Published in final edited form as:

Ann Thorac Surg. 2008 February ; 85(2): 454–458. doi:10.1016/j.athoracsur.2007.08.039.

Retrograde Hot-Shot Cardioplegia in Patients With Left Ventricular Hypertrophy Undergoing Aortic Valve Replacement

Raimondo Ascione, MD, Saadeh M. Suleiman, PhD, and Gianni D. Angelini, FRCS

Bristol Heart Institute, University of Bristol, Bristol, United Kingdom

Abstract

Background—Intermittent antegrade cold-blood cardioplegia followed by terminal warm-blood cardioplegic reperfusion or hot-shot is reported to reduce myocardial injury in the setting of coronary surgery. The efficacy of this cardioplegic technique in patients with left ventricular hypertrophy secondary to aortic stenosis remains uncertain.

Methods—Thirty-six patients with left ventricular hypertrophy undergoing aortic valve replacement were prospectively randomized to cold-blood cardioplegia either alone (cold-blood cardioplegia group) or with retrograde hot-shot (hot-shot group). Reperfusion injury was assessed by measuring myocardial levels of adenosine triphosphate and lactate in left and right ventricular biopsies taken 5 minutes after institution of cardiopulmonary bypass and 20 minutes after removal of cross-clamp using high-performance liquid chromatography and enzymatic techniques. Myocardial injury was assessed by serial release of troponin I up to 48 hours postoperatively. Overall clinical outcome was prospectively collected.

Results—Baseline and intraoperative characteristics were similar between groups. In the hot-shot group, there were no significant changes in the myocardial concentration of adenosine triphosphate and lactate in both left and right ventricular biopsies after reperfusion. In the cold-blood cardioplegia group, there was a trend to a fall in adenosine triphosphate levels in the left and right ventricular biopsies after reperfusion, but this reached statistical significance only in the right ventricle. Troponin I release was raised in both groups at 4 and 12 hours after surgery ($p < 0.05$), but did not reach levels of myocardial infarction.

Conclusions—The terminal retrograde hot-shot reperfusion does not add any extra benefit to antegrade cold-blood cardioplegia in preventing myocardial injury in patients with left ventricular hypertrophy undergoing aortic valve replacement. Nevertheless, it appears to reduce ischemic stress in the right ventricle. There was no difference in clinical outcome between groups.

Left ventricular (LV) hypertrophy increases end-diastolic volume and pressure, myocardial work, and oxygen demand [1]. Its metabolic state is anaerobic [2], with increased vulnerability to ischemia and reperfusion injury. Surgically induced ischemia and reperfusion continues to be a major contributor to morbidity and mortality after cardiac surgery in such patients and has been attributed to inadequate myocardial protection [3, 4]. Nevertheless, little work has been carried out on myocardial protection in patients with LV hypertrophy in whom the choice of optimal cardioplegia remains controversial [5–8]. We have previously shown that the metabolic state of hypertrophic hearts is different from that with ischemic disease [9]. Therefore, cardioprotective strategies developed for ischemic hearts should not be extrapolated uncritically to hypertrophic hearts.

Postischemic recovery might be improved by using a terminal warm-blood cardioplegic reperfusate or hot-shot (HS), which allows cellular energy stores to be regenerated and channeled into repairing reversibly injured myocardium during a period of electromechanical quiescence [10, 11]. This has been shown to improve metabolic and short-term functional recovery and to decrease mortality in cardiac surgery operations [12, 13].

The aim of this prospective study was to compare the efficacy of intermittent antegrade cold-blood (CB) cardioplegia with or without retrograde terminal warm-blood cardioplegic reperfusion HS on the intracellular concentrations of biochemical markers of ischemic and metabolic stress and on clinical outcome in patients with LV hypertrophy secondary to aortic stenosis undergoing aortic valve replacement. Our rationale of using a retrograde delivery for the HS is mostly to optimize coronary artery and aortic root removal of air and to shorten ischemic time as the retrograde HS can be delivered while closing the transverse aortotomy.

Material and Methods

Adult patients undergoing elective aortic valve replacement surgery for aortic stenosis between October 2001 and September 2003 at the Bristol Royal Infirmary were prospectively randomized to receive CB cardioplegia either with terminal HS (HS group; n = 16) or without (CB group; n = 20).

Exclusion criteria included coronary artery disease, concomitant aortic regurgitation, LV ejection fraction of less than 0.30, history of congestive heart failure, diabetes mellitus, and reoperation, emergency, or salvage procedures. Eligibility for surgery was based on the medical history, echocardiography, and the most recent angiogram.

