

Is there a rationale for short cardioplegia re-dosing intervals?

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Author contributions: Durandy YD solely contributed to this paper.

Conflict-of-interest statement: I do declare that I have no conflicting interest including but not limited to commercial, personal, political, intellectual, or religious interests.

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Received: May 26, 2015

Peer-review started: May 29, 2015

First decision: August 4, 2015

Revised: August 16, 2015

Accepted: September 10, 2015

Article in press: September 16, 2015

Published online: October 26, 2015

Abstract

While cardioplegia has been used on millions of patients during the last decades, the debate over the best technique is still going on. Cardioplegia is not only meant to provide a non-contracting heart and a field without blood, thus avoiding the risk of gas emboli, but also used for myocardial protection. Its electromechanical effect is

easily confirmed through direct vision of the heart and continuous electrocardiogram monitoring, but there is no consensus on the best way to assess the quality of myocardial protection. The optimal approach is thus far from clear and the considerable amount of literature on the subject fails to provide a definite answer. Cardioplegia composition (crystalloid vs blood, with or without various substrate enhancement), temperature and site(s) of injection have been extensively researched. While less frequently studied, re-dosing interval is also an important factor. A common and intuitive idea is that shorter re-dosing intervals lead to improved myocardial protection. A vast majority of surgeons use re-dosing intervals of 20-30 min, or even less, during coronary artery bypass graft and multidose cardioplegia has been the "gold standard" for decades. However, one-shot cardioplegia is becoming more commonly used and is likely to be a valuable alternative. Some surgeons prefer the comfort of single-shot cardioplegia while others feel more confident with shorter re-dosing intervals. There is no guarantee that a single strategy can be safely applied to all patients, irrespective of their age, comorbidities or cardiopathy. The goal of this review is to discuss the rationale for short re-dosing intervals.

Key words: Myocardial protection; Del Nido cardioplegia; Continuous cardioplegia; Intermittent cardioplegia; Single-shot cardioplegia; Multidose cardioplegia; Crystalloid cardioplegia; Blood cardioplegia; Custodiol®; Histidine-ketoglutarate-tryptophan

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Core tip: During myocardial ischemia, cardioplegia is the preferred method of myocardial protection. However, decades after its implementation, there is still no consensus on the optimal re-dosing interval. Shorter re-dosing (15-30 min) has been preferred to longer intervals (45-60 min), but the choice of one approach over another relies more on the surgeon's preference than on clear advantages. As the interest for one-shot

cardioplegia has been increasing recently, we intend to discuss the rationale, if any, for short cardioplegia re-dosing interval.

Durandy YD. Is there a rationale for short cardioplegia re-dosing intervals? *World J Cardiol* 2015; 7(10): 658-664 Available from: URL: <http://www.wjgnet.com/1949-8462/full/v7/i10/658.htm> DOI: <http://dx.doi.org/10.4330/wjc.v7.i10.658>

INTRODUCTION

The successful curative treatment of certain congenital or acquired heart diseases requires a method allowing direct vision of the open heart. For decades, cardioplegia has been the preferred and best method to provide a non-contracting heart and a field without blood. However, despite its use on millions of patients, the debate over the ideal cardioplegic technique is still going on. Strictly speaking, cardioplegia means paralysis of the heart: the visual appearance of standstill heart and continuous monitoring of the electrocardiogram allow for an easy control. But cardioplegia is also the major component of myocardial protection. There is no consensus on the best tools for myocardial protection assessment. First, there is no way to routinely perform real-time myocardial protection evaluation. Second, myocardial protection is clinically assessed post-operatively *via* a number of indirect factors such as troponin I/T or creatine kinase MB levels, ischemic electric signs on EKG or myocardial infarction, stroke, atrial fibrillation, myocardial function on echo, low cardiac output state, inotropic support, intra-aortic balloon pump, extracorporeal membrane oxygenation, as well as time to extubation and length of stay in intensive care unit^[1-6]. These indirect factors are affected by several causes including surgery, anesthesia, intensive care, and, in the case of complex cardiopathies, resultant physiology following surgical palliation or cure. It is impossible to determine the role played by each cause. Myocardial protection is a concept without clear and specific clinical signs.

