Editorial

Comparison of the different cardioplegic strategies in cardiac valves surgery: who wins the "arm-wrestling"?

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Cardioplegic arrest represented one of the most important (probably the greatest) achievement of cardiac surgery in the last 40 years because it allowed, on one hand, the feasibility of treating all heart pathologies with a stopped and bloodless heart and then to ensure, at the same time, myocardial protection during the ischemic period. Cardioplegic solutions usually used can be crystalloid or blood based. Custodiol® solution, also called histidine-tryptophan-ketoglutarate (HTK) or Bretschneider's solution, is a particular kind of long-acting intracellular crystalloid cardioplegia (CCP) that differs from other extracellular cardioplegic solutions because of its low sodium and potassium content that induce the diastolic cardiac arrest through an hyperpolarization of the myocyte plasma membrane. A low sodium solution seems to effect the lowest energy turnover compared with high potassium cardioplegia (1), histidine acts as buffer of anaerobic metabolites produced during the ischaemic period, ketoglutarate is used as precursor for ATP production, tryptophan as membrane-stabilizator and mannitol to reduce cellular oedema and for its radical scavenger properties. Custodiol®, moreover, for its attractive capacity to provide a long myocardial protection with a single infusion is widely used in complex cardiac surgery and for organ preservation in allowing performance of complex procedures without interruption. On the other hand, blood-based cardioplegic solutions (like Calafiore-cardioplegia) are characterized by high potassium levels as depolarisation factor inducing cardiac arrest in diastole (2). This kind of cardioplegia, that can be administred with continous or intermittent flow and at body or low temperature, seems to provide a "more physiologic" cardiac arrest because blood could reduce the damaging effects of prolonged ischemia (3,4). According to other, high-potassium cardioplegia "era" seems to come to an end due to discover of harmful effects onto ischemic myocardium (5).

In the last years, a lot of studies analyzed pros and cons of these two types of cardioplegic solutions in the different areas of cardiac surgery (6), both in adults and in pediatrics (7,8), in order to find unique and shared indications but today the debate is still open especially in valve surgery. In fact, while literature swarms of clinical investigations about use of cardioplegic strategies in coronary artery bypass (CAB) surgery (9), there are few and conflicting studies comparing their use in valve surgery.

The most recent review about this topic belong to Hoyer *et al.*, where it was analyzed a single-centre experience on 7,263 patients undergone isolated aortic valve surgery with the aim of compare cold blood cardioplegia (BCP) and cold CCP (10). Among patients that received one of the two types of cardioplegia, exploratory analysis revealed that group treated with cold BCP had an high percentage of associated comorbidities such as diabetes, peripheral vascular disease (PVD) or chronic obstructive pulmonary disease (COPD). Furthermore, the main indications for the use of BCP seemed to have been an impaired cardiac

function (LVEF <30%, NYHA ≥III) or prior cardiac surgery probably for the widespread opinion that intermittently BCP provides higher myocardial preservation due to its more physiological properties and oxygen-carrying capacity (4,11). This seems to be in accordance also with Braathen et coll. where percentage of patients with LVEF >50% were higher, even if statistically not significant, in the group treated with CCP (12) but not with Viana *et al.* that, on the other hand, reported a lower percentage of patients with impaired cardiac function (Severe LV dysfunction or NYHA > II) in CCP group compared with BCP group (13).

A really important factor that influence distribution and effectiveness of a cardioplegic solution, beyond the chemical composition, is the anatomical state of the coronary tree and the myocardium; infact, although in isolated aortic valve surgical patients coronary arteries are usually free of haemodynamic significant stenosis, the distribution of cardioplegia can be hampered by microcirculatory dysfunctions that are typically present in hypertrofied hearts (14). In the cases, a good option to prevent poor distribution of cardioplegia could be the BCP that, for its features, allow an intermittent antegrade/retrograde administration even if Ascione *et al.* demonstrated that also only antegrade intermittent administration of cold BCP can be useful for patients with hypertrophied hearts undergoing aortic valve surgery (15). Hoyer *et al.*, in this regard, reported a statistically significant difference in the percentage of patients that received anterograde/retrograde cardioplegia between two group that was higher among BCP patients (10). According to others, it seems even that warm BCP gives an higher myocardial protection in aortic valve repair (AVR) surgery compared to cold BCP (16). Øvrum *et al.*, on the contrary, showed that retrograde cold BCP was not superior to retrograde cold CCP for patients undergoing AVR (17).

