

# Cardioplegic solution challenges

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A recent survey of the outcome in 8641 patients who underwent coronary artery bypass grafting operations in northern New England reported an overall mortality of 4.48%<sup>1</sup>, 65% of which could be directly attributed to postoperative heart failure. The conclusion drawn from these data is that in spite of the improvement in myocardial protection accomplished in past years, there is room for further improvement, in particular in high risk patient subsets. Although strategies that attenuate the systemic inflammatory effects of cardiopulmonary bypass (CPB) can indirectly enhance cardioprotection, only those directly targeted at the myocardium will be considered here.

These direct strategies of myocardial preservation can be categorized as those involving aortic cross-clamping and cardioplegic arrest and those which are not cardioplegia-based.

As far as cardioplegia is concerned, the available literature allows to summarize the state of the art as follows:

cold crystalloid cardioplegia is associated with an excellent clinical outcome<sup>2</sup>, but blood cardioplegia offers superior cardioprotection in high risk situations, such as hypertrophied myocardium<sup>3</sup>, extended aortic cross-clamp times<sup>4</sup>, and evolving myocardial ischemia<sup>5</sup>. In this respect, a recent study by Tomasco et al.<sup>5</sup> shows (by multivariate analysis) that the nonuse of blood cardioplegia in patients undergoing urgent or emergency bypass surgery is a predictive factor of increased mortality;

antegrade delivery of cardioplegia is quite effective in many cases but retrograde coronary sinus perfusion is preferable in the presence of complete coronary occlusions with poorly collateralized myocardial areas<sup>6</sup>. Indeed, the nonuse of retrograde cardioplegia has been identified by multivariate analysis as one of the predictive factors of a

poor outcome in patients with left ventricular dysfunction<sup>7</sup>;

the controversy about cold versus warm blood cardioplegia is probably obsolete since there is increasing evidence that a tepid temperature (32-34 C) is an acceptable trade-off. It acts as a buffer against ischemic injury if cardioplegia delivery has to be transiently discontinued and, in addition, tepid bypass limits systemic vasodilation while improving cerebral protection. Indeed, temperature of cardioplegia might be less critical for adequate cardioprotection than the route of delivery; thus, in one study where the authors failed to detect differences between cold and warm blood cardioplegia in patients with poor left ventricular function<sup>8</sup>, the systematic use of retrograde cardioplegia in all patients may have masked the potential effect of temperature;

the Buckberg's approach (which associates warm induction, intermittent cold blood cardioplegia and warm substrate-enriched initial blood cardioplegic reperfusion) is widely used and has shown its efficacy (with the caveat that a recent randomized trial failed to document any benefit of the terminal hot shot in low risk patients). We believe, however, that this technique can be simplified and made possibly more effective by using minimally diluted blood cardioplegia (that we have coined mini-cardioplegia<sup>9</sup>). Basically, this approach entails the continuous combined (antegrade/retrograde) delivery of arterial blood simply supplemented with a small volume of concentrated cardioplegia (in our practice, a mixture of potassium and magnesium). This solution is continuously added to the arterial tubing through an electrically-driven syringe pump, the flow rate of which is adjusted on-line to keep the heart arrested with the minimum amount of potassium. Along with a continuous mode of

delivery, limited hemodilution allows us to optimize oxygen supply to the heart and helps maintaining an aerobic environment which translates into a better functional preservation. If cardioplegia is delivered through the coronary sinus, continuous perfusion is not a problem because the low-flow, low-pressure backbleeding from the coronary arteriotomy can be easily dealt with to dry the operative field. We still consider it important to run cardioplegic perfusion in an uninterrupted fashion to optimize oxygen delivery and hence achieve a true aerobic arrest. In addition to its effectiveness, the set-up is simple, friendly-user and cheap as the only disposable consists of a piece of tubing (for the blood cardioplegia line) and a stopcock (for connecting it to the potassium pump). No heat exchanger is interposed into the circuitry as cardioplegia is given at the same tepid temperature as the systemic perfusate. More sophisticated delivery devices are now available which provide a more accurate titration of the drug infusion rate while offering a greater flexibility with regard to temperature control, infusion pressure monitoring, blood to crystalloid dilution ratio and delivery of supplemental ingredients (which we do not currently feel validated by sound clinical data).

Noncardioplegia-based techniques encompass intermittent aortic cross-clamping with moderately hypothermic ventricular fibrillation and beating-heart operations. Intermittent cross-clamping has been reported to be efficacious<sup>10</sup> but it has failed to gain wide clinical acceptance, possibly because of time constraints (the period of aortic occlusion must not exceed 10 min). In addition, the technique requires repeated aortic side-clamping for construction of the proximal venous graft anastomoses and this raises obvious concerns about the risk of dislodgment of atheromatous material and subsequent neurologic injury.

Conversely, maintenance of a beating heart throughout the operation has gained quicker acceptance in the surgical community. The true rationale behind this approach is that CPB with aortic cross-clamping and cardioplegia may cause (or worsen) myocardial dysfunction through two distinct mechanisms: 1) the inflammatory response to CPB, which involves the release of negatively inotropic mediators<sup>11</sup>; 2) myocardial ischemia/reperfusion injury inherent to cardioplegic arrest, regardless of the efficacy of current preservation techniques. Even if one hypothesizes that myocardial ischemia could be virtually abolished by the technique of aerobic arrest described above, one would still have to deal with myocardial edema intrinsic to a cardioplegic state<sup>12</sup>. Off-pump surgery largely addresses these two issues but raises its own concerns that still limit its widespread clinical use.

Thus, assuming that cardioplegia will still remain the cornerstone of myocardial protection in the forthcoming years, it is worth pursuing attempts at further improving its cardioprotective effects through appropriate

new formulations. From this standpoint, two approaches, which are not mutually exclusive, can be considered. The first is based on the use of preconditioning mimetics, i.e., agents that pharmacologically reproduce the protective effects of ischemic preconditioning. Both adenosine and potassium channel openers fall into this category. It is fair, however, to acknowledge that the hopes raised by the numerous experimental studies that have tested these drugs have not been really met by the initial clinical results. Only one trial has reported some benefits with adenosine added to blood cardioplegia and also given before and after cardioplegic arrest<sup>13</sup> but these results have to be confirmed. On the other hand, the clinical use of potassium channel openers has been hampered by the fact that the only drug available for human use, i.e., nicorandil, cannot be used intravenously. It is possible that volatile anesthetics like isoflurane which have also been reported to open potassium channels may find a place among cardioprotective strategies but their mode of administration does not allow us to consider them as potential cardioplegia additives. A second promising approach is based on inhibitors of the sodium/proton exchange. Protons accumulating during ischemia are extruded at the time of reperfusion in exchange for sodium ions. The resulting sodium overload cannot be adequately handled by the sodium/potassium pump because the ischemia-induced shortage of energy makes it inefficient. This excess of intracellular sodium ions is thus extruded from cells through the sodium/calcium exchanger which functions in a reverse mode in that it brings calcium ions in, thereby setting the stage for calcium overload-induced tissue injury<sup>14</sup>. The consistent efficacy of sodium/proton exchange inhibitors in improving preservation after cardioplegic arrest in various animal models tends to be corroborated by the preliminary results seen in the coronary artery bypass surgery segment of the GUARDIAN trial (which assessed the effects of cariporide, a selective inhibitor of the myocardial isoform of the sodium/proton exchanger). The soundness of the rationale behind this approach along with the bulk of available data allow us to reasonably predict that these drugs may, in the near future, significantly contribute to improve current methods of cardioplegic protection.

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