Simple random treatment allocations (ie, not blocked or stratified) were generated in advance of starting the study and were concealed in sequentially numbered and sealed opaque envelopes. After written informed consent was obtained, a patient was randomized by opening the next numbered envelope. The study was approved by the United Bristol Healthcare Trust Ethics Committee, and all patients gave informed consent.

Operative Procedures

Anesthetic and surgical techniques have been reported previously [14, 15]. Briefly, a standard cardiopulmonary bypass circuit was primed with 1,000 mL of Hartmann's solution, 500 mL of colloidal solution, 0.5 g/kg mannitol, 7 mL of 10% calcium gluconate, and 6,000 IU of heparin. Nonpulsatile flow rates throughout bypass were 2.4 L/m² per minute. Systemic temperature was actively cooled down to 32°C. The LV was vented in all patients through the right superior pulmonary vein. Myocardial protection was achieved with antegrade CB (6° to 8°C) cardioplegia, with added potassium and magnesium to give a final concentration of 20 mmol/L potassium and 5 mmol/L magnesium. The CB cardioplegic solution was similar in the two groups; it was a mixture of the patient's blood withdrawn from the cardiopulmonary bypass circuit and St. Thomas's I cardioplegic solution (4 parts blood to 1 part St. Thomas's I) [7, 11]. The delivery of CB cardioplegia was similar between the two groups. After cross-clamping and opening of the ascending aorta, the cardioplegia was administered directly into the coronary ostia as a 1-L bolus (700 mL in the left and 300 mL in the right ostia) at a pressure of 120 mm Hg (total delivery time approximately 3 minutes). Infusions of 200 mL for each ostium were repeated at 15-minute intervals. In the CB with HS group, CB cardioplegia was also delivered directly in the coronary ostia, and the final HS was delivered by means of the retrograde route (to optimize coronary and aortic root air removal and to save 6 to 8 minutes of ischemic time required for aortotomy).

suturing). A retrograde coronary sinus cardioplegic catheter (Edwards LifeSciences, Irvine, CA) was introduced through a pursestring suture into the right atrium and guided into the coronary sinus. The catheter was inserted for 1.5 cm in the coronary sinus, and its position was checked by manual palpation and pressure, and by the type of peculiar wave pressure. The HS solution was identical in composition to the induction and maintenance doses and was administered at 300 mL for 2 minutes at 37°C immediately before unclamping the aorta.

Postoperative Management and Assessment of Clinical Outcome

Patients were admitted to the intensive care unit after the operation and managed by intensivists. Decisions regarding inotropic support and ventilation were based on unit protocols, hemodynamic status, and clinical judgment [14, 15]. Intraoperative and postoperative clinical variables were prospectively recorded. Heart rate and rhythm were continuously monitored and displayed on a monitor inclusive of an automated detector of arrhythmia during the first 72 hours postoperatively. Twelve-lead electrocardiographic recordings were performed preoperatively, 2 hours postoperatively, and then daily thereafter until discharge. Clinical diagnostic criteria for perioperative myocardial infarction were new Q waves of greater than 0.04 ms or a reduction in R waves greater than 25% in at least two leads. Biochemical diagnostic criteria for perioperative myocardial infarction were peak troponin I concentrations higher than 3.7 g/L and a troponin I concentration greater than 3.1 g/L 12 hours postoperatively or greater than 2.5 g/L 24 hours postoperatively [16, 17].

Collection of Ventricular Biopsy Specimens

Transmural biopsies of the LV apical or anterolateral free wall and the right ventricular (RV) free wall (4 to 12 mg wet weight) were taken using a Trucut needle (Baxter Healthcare Corporation, Northbrook, IL). Two biopsies were collected from each ventricle; the first biopsy 5 minutes after institution of cardiopulmonary bypass before aortic cross-clamping (control), the second after 20 minutes of reperfusion after removal of the aortic cross-clamp. Each specimen was immediately frozen in liquid nitrogen until processing for analysis of adenosine triphosphate (ATP) and lactate, as previously reported [9, 14, 18]. A research technician blind to the operative technique performed the analyses.

Measurement of Cardiac Troponin I

Serum concentrations of cardiac troponin I were determined before surgical intervention and at 1, 4, 12, 24, and 48 hours postoperatively by using the ACCESS Immunoassay System (Beckman Instruments, Fullerton, CA).

Statistical Analysis

Data were expressed as mean $\pm$ standard error of the mean unless stated otherwise. Categorical variables were analyzed using either the Fisher's exact test or the χ^2 test as appropriate. Comparison between continuous variables within and between groups was tested using a nonparametric test (Wilcoxon's signed rank test). Because ATP measurements were carried out using enzymatic and high-performance liquid chromatography techniques, the actual values are given in the results section but are expressed as percentage of change at reperfusion versus baseline values in the relevant figure. All statistical analyses mentioned were performed with the aid of a computerized software package (Statview for Windows; SAS Institute Inc, Cary, NC).

