Editorial

Different strategies of myocardial protection: the age of perfectionism

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Intraoperative myocardial protection obtained with administration of cardioplegia is one of the crucial aspects that determine the success of modern cardiac surgical procedures. After the onset of "elective" ischemia a cascade of biochemical reactions starts: due to reduced oxygen availability contractile failure of the myocardium can be observed leading to a stimulation of anaerobic metabolism. Adenosine triphosphate (ATP) depletion and lactate accumulation eventually lead to myocardial acidosis and cause cell swelling and irreversible structural damage. In order to counteract these processes different compositions of cardioplegic solutions have been established in the past. They all aim to achieve a reversible electromechanical cardiac arrest and to protect the heart during surgery simultaneously.

There is an ongoing discussion in the surgical community about the "best" cardioplegia although we can most probably only define an "optimized" one. The main target of any cardioplegic solution is the patient's safety during the procedure but, with the knowledge that both types [either blood cardioplegia (BCP) or crystalloid cardioplegia (CCP)] are safe and effective for myocardial protection, it's also the surgeon's comfort that needs to be considered.

In the current era it is finally possible to choose the cardioplegic solution in function of the cardiac pathologies we plan to treat, the estimated ischemic time, the preoperative cardiac function and the patient's comorbidities, to gain a better intraoperative myocardial protection and achieve the best postoperative outcome. One can define this era as a time of perfectionism aiming at an even more progressive decrease of mortality and morbidity.

What have we learnt in the last decades about cardioplegic solutions? The article proposed by the Leipzig group (1) in the issue of *The European Journal of Cardiothoracic Surgery*, "*Custodiol versus cold Calafiore for elective cardiac arrest in isolated aortic valve replacement: a propensity-matched analysis of 7,263 patients*", compared these two different strategies of myocardial protection in adult cardiac surgery. Two hundred and fifty-eight patients were excluded from further analysis because they received another type of cardioplegia, most probably according to the surgeon's preference. Five thousand nine hundred and ninety-eight of the remaining 7,005 patients received CCP (Custodiol®, Dr. Franz Köhler Chemie, Alsbach, Germany) and the others (n=1,007) intermitted cold BCP according to Calafiore *et al.* (2). The authors started with an ancient but still actual axiom: an insufficient intraoperative myocardial protection compromises the postoperative outcome and "*the convenience of a bloodless and motionless operating field comes at the price of myocardial damage, characterized as ischemia-reperfusion injury*". That's true and therefore it is compulsory to decrease the myocardial damage as much as possible.

Hoyer *et al.* analysed their surgical results in terms of the primary outcome, which was the operative mortality,

and a combined end-point outcome defined as a composite of 30-day mortality, postoperative myocardial function, post-cardiac arrhythmia, dialysis and new pacemaker implantation. Their data confirmed that there were no significant differences in postoperative outcomes between both cardioplegic solutions regarding hard end-points.

Some data is missing: e.g., cardiac enzymes levels were not evaluated—neither preoperatively nor postoperatively. Furthermore, Calafiore solution was injected at 15 ℃, although this cardioplegic solution was introduced as tepid blood cardioplegia. Probably, the surgeons intended to combine both the effects of blood cardioplegia and of hypothermia to preserve the myocardial function but the metabolic substrate uptake is limited, independent of the temperature of the cardioplegic solution. Böning *et al.* (3) even proved that the cellular edema is more pronounced when cold BCP is applied and postischemic recovery seems to be better after warm BCP administration.

The contemporary preservation strategies are based on different principles. Zeng *et al.* (4) proposed a suggestive meta-analysis for myocardial protection in adult cardiac surgery, comparing the effects of cold BCP versus CCP, hypothermia and potassium induced electromechanical arrest versus blood used as a carrier of potassium delivery and myocardial protection.

The purported advantages of BCP include the large amount of oxygen carried by the haemoglobin, the metabolic substrates contained in the blood, the physiologic buffers and the physiologic osmotic pressure provided by this type of cardioplegia. In contrast, as already reported by Preusse *et al.* (5) in 1985, we know that the myocardial oxygen consumption of cardioplegically inactivated human hearts being perfused with cold histidine-buffered Bretschneider solution decreases during the whole perfusion period as well as the energy demand. In addition, we know that the application of oxygen to ischemic myocardium during intermittent re-perfusion that is compulsory for BCP may provide substrates for the production of deleterious oxygen free radical exacerbating the ischemia-reperfusion injury (4,6).

Of course, both strategies (intermittent reperfusion and effective extracellular buffering) are well-established methods to delay the inhibition of anaerobic glycolysis during ischemia. One needs to keep in mind that several aspects determine the effectiveness of any cardioplegic solution: first of all the composition to extract as much energy for cellular metabolism as possible, second viscosity to obtain an optimal organ perfusion and third enough buffering capacity to attenuate myocardial acidosis.

Recently, an emphasis was put on the buffering effect of Custodiol® cardioplegia that differs from others crystalloid solutions: histidine, which is present in the Custodiol® cardioplegia, acts as a free radical scavenger as well as mannitol. Both are components of this type of extra cardioplegia. Therefore, using this solution bears no danger for ischemic-reperfusion injury, since the concentration of scavengers is too high (7).

Braathen *et al.* (8) presented a study where they affirmed that, in elective aortic valve surgery, cold BCP seemed to provide a better myocardial protection in comparison to modified St. Thomas' Hospital solution which is also a CCP solution. Based on this analysis the authors decided to examine whether, in mitral valve surgery, a single dose administration of Custodiol® solution could guarantee the same top level of myocardial protection than cold BCP (9). They established two markers of myocardial injury as end points of their study: troponin-T and creatine kinase isoenzyme MB (CK-MB) release. Except for a significant difference between the two groups of patients regarding spontaneous ventricular fibrillation at cross clamp removal in the group of patients receiving histidine-tryptophan-ketoglutarate (HTK), although this did not influence cardiac enzyme release, maximum CK-MB and troponin-T release did not differ significantly between the groups. Thus, they concluded that the cardioprotective effect achieved with one single dose of Custodiol® solution is comparable with that obtained with repeated cold BCP in mitral valve surgery. Differently, Sakata *et al.* (10) documented even more spontaneous defibrillation and lower requirement of inotropic drugs in valve repair using Custodiol® instead of cold BCP.

Overall, clinical evaluations of cold BCP and CCP (especially Custodiol®) protection do not differ significantly in the recent literature. Anyway Hoyer *et al.* (1) did not forget that the surgeon's impetus for utilizing Custodiol® solution also stems from the expectation of a single dose application, providing a quiet and bloodless operative field to facilitate surgical procedure without interruption during the long and complex cases that are, at present, the most common scenario in all cardiac surgery operating theatres.

If we look to the experience of neonatal cardiac surgery some procedures require, even in very expert hands, prolonged aortic cross clamp time and selective administration of cardioplegia in the coronary ostia, representing one of the main concerns as the intimal layer of the coronary arteries can be easily damaged and frequent

interruptions are necessary. After a time of scepticism, facing of the results reported in the literature (11), there is an increasing preference for using Custodiol® solution to avoid repeated administrations of the routinely used BCP every 15–20 minutes selectively in the coronary ostia realizing these complex procedures without interruption.

All in all, we would like to conclude that different cardioplegic methods are feasible and mandatory as long as its administration is performed carefully. It's not just the surgery that needs to be performed accurately but also the setting of myocardial protection to delay the onset of irreversible damage of the heart as much as possible.

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Footnote

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

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