Experimental works on cardioplegia aiming to assess myocardial protection use time-consuming, invasive and often expensive approaches such as continuous monitoring of intra-myocardial pH, myocardial lactate production, or myocardial biopsy for ATP dosage, which are unrealistic in routine clinical practice^[7-9]. However, there is a huge amount of publications on cardioplegia trying to find the best technique for cardiac arrest and myocardial protection. The composition of the cardioplegic solution (blood vs crystalloid, with various substrate enhancement), the injection site(s) (antegrade, retrograde or both), the temperature (cold, tepid or warm) and the re-dosing intervals were the main factors explored. The large number of combinations of these factors makes studies difficult to compare.

Furthermore, the type of cardiac repair interferes with re-dosing intervals. During coronary artery surgery, re-dosing is usually done after each distal anastomosis, *i.e.*, every 10 ± 5 min, but 60-min re-dosing intervals have also been described^[10]. During valvular or complex procedures, re-dosing intervals are variable from one surgeon to another^[2,11-22].

Shorter re-dosing intervals could be a more critical factor than total aortic cross-clamp time in terms of myocardial protection, which would imply that shorter intervals lead to improved protection^[23]. This intuitive observation was supported by experimental and clinical works^[24-26]. Unexpectedly though, other works suggested that single-shot cardioplegia was better or at least equivalent to multidose cardioplegia^[27-30].

We have learned from heart transplantation that myocardial ischemia may be tolerated for several hours^[31]. The upper limit for donor heart ischemic time, which was 4 h in the early days of heart transplant surgery, was progressively increased to 6-8 h^[32]. Successful heart transplantation with a donor heart ischemic time of 13 h was published, but in this clinical case, the follow-up was limited to three months^[33]. Cold blood cardioplegia^[34], histidine-tryptophan-ketoglutarate (HTK) solution or Custodiol[®], a solution developed for organ preservation in transplantation^[35,36], and Del Nido cardioplegia were all proposed for single-shot cardioplegia^[37,38].

The debate over the best re-dosing interval is not new but while multidose cardioplegia has been the "gold standard" for decades, one-shot cardioplegia is becoming more commonly used and is likely to be a valuable alternative. This is particularly true for minimally invasive vascular surgery^[39,40]. However, the use of single-shot cardioplegia relies more on the surgeons' preference than on true advantages in terms of immediate outcomes^[41].

The goal of this work is to discuss the rationale for short re-dosing intervals.

FROM CONTINUOUS BLOOD CARDIOPLEGIA TO SINGLE-SHOT CARDIOPLEGIA *VIA* INTERMITTENT CARDIOPLEGIA

From a theoretical point of view, a continuous injection of normothermic oxygenated blood containing the arresting agent is the best way to perform cardiac arrest and optimal myocardial protection. Gott *et al*^[42] proposed this technique of aerobic arrest in 1957, but it was long to establish itself. In 1989, a clinical case was published on retrograde continuous blood cardioplegic warm infusion *via* the coronary sinus during mitral surgery. After a cross-clamp time of 393 min, the patient was easily weaned from bypass without intra-aortic balloon pump or inotropic support. It is noteworthy that the cardiac output was higher

immediately after bypass than before surgery^[43]. The same team used the same technique of aerobic arrest in 308 consecutive procedures with warm surgery. Twenty-two of these patients needing an aortic cross-clamp time greater or equal to 3 h had excellent results^[44]. The technic never became really popular for several reasons. First, it is technically more demanding and blind insertion of the cannula into the coronary sinus may be uneasy. Second, drawbacks were described, such as hyperkalemia, coronary sinus damage, catheter misplacement, migration or dislodgment in the right atrium^[45-47]. Third, a major concern was the distribution of cardioplegia to the right hypertrophic ventricle or when the right coronary vein is next to the coronary sinus^[48,49]. Last, for coronary artery bypass graft, a micro blower delivering compressed air is often needed for completion of distal anastomosis^[50].

To overcome constraints related to retrograde continuous cardioplegia, intermittent, antegrade warm blood cardioplegia was proposed as an alternative. From November 5, 1990 to December 31, 1992, a study was conducted at three adult cardiac surgical centers of the University of Toronto on 720 patients operated on for aortocoronary. Warm blood cardioplegia was interrupted during 5-15 min for enhancing visualization during distal anastomosis. The longest ischemic time, equivalent to the longest time off cardioplegia (LTOC, in minutes per patient) and the total duration of ischemic time as a proportion of the aortic cross-clamp time were collected. The quality of myocardial protection was assessed on post-operative mortality at 30 d (or in-hospital deaths for patients with a length of stay > 30 d), myocardial infarction by enzyme criteria and low-output syndrome. The authors postulated that short periods of normothermic ischemia should be well tolerated if followed by adequate cardioplegic reinfusion. Their study aimed to evaluate the relation between intermittency of cardioplegia and cardiac events.

