ORIGINAL ARTICLE

Metabolic Markers Evolution During Antegrade and Retrograde Normothermic Blood Cardioplegia

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Background: Several studies suggested that the ventricular myocardium is suboptimally protected during retrograde blood cardioplegia.
Methods: Twenty patients (10 patients for subgrups) undergoing an elective valvular replacement mitral and aortic, with right atrial approach, mitral transeptal or tricupid procedures were randomized to receive antegrade or retrograde normothermic blood oxigenated cardioplegia. Astrup determinations (astrup values, lactate production, pH and BE) and ventricular differences in oxygen extraction from separate coronary ostium canulation were monitored during aortic cross-clamping at time at cardioplegic delevery immediately after cross clamping, at first, 20 minutes or 30 minutes of ischemia, after aortic declamping immediately and after 10 minutes. Hemodynamic recovery and postoperative complications were noted.
Results: The preoperative characteristics of the two groups were similar. Lactate production and oxygen extraction in the right ventricular myocardium were higher in the retrograde group. In this group, the right ventricle also extracted more oxygen and produced more lactate and acid than did the left ventricle. A typical cumulative ischemic pattern with progressively decreasing pH, BE values and progressively increasing lactate values could be observed similar in both groups in all patients. It was not the degree of lactate washout, but the lactate concentration at the end of each reperfusion wich increased proportional with ischemic time bettewen cardioplegic administration and after declamping — that correlated significantly with global metabolic recovery time. Nevertheless, the postoperative course was uneventful in both groups.
Conclusions: Despite of value of lactate production, acidosis and oxygen extraction, were more prominent in the right ventricular myocardium during retrograde cardioplegia after declampation, at 10 minutes this value became similar, and clinical and inotropic necesity were similar in this two groups. During antegrade cardioplegia the washout of myocardial metabolites is very efficient and the peak levels of lactate decrease rapidly at the end of cardioplegic administration and after declampation compared with retrograde administration. No diference seems to be seen between retrograde or anterograde cardioplegic administration 10 minutes after declampation. Nevertheless the postoperative course seems to be unproblematic in two series.

Keywords: acidosis, valvular replacement, cardiac arrest, coronary sinus, myocardial ischemia, myocardium metabolism, anterograde and retrograde cardioplegia

Introduction

Optimal myocardial protection relies on adequate delivery of the cardioplegic solution to all parts of the heart. Retrograde administration of cardioplegia through the coronary sinus offers a good alternative for protecting the myocardium during cardiac operation [1].

Controversy over the uniformity of the protective capacity of retrograde blood cardioplegia still exists, however. Approximately one quarter of human hearts have a cardiac vein draining the dorsal wall of the right ventricle and entering the coronary sinus near its orifice. Retroperfusion through this vein is endangered if the balloon-tipped coronary sinus catheter is positioned too distally [2]. This concern is based largely on findings that a large percentage of retroperfusate is shunted through the arteriosinusoidal system and thebesian veins into the ventricular cavities as nonnutritive flow, leading to non-homogeneous distribution of cardioplegia and inadequate protection of the right ventricle and the posterior left ventricles [3–8]. The occasional need to discontinue cardioplegia can also predispose the myocardium to ischemia, especially when normothermic cardioplegia is used [9,10]. Despite these theoretical pitfalls, good clinical results have generally been achieved with retrograde cardioplegia even in the case of hypertrophied hearts [10,11,12].

We conducted a randomized trial to study the myocardial protection during antegrade or retrograde normothermic blood cardioplegia. Metabolic changes in the left and the right ventricular myocardium were monitored during the aortic cross-clamp period by repeatedly determining lactate production, pH and oxygen content, hemodynamic recovery and postoperative complications were also recorded.

Material and methods

Patients

Twenty patients admitted for elective valvular replacement with right atrial approach (mitral transeptal or tricupid and aortic) were randomized into two groups: antegrade normothermic blood cardioplegia and retrograde normothermic blood cardioplegia. An ejection fraction of less than 0.45 was the only exclusion criteria (table I).

Anesthesia and perfusion

Anesthesia was induced and maintained principally using intravenos drugs. A membrane oxygenator was used (Compactflo; Dideco, Mirandola, Italy). The hematocrit was kept higher than 28% during cardiopulmonary bypass, pump flow was 2 to 2.4 L × min^{-1} × m^{-2}, and mean arterial pressure was kept at 60 to 90 mmHg with the aid of nitroglycerin or phenylephrine hydrochloride. The systemic temperature of the patients was maintained in normothermia at 34/37˚C.