As previously mentioned, it's clearly evident of how there are a lot of contradictory results about comparison between crystalloid or blood cardioplegic solution in cardiac surgery especially because populations or outcome variables are generally various among the different works.

In the study of Hoyer *et al.*, the author analyzed retrospectively 825 matched patients in order to avoid as much as possible selection biases. Patients undergone isolated AVR and treated with HTK solution or Calafiore Cardioplegia were retrospectively included; CCP were readministered if aortic cross-clamp exceeded 90 min while BCP, in contrast with the original protocol (2), was infused by cooling to 15 ℃. Outcomes analyzed were mainly clinic: in fact, operative mortality (OM, death within 30 days of surgery), re-exploration for bleeding, low cardiac output syndrome (LCOS), intra-aortic balloon pump (IABP) implantation, extracorporeal membrane oxygenation (ECMO) implantation, onset of myocardial infarction or cardiac arrhythmias were studied as indirect indicators of myocardial damage without considering cardiac enzymes release, as often done by other authors. OM, of about 2%, was the same between the two groups as well as for the other outcome variables; only cardiac arrhythmias were slightly more frequently observed among BCP patients. On these bases, authors concluded that it seems that are no difference in myocardial protection using cold blood or crystalloid cardioplegia in mitral valve surgery, in accordance with other reports found in the literature. Braathen *et al.* demonstrated that HTK in elective mitral surgery protects the myocardium equally well compared to repetitive antegrade cold BCP according to post operative serum levels of myocardial enzymes (12); he found only a significant increase in spontaneous ventricular fibrillation after the cross-clamp removal in patients receiving HTK that, however, did not influence the release of myocardial enzymes compared with BCP. In contrast with the observations there is the work of Sakata *et al.* (18): he reported more adequate myocardial protection in mitral valve surgery provided by HTK solutions compared to BCP because there were more spontaneous defibrillation and a lower requirement of inotropic in CCP group. Gaudino *et al.*, on the other hand, concluded that HTK solution offers inferior RV protection compared with warm BCP, mainly in the hearts with depressed pre-operative RV function, in patients undergone mitral valve surgery (19). Fannelop *et al.* found the same results (11) for what concerns LV protection in the pig.

In conclusion, as resulted from the analysis of the literature, the debate about effectiveness of Custodiol and BCP in myocardial protection and on mid or long-term clinical outcome in aortic valve surgery is still open even if there are some points of agreements. Custodiol®, in this regard, seems to be attractive for its capacity to give long myocardial protection and a bloodless and motionless operative field after single-dose application; this is very important for open-heart procedures like AVR or in all minimally invasive approaches where a clear and unobstructed view is of particular importance and where a repetitive application of BCP is non really suitable (20). In this regard, in our center experience Custodiol® is routinely used, even in congenital heart surgery, for all procedure

performed with a thoracotomy approach as minimally invasive aortic valve replacement. On the other hand, the use of cold BCP seems to be the preferred approach in patients with impaired cardiac functions; in fact, while the heart remains completely ischaemic during the long arrest obtained with Custodiol®, intermittent administration of blood-based cardioplegic solution seems to provide a better myocardial protection especially for it high oxygen and metabolites-carrying capacity. This results are shared also by Hoyer *et al.* that found superior long-term survival when BCP was used intraoperatively in patients with low LVEF undergone AVR. Similarly, Jin *et al.* reported that in these patients, post-operative catecholamine infusion can be avoided when myocardial protection is achieved with cold BCP (21).

In summary, CCP seems to produce good operative and post-operative results as BCP both in myocardial protection and in peri-OM and post-operative complications so each case have to be individually evaluated. The best cardioplegic solution, in fact, remains surely still unknown, expecially for aortic valve surgery, but further investigations about patients with a lot of comorbidities, like impaired cardiac function that might significantly influence the susceptibility of the myocardium to ischaemia-reperfusion injury, are maybe necessary.

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Footnotes

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

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