There are publications of mostly retrospective nature which suggest that crystalloid solutions might be inferior to blood cardioplegia concerning patients with reduced left ventricular ejection fraction (12).

In conclusion, HTK-Bretschneider is an excellent preservation solution for a broad range of cardiac operations and has contributed to the excellent results in cardiac surgery to date. Still subgroups of patients for whom another solution or strategy could be beneficial are of further interest.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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