Surgical technique

All operations were done by the same cardiac surgeon (V.R.). Cardiopulmonary bypass was established with two right atrial cannula in superior and inferior vena cava, snare both and an ascending aortic cannula. A cardioplegia delivery cannula with venting and pressure-monitoring ports (DLP Inc, Grand Rapids, MI) were used in the antegrade group. The heart was arrested in an antegrade manner in both groups. A coronary sinus catheter without a manually inflatable balloon (DLP Inc) using a 4.0 ticron purstring. The retrograde group and a pediatric sinus catheter (DLP Inc) in the antegrade group were positioned using open technique after initiation of cardiopulmonary bypass.The catheter was placed as proximally as possible under visual control.

Cardioplegia

The same cardioplegic solution was used in both groups.. One part of solution and 9 parts of blood (1:9) were delivered using a commercial cardioplegia set (CSC 14; Dideco). After aortic cross-clamping, hearts in both groups were arrested by inducing antegrade normothermic cardioplegia with 8 mEq KCl at 300 mL/min for 3 minutes, with the aortic root pressure kept lower than 80 mm Hg. Thereafter, cardioplegic solution was infused by either the antegrade (group 1) or the retrograde route (group 2) at 20 or 30 minutes interval depends on the surgical procedures. In the retrograde group, cardioplegia administration was switched to retrograde delivery after the arrest of the heart and continued at 200 mL/min. Aortic root pressure was monitored continuously in the antegrade group and maintained at less than 80 mmHg. Coronary sinus pressure was monitored continuously and maintained lower than 50 mmHg. A total of 1000 ml of cardioplegia was delivered each time in both groups. A cardioplegic sample was remove from coronary ostium trans aortotomy when cardioplegic retrograd administration and from coronary sinus when anterograde cardioplegic solution are used.

Laboratory data

Blood samples were taken simultaneously from the cardioplegia line (inflow) through the coronary sinus and from the right and left coronary ostium in the retrograde group and from the cardioplegia line (inflow) and coronary sinus catheter in the antegrade group. Blood samples were taken immediately when cardioplegic solution is delivery after declamping and 10 minutes after. Oxygen content and pH were determined with a 288 blood gas system (Ciba-Corning, Medfield, MA). Lactate production was assayed using an electrode-based lactate analyzer (model 1500; Yellow Springs Instrument Co, Inc, Yellow Springs, OH). The oxygen extraction were calculated using Fick Equation

$$VO_2 = (CaO_2 - CvO_2) \times CO \times 10$$

or

$$VO_2 = 1.38(Hb) \times (CO)(SaO_2 - SvO_2) \times 10$$

Statistical analysis

The statistical analyses were performed using the Excel (Office 2003). The unpaired Student t test and 2 test were used to compare the clinical variables between the two groups, and multiple analysis of variance was used to test time-dependent changes in the measured variables. The resulting design was a 2 (group) by 3 (time) by 2 (ventricles) analysis of variance. Group was a between-group factor, and time and ventricles were repeated measures factors. When the F values indicated that significant differences were present, Scheffé's post-hoc test was used. The data are presented as the mean±SD. Significance was assumed when the p value was less than 0.05.

Results

Patients

Ten patients were randomized into each cardioplegia group. The two groups had no significant differences in New York Heart Association classification of cardiac disfunction and EF and similar preoperative characteristics (table I).

Perioperative course

The cardiopulmonary bypass and aortic cross-clamp times were similar in this two groups. The cumulative ischemia times were between 80 and 110 in group 1 and between 82 and 98 minutes minutes in group 2 ($p < 0.0001$) of the corresponding aortic cross-clamp times in the antegrade and retrograde groups, respectively. The time of cardioplegia administration was higher in the retrograde group because of the shorter rate administration of 200 mL/min than anterograde administration of 300 mL/min in delivery, but ischemic time was shorter in the retrograde group because there were no stops on the surgical procedures in time of cardioplegic administration.