Results

Clinical Outcome

A total of 36 patients were recruited into the study. Preoperative characteristics are shown in Table 1. Intraoperative and postoperative data are shown in Table 2. There were neither in-hospital deaths nor perioperative myocardial infarction as per predefined troponin I levels or serial postoperative electrocardiographs. The total incidence of postoperative arrhythmias including requirement for temporary pacing, permanent pacemaker, and atrial fibrillation did not differ between groups. No differences were observed between groups with regard to postoperative incidence of renal, respiratory, and neurologic complications (data not shown).

Myocardial Metabolic Changes

Percent changes between control and reperfusion in ATP levels for both LV and RV are shown in Figure 1. In the HS group there were no significant differences in levels of ATP as a result of reperfusion in LV biopsies (from 25 ± 2 to 25 ± 2 nmol/mg protein), but there was a small insignificant decrease in ATP in RV biopsies (from 27 ± 3 to 23 ± 3 nmol/mg protein; $p = 0.13$). On the other hand, the changes in the CB group showed a small significant fall in ATP in the RV biopsy (39 ± 3 to 32 ± 2 nmol/mg protein; $p < 0.05$) but not in the LV biopsy (34 ± 2 to 30 ± 3 nmol/mg protein; $p = 0.17$).

Changes in lactate are shown in Figure 2. In the CB group there was a trend for a higher release of lactate at reperfusion in the LV biopsy, but this did not reach statistical significance (from 42 ± 8 to 50 ± 13 nmol/mg protein and from 46 ± 7 to 41 ± 6 nmol/mg protein, CB versus HS groups, respectively; $p = 0.1$).

Myocardial Injury

Troponin I release is shown in Figure 3. Postoperative release increased 1 hour after surgery, reaching a maximum at 4 hours with subsequent gradual decline up to 48 hours after surgery. However, comparisons between groups did not show any difference at any of the times investigated.

None of the patients in either group had a postoperative myocardial infarction as per predefined criteria of troponin I release.

Comment

Reperfusion after cardioplegic arrest-induced myocardial ischemia is known to cause irreversible cellular changes [19, 20]. The potential for reperfusion damage exists in all cardiac operations requiring temporary interruption of the coronary circulation to perform surgery. This may contribute to the impaired cardiac performance that develops during the postoperative period, and to the eventual myocardial fibrosis that may result after surgical correction of congenital or acquired cardiac diseases [19-22].

Previous studies in adults have shown that the fate of the myocardium jeopardized by global ischemia might be determined by careful control of the conditions of reperfusion and the composition of the perfusate [19, 20, 23]. As result, the terminal HS is now used in most adult cardiac surgical procedures even if this method of myocardial protection has been tested mostly in the setting of coronary surgery. The rationale of using HS is to actively resuscitate the ischemically damaged, energy- and substrate-depleted heart by maximizing the kinetics of repair and minimizing oxygen demands by maintaining arrest.

Our study investigates the efficacy of terminal HS in patients with LV hypertrophy, following other studies we have carried out at our institution on this topic. We have

demonstrated that CB cardioplegia is associated with less ischemic stress and myocardial injury compared with warm-blood cardioplegia in hypertrophic hearts [15], and that when using CB cardioplegia the route of delivery (ie, retrograde or antegrade) does not affect the degree of injury [14]. However, with CB cardioplegia alone the myocardial protection of hypertrophic hearts was still suboptimal, and this prompted us to undertake the present study.

The data suggest that for an average cardioplegic arrest time of 70 minutes the use of retrograde HS is associated with full metabolic recovery in both LV and RV biopsies. This is supported by the complete preservation of ATP and by the lack of increase of lactate. However, the use of CB cardioplegia alone, although seeming to provide protection for the LV, was associated with a small drop in ATP in the RV biopsy. This drop in ATP was not observed in the HS group, suggesting that retrograde delivery of HS might be protective for the RV. We could not find any metabolic explanation for this finding. Nevertheless, one possible explanation might be the air removal effect of the retrograde delivery of HS on the right coronary artery as, owing to its anatomic position on the anterior wall of the ascending aorta, it is more exposed than the left coronary artery to air microembolization.

Our finding also confirms the value of retrograde delivery in protecting the RV as some investigators are concerned that this route of delivery may affect distribution of cardioplegia to the RV free wall [24].