The results suggested that the longest ischemic time was more important than the cumulative ischemic time and that prolonged LTOC > 13 min was a risk factor for adverse outcomes^[23]. For a vast majority of surgeons, thirteen minutes is a reasonable time for distal anastomosis construction. In summary, intermittent, antegrade warm blood cardioplegia is a valuable alternative to antegrade cold blood cardioplegia when the time off cardioplegia remains under 13 min. In a clinical scenario, this time off cardioplegia is more realistic than the maximal cardioplegia halted time of 5 min proposed by Menasché *et al*^[51] in 1992. In 1995, a simpler technique was described, allowing a re-dosing interval of 15 min. Two groups of 250 patients undergoing elective coronary artery bypass grafting were compared using either intermittent warm blood cardioplegia or intermittent cold blood cardioplegia. For the surgeon, the two types of cardioplegia were similarly demanding. After an initial injection in the aortic root, re-dosing was done after each distal anastomosis or after 15 min. This maximal ischemic

time was chosen to be long enough for a difficult distal anastomosis. The outcome was superior in the warm group, with significantly less cardiac-related deaths and a dramatic decrease in morbidity. There was lactate washout in both groups 1 min after aortic cross-clamping, but lactate production was still present 20 min after reperfusion in the cold group, while there was evidence of normal lactate extraction in the warm group, suggesting a rapid restoration of a normal metabolism. In summary, in this study, intermittent warm cardioplegia was superior to intermittent cold blood cardioplegia, with lower morbidity, mortality and decreased length of stay in ICU and hospital^[52]. The re-dosing interval was later increased to 20-30 min without complication^[53,54]. Other authors confirmed the good tolerance of 30-min warm ischemia time in 1996 and 2000^[55,56]. In 2009, a comparison between intermittent warm blood cardioplegia and single-shot warm blood cardioplegia was published. The study was done from January 2001 to December 2006 and included 4014 patients: 1708 had single-shot cardioplegia and 2306 had intermittent warm blood cardioplegia with a 20-min re-dosing interval. There was statistical insignificance for mortality, intra or postoperative intra-aortic balloon pump, postoperative inotropics or postoperative arrhythmia. Single-shot had a favorable effect on post-operative myocardial infarction and an unfavorable effect on intraoperative inotropics and postoperative dialysis. Authors found that the first shot of warm cardioplegia may safely exceed 20 min and, in case of short cross-clamping (35 to 40 min), cover the whole cross-clamping time without increased risk^[57]. However, there is probably an individual threshold for tolerance due to pre-, intra- and post-operative factors.

Interestingly, the same evolution in re-dosing interval was described in pediatric cardiac surgery. We introduced this technique in 2002 with a cardioplegia protocol identical to the one described in adults in 1995: warm oxygenated blood was diverted from the arterial line *via* a roller pump and St Thomas' solution was added downstream the pump with an electrical syringe. The blood to arresting agent ratio was 60:1, therefore the hydric balance of cardioplegia was negligible and it was named microplegia^[58]. The re-dosing interval was 15 min and a nomogram was developed for volume and duration of the first injection and re-injection^[59].

Another group implemented the same approach of intermittent warm blood microplegia, except for the re-dosing interval (10 min). They also suggested, on a group of arterial switch, that intermittent warm blood microplegia was a valid alternative to intermittent cold blood cardioplegia^[60].

Following our initial experience on 1400 pediatric patients, we demonstrated that the technique was safe for long aortic cross-clamp time on 38 patients with a cross-clamp time > 90 min^[61]. Using the same protocol for cardioplegia with a 15-min re-dosing interval, a group from Brussels used cardiac biopsies to demonstrate a significant increase in myocardial ATP

stores during the first cardioplegic ischemic time and a return to initial values after coronary reperfusion. This reproducible method was considered safe, with low morbidity and mortality and a similar quality of cardiac repair^[62].

The technique was gradually implemented in several European units and more than 10000 cases with re-dosing intervals varying from 10 to 25 min were published in 2010^[63]. As in adult surgery, intervals gradually increased between 2001 and 2013, from 10 to 35-40 min, without any adverse effect^[64,65]. However, the major issue remains: how long is too long? It is likely that re-dosing intervals cannot be indefinitely increased without inducing adverse cardiac events.