Metabolic changes

Blood samples for the analysis of oxygen content, lactate production, and pH were taken simultaneously from the cardioplegia line and the coronary sinus in the antegrade group and from the cardioplegia line and the aortic root in the retrograde group, and the outflow-inflow differences representing both ventricles were subsequently calculated. Lactate efflux from the right ventricle was higher in the

Table I. Clinical characteristics*

Variable		Retrograde group (n=10)	Anterograde group (n=10)
Age	(year)	61.4±7.9	64.5±8.1
Sex	Male	7	6
	Female	3	4
Weight	(kg)	80.2±10.4	77.5±11.6
Height	(cm)	170.2±9.5	168.1±8.3
NYHA class	II	3	2
	III	7	8
EF		0.51±0.4	0.47±0.62
Mitral, aortic valvular patology		10	10
Aortic cross-clamp time (min)		95±14	103±17
Perfusion time (min)		140±15	143±20
Ischemia between Cardioplegia time (min)		28±5**	23±13
Ischemia time (% of cross-clamp time)		36±5**	41±10
Volume of cardioplegia (mL)		1000	1000

* Where applicable, data are shown as the mean ± the standard deviation.
** Significance: p <0.0001 versus antegrade group.
EF = ejection fraction; ischemia time = time for which cardioplegia was interrupted; NYHA = New York Heart Association;

retrograde group during aortic cross-clamping (p = 0.013), and there was a relatively large variation between patients (14 values exceeding 2.0 mmol/L in 6 patients with the highest value being 6.06 mmol/L), although the flow of cardioplegia was kept constant at 200 mL/min (table I, fig. 1). Oxygen extraction in the right ventricle was higher in the retrograde cardioplegia group, and it also increased during aortic cross-clamping (p <0.001) (table II, fig. 2). On the other hand, oxygen extraction on the left ventricular side was similar in both groups.

Postoperative course

The hemodynamic changes resembled those observed in our study with retrograde normothermic blood cardioplegia and anterograde blood cardioplegia were similar in both groups. None of the patients had development of low-output syndrome and there was no difference in the need of inotropic agents between two groups.

Discussions

Especially under normothermia it has been suggested that the right ventricular myocardium is suboptimally protected during retrograde blood cardioplegia. Allen and colleagues [7] used intraoperative transesophageal contrast echocardiography to examine the retrograde delivery of cardioplegic solution in patients undergoing coronary bypass and valve procedures and demonstrated that retrograde perfusion resulted in an almost fourfold perfusion of the left ventricular free wall and septum compared with the right ventricular free wall. Several experimental studies have demonstrated that retrograde cardioplegia is poorly distributed to the right ventricle [4,6], leading to depressed recovery of its function [10]. In addition Allen and colleagues showed that the right ostial drainage in patients with valve operations and aortotomy was only 5 mL/min compared with a left ostial drainage of 80 mL/min when retrograde cardioplegia was delivered at a rate of 150 to 200 mL/min.

Table II. Lactate Production, pH, and Oxygen Content[1,2,3]

Time	Lactate (mmol/L)	pH (U)	Oxygen (vol/100 mL)
Before aortic clamping			
Antegrade group			
Cardioplegia line	1.81±0.40	7.42±0.04	12.7±1.4
Coronary sinus	3.90±0.65	7.44±0.03	9.2±2.4
Retrograde group			
Cardioplegia line	1.79±0.31	7.42±0.02	12.9±1.7
Right ostium	4.33±0.94	7.39±0.05	8.5±1.6
Left ostium	3.95±0.53	7.35±0.04	10.6±1.8
After 30 min ischemia			
Antegrade group			
Cardioplegia line	1.83±0.35	7.46±0.03	12.4±1.4
Coronary sinus	5.55±0.37	7.44±0.02	10.4±1.9
Retrograde group			
Cardioplegia line	1.86±0.30	7.46±0.05	13.1±1.4
Right ostium	6.03±1.53[4]	7.37±0.10[6]	6.4±2.2[7]
Left ostium	5.76±0.49	7.41±0.04	9.7±2.0
Immediately After Aortic Declamping			
Antegrade group			
Cardioplegia line	1.88±0.36	7.47±0.03	12.4±1.3
Coronary sinus	3.21±0.77	7.42±0.03	9.8±2.1
Retrograde group			
Cardioplegia line	1.73±0.55	7.47±0.04	13.1±1.0
Right ostium	4.99±0.82[5]	7.39±0.06	6.1±2.6[8]
Left ostium	2.86±0.49	7.43±0.04	9.8±1.7

[1] Data are shown as the mean ± the standard deviation.
[2] In the antegrade group, the cardioplegia line represents inflow; Right ostium outflow from the right ventricle; and the Left ostium, outflow from the left ventricle.
[3] In the retrograde group, the cardioplegia line is inflow; the right-ostium outflow from the right ventricle; and the left ostium, outflow of left ventricle.
[4] Significance: p = 0.00000 between groups.
[5] Significance: p = 0.015 between groups;
[6] Significance: p = 0.0002 between groups;
[7] Significance: p = 0.0006 between groups.
[8] Significance: p = 0.01 between groups.