It is worthy noting that the mean cardioplegic arrest time in our groups was relatively short. It is possible that for complex operations requiring prolonged cardioplegic arrest time, the use of terminal HS might prove to be more beneficial when compared with CB, but this hypothesis should be tested in another study. Nomura and coworkers [25] reported a clear metabolic advantage of terminal HS in neonatal lamb hearts. However, in their study the hearts were more stressed as a result of almost double the duration of global ischemia (120 minutes).

The increase of troponin I after surgery was observed to an equal extent in both groups, and was statistically significant as compared with baseline values. This finding is consistent with the occurrence of a degree of myocardial injury and suggests that both these techniques provide suboptimal myocardial protection. A possible explanation of the lack of beneficial effect of HS on troponin I release might be that we used a protocol with 2 minutes of retrograde delivery, which was adapted from our previous experience in coronary artery bypass grafting surgery [13] and might have been insufficient to protect these hypertrophic hearts. Nevertheless, the release of troponin I at no time of observation reached the predefined level suggesting occurrence of myocardial infarction [16, 17]. Also, there were no episodes of low cardiac output in either group. Levels of ATP have been shown to correlate with function, and indeed ATP levels in LV biopsies were preserved with both cardioplegic techniques at reperfusion.

In summary, the terminal retrograde HS does not add any extra benefit to antegrade CB cardioplegia in preventing LV reperfusion and myocardial injury in patients with LV hypertrophy undergoing aortic valve replacement with relatively short cardioplegic arrest time. Nevertheless, it appears to reduce metabolic stress in the RV. Both cardioplegic techniques are associated with a minor degree of myocardial injury, which does not reach levels of clinical relevance.

Acknowledgments

This study was supported by the British Heart Foundation. Doctor Ascione is also supported by the Garfield Weston Trust. We thank colleagues in the unit, especially Attilio A. Lotto, MD, and Massimo Caputo, MD, for help with collecting some biopsies.

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Fig 1.

Changes in adenosine triphosphate (ATP; percent change compared with preischemia; gray bars) in left and right ventricles during cold-blood cardioplegia with (HS; black bars) or without (CB; white bars) terminal hot-shot. Biopsies were collected from left and right ventricle before cross-clamping the aorta (control = 100%) and 20 minutes after reperfusion. * $p < 0.05$.

Fig 2. Changes in myocardial lactate concentration in left and right ventricles during cold-blood cardioplegia with (HS; black bars) or without (CB; white bars) terminal hot-shot. Biopsies were collected from the left and right ventricles before cross-clamping the aorta (preischemia) and 20 minutes after reperfusion.

Fig 3. Myocardial troponin I release shown at different times postoperatively after cold-blood cardioplegia with (HS; black circles) or without (CB; white circles) terminal hot-shot. Data are presented as mean $\pm$ standard error of the mean and expressed as nanograms per milliliter.

Preoperative Data^a

Table 1

Variable	CB (n = 20)	CB + HS (n = 16)
Male	12 (60%)	10 (62.5%)
Age (y)	65.3 ± 9.6	64.8 ± 7.3
BSA (m ²)	1.91 ± 0.22	1.87 ± 0.19
History of hypertension	13 (65%)	10 (62.5%)
Ejection fraction		
Good (>0.49)	16 (80%)	12 (75%)
Fair (0.30–0.49)	4 (20%)	4 (25%)
Ventricular mass index (g/m ²)	181 ± 42	179 ± 37
Transvalvular peak gradient (mm Hg)	75.7 ± 21.4	79.1 ± 18.2
NYHA class		
I–II	12 (60%)	10 (62.5%)
III–IV	8 (40%)	6 (37.5%)
Euro score	4.1 ± 0.8	4.0 ± 1.1

BSA = body surface area; CB = cold-blood cardioplegia; HS = retrograde hot-shot cardioplegia; NYHA = New York Heart Association.

^aData are presented as mean ± standard deviation or as number with percentage in parenthesis.

Table 2
Intraoperative and Postoperative Data^a

Variable	CB (n = 20)	CB + HS (n = 16)
CPB time (min)	112.5 ± 23.8	108.9 ± 27.3
Cross-clamp time (min)	68.7 ± 21.7	73.2 ± 19.8
Mean valve size inserted (mm)	21.6 ± 3.1	21.8 ± 2.9
Rhythm after cross-clamp removal		
Sinus	15 (75%)	12 (75%)
Pacing	3 (15%)	4 (25%)
VF	1 (5%)	0
Perioperative MI	0	0
Low cardiac output	0	0
Postoperative arrhythmia	5 (25%)	2 (12.5%)
Reopening for bleeding	0	0

CB = cold-blood cardioplegia; CPB = cardiopulmonary bypass; HS = retrograde hot-shot cardioplegia; MI = myocardial infarction; VF = ventricular fibrillation.

^aData are presented as mean ± standard deviation or as number with percentage in parenthesis.