The merits of single-dose vs multidose cardioplegia in the infant heart were described in animal experiments several decades ago^[27-30], but there was a certain lack of enthusiasm for its clinical use. However, in 1988, a clinical study was published, comparing two groups of arterial switch operated on with single-dose or multidose cold blood cardioplegia with a 15-min re-dosing interval. The incidence of mortality and ST-T changes was significantly higher in the multidose group. The conclusion was that single-dose is as good as, or better than, multidose cardioplegia^[34]. In 1989, another group confirmed the efficiency of single-shot cold crystalloid cardioplegia in arterial switch procedure^[66].

There is increasing interest in HTK or Custodiol[®] single-dose cardioplegia. In 1998, Sakata suggested that single high-volume HTK provided a more adequate myocardial protection for mitral surgery than multidose cold blood cardioplegia^[67]. In 2001, the benefit of single-dose HTK cardioplegia over multidose cold crystalloid cardioplegia was also suggested in a clinical work comparing two groups of 15 patients. The incidence of arrhythmia and inotropic support decreased significantly in the HTK group and so did the ICU length of stay^[68]. The feasibility and safety of single-shot HTK cardioplegia was suggested in adult and pediatric surgery^[35,36,69,70]. A new modified HTK solution named Custodiol-N, likely to enhance the organ protective potential of the previous solution, was tested on animals during a 60-min hypothermic cardiac arrest^[71,72].

Del Nido cardioplegia has been used for two decades at the Boston Children's Hospital, generally in a single-dose fashion^[73]. Its use was expanded to adult surgery, triggering a growing interest in this solution^[74]. Recent works in adults and pediatrics suggest that it is a safe and valuable alternative to conventional multidose cardioplegia^[37].

WHERE ARE WE? WHERE DO WE GO FROM HERE?

A review of the literature published prior to 1975

concluded that a 20-min ischemic period at 32 °C could be tolerated by the heart without the need for inotropic support, while the anoxic safe period was extended to 30 min when temperature was lowered to 16 °C-20 °C^[75]. Forty years later, despite ample evidence that the ischemia time can be safely increased, even during warm surgery, a vast majority of surgeons use re-dosing intervals of 20-30 min, or even less, during coronary artery bypass graft. Some surgeons prefer the comfort of single-shot cardioplegia while others feel more confident with shorter intervals. How can we explain the myocardial tolerance to anoxia? Is it due to the composition of the arresting solution, the temperature of cardioplegia, or both?

We have seen that for cold and warm blood cardioplegia, short-term outcomes are equivalent with identical re-dosing intervals, just as they are identical for cold blood and cold crystalloid cardioplegia. The temperature is likely to have little effect, if any, but studies focused on aortic cross-clamp times < 90 min. We have also seen that different cardioplegic solutions can be safely used for hypothermic single-shot cardioplegia^[34-38]. The composition did not seem to be critical, or, at least, different solutions can be used for single-shot cardioplegia and comparisons between these solutions are missing.

It is probably a fool's errand to look for a universal gold standard. The best cardioplegia with optimal re-dosing interval is likely to vary with different patients having different pathologies, and different aortic cross-clamp time. Dr J Vaage's stated: "If you had a clamp time of < 60 min, you could actually use whatever cardioplegia or myocardial protection you wanted, you could always get to the shore, so to say"^[57]. It is probably true, but we are still looking for the optimal cardioplegia, for simple and complex cardiopathies. The goal is not just to get to the shore, but also to use the best, simplest, fastest and cheapest way to deliver optimal results to our patients. Furthermore, we intend to prevent cardiac events not just during the initial outcome - the one that allows getting to the shore - but also during mid- and long-term outcomes^[76]. Myocardial fibrosis could be a late side effect of cardioplegia^[77]. This is more challenging and less extensively studied.

CONCLUSION

This review does not solve the issue on the rationale for short-term re-dosing interval. However, facts are facts, and many works suggest or demonstrate that short-term re-dosing intervals are not critical for every patient. There is probably no rationale to use the same re-dosing interval for all patients needing aortic cross-clamping for surgical cardiac repair. Despite the lack of consensus on cardioplegia composition, temperature, way of administration and re-dosing interval, the outcomes of adult and pediatric cardiac surgery are continuously improving.

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