Lactate production in the left ventricle remained similar in both groups, although ischemia was as longer in the both group. The transventricular pH differences resembled those of lactate (p = 0.014 between groups for the right ventricle) (table II).

Menasché and coworkers [16] studied metabolic changes in the myocardium during aortic valve replacement operations and concluded that retrograde mild hypothermic blood cardioplegia is able to preserve hypertrophied myocardium. Their samples for the analysis of blood gases, oxygen content, and lactate concentration were obtained from the coronary sinus (inflow) and the left coronary ostium (outflow from the left ventricle) and not from the right coronary ostium, so that little could be said about the preservation of right ventricular metabolism.

In another study, Menasché and his group [12] adopted a different approach when studying coronary bypass patients and took blood samples from the radial artery, the right ventricle, and the coronary sinus within 1 minute of retrograde cardioplegia during antegrade washout of metabolites and found no differences in lactate concentrations. This study can be criticized for several reasons. First, the trial was not a randomized, comparative one. Second the washout of myocardial metabolites during antegrade cardioplegia is, in our experience, very efficient, and the peak levels of lactate decrease rapidly [18]. Third, the samples were taken only after the end of retrograde cardioplegia,

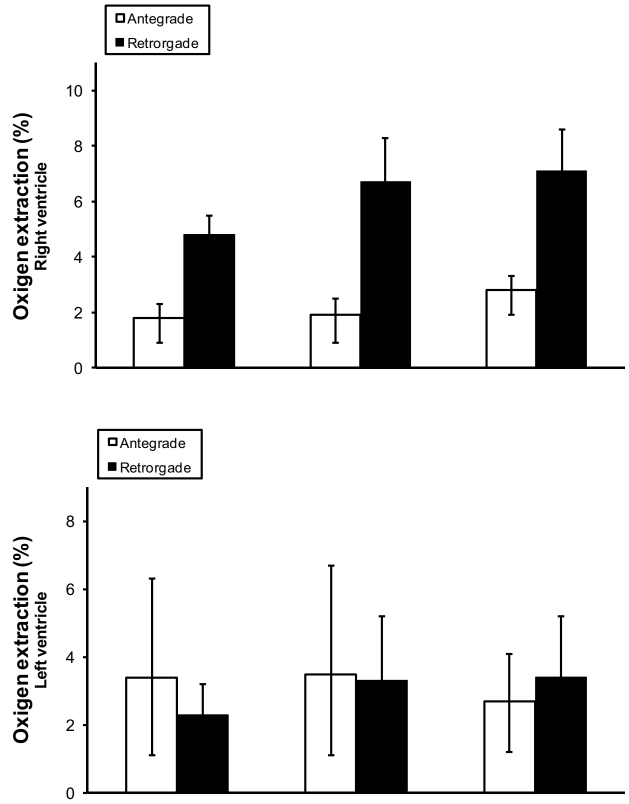

Fig. 1. Oxygen extraction in left and right ventricular myocardium. Oxygen extraction in the right ventricular myocardium was higher in the retrograde cardioplegia group and increased with time. (a = p <0.05 between groups; b = p <0.001 between groups; c = p <0.05 between ventricles in retrograde group [Scheffé's test].)

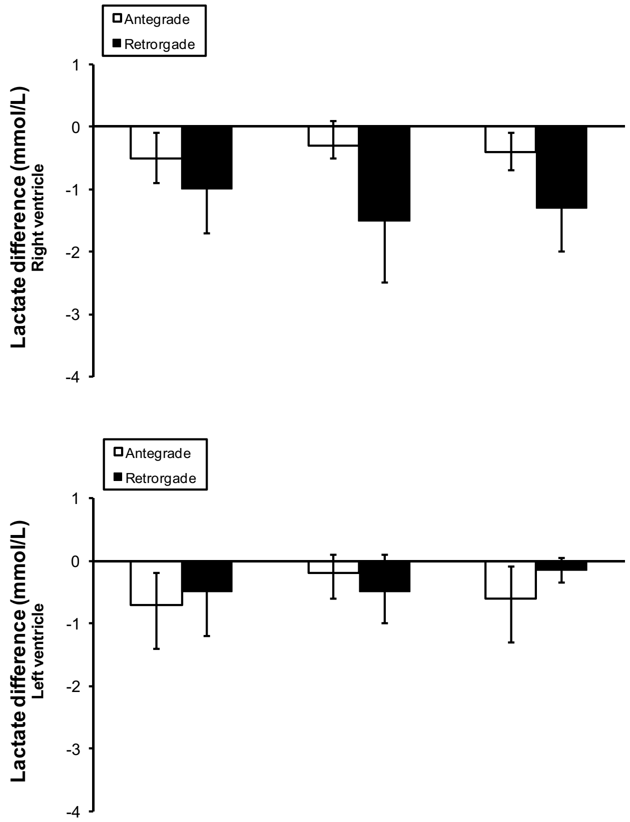

Fig. 2. Left and right ventricular myocardium lactate production. The right ventricular myocardium produced more lactate in the retrograde cardioplegia group. (a = p <0.05 between groups; c = p <0.001 between ventricles in retrograde group; see Fig 1 for definitions of A, B, and C.). Detailed description of sampling sites in the Material and methods section.

not during it, when the right ventricular blood samples are diluted with blood derived from thebesian flow and collaterals, which is almost impossible to quantify. Although the conclusions based on the metabolic data from this study [12] can be faulted, it is clear from the hemodynamic data that right ventricular function recovered equally well in the retrograde warm and antegrade cold cardioplegia groups.

Our present results demonstrate that the right ventricular myocardium produced more lactate and acid and extracted more oxygen than the left ventricle during retrograde normothermic blood cardioplegia, There were no significant differences in right and left ventricular metabolism in the antegrade cardioplegia group. In addition, left ventricular metabolism behaved similarly in both cardioplegia groups (see Table I, Fig 1, 2), even though the ischemia time (cardioplegia off) was significantly longer in the antegrade group because in retrograde group does not stop the surgical procedures when cardioplegic solution is administrat like in anterior administration.

We studied patients having elective valvular procedures with aortotomy and right atriotomy. Therefore, selective sampling from the right and left coronary ostia was ethically desirable. We realize that retrograde outflow samples taken from the aortic coronary ostia represent a blood cardioplegia draining directly from the left and right ventricle but Allen and coauthors [6] measured right ostial drainage and found it to be only about 6% of left ostial drainage using the same delivery rate of retrograde cardioplegia as we did. The lactate differences between the aortic root (outflow) and the cardioplegia line (inflow) during retrograde cardioplegia in our patients were 0,5 mmol/L on average on anterior administration and 2,5 mmol/L in retrograde administration, which is of the same magnitude as measured between the coronary sinus catheter and left coronary ostium by Menasché and coworkers [12].

Although lactate production, acidosis and oxygen extraction were more prominent in the right ventricular myocardium during retrograde cardioplegia (table II).

There was quite a lot of variation in oxygen extraction and lactate production between individual patients, especially for the right ventricle during retrograde cardioplegia. The reasons for this are not obvious, but one possible explanation is that the distribution of retrograde blood cardioplegia and its protective capacity vary according to the individual venous anatomy, which is hard to predict.

Nor were there any major hemodinamic postoperative complications in the series.

Our results are in accordance with those of Hoffenberg and associates [11], who demonstrated increased levels of myocardial inorganic phosphate and decreased levels of creatine phosphate during retrograde normothermic blood cardioplegia in isolated porcine hearts studied with phosphorus 31 magnetic resonance spectroscopy. The relatively well preserved adenine nucleotide levels in Hoffenberg study, however, explain the good clinical results obtained with retrograde cardioplegia by us and others [2,3,16,17,18].

Conclusion

Our study demonstrated that retrograde normothermic blood cardioplegia leads to anaerobic metabolism in the right ventricular myocardium. Despite value of lactate production, acidosis and of oxygen extraction were more prominent in the right ventricular myocardium during retrograde cardioplegia after declampation at 10 minutes this value became similar, and clinical and inotropic necesity were similar in this two groups. Retrograde cardioplegic delivery represents an available method of myocardial protection even in cases with longer ischemic period (both mitral and aortic procedures).

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