OPTIMAL FLOW RATES FOR INTEGRATED CARDIOPLEGIA

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Background: Antegrade cardioplegic delivery may be impaired by coronary occlusions, whereas retrograde delivery of cardioplegic solution may be inhomogeneous, leading to an accumulation of lactate and hydrogen ions, the products of anaerobic metabolism. Integrated cardioplegia using continuous retrograde cardioplegia and antegrade infusions into completed vein grafts washes out metabolites accumulated in regions inadequately perfused by retrograde cardioplegia alone. To determine the flow rates required to achieve the greatest washout, we compared a *high* flow rate (200 ml/min) to a *low* flow rate (100 ml/min). **Methods:** Twenty patients scheduled for isolated coronary bypass surgery were prospectively randomized to compare two flow rates for integrated cardioplegic protection using tepid (29° C) blood cardioplegia. Arterial and coronary sinus blood samples were collected to evaluate myocardial metabolism. After antegrade arrest, cardioplegic solution was delivered by coronary sinus perfusion and simultaneous infusions into each completed vein graft at either *high* or *low* flow. **Results:** Increasing from *low* to *high* flow increased the washout of lactate and hydrogen ions during the aortic crossclamp period. Two hours after crossclamp removal, ventricular function was better in the *high* flow group. **Conclusions:** Tepid retrograde cardioplegia resulted in an accumulation of toxic metabolites. The addition of antegrade vein graft infusions at a flow rate of 100 ml/min resulted in a washout of these metabolites. A flow rate of 200 ml/min further improved this washout and resulted in improved ventricular function. An integrated approach to myocardial protection using a flow rate of 200 ml/min may improve the results of coronary bypass surgery. (J Thorac Cardiovasc Surg 1998;115:226-35)

Critical coronary stenoses may limit the delivery of antegrade cardioplegia to ischemic regions of the heart, particularly when revascularization with the

internal thoracic artery prevents vein graft infusions to the left anterior descending coronary artery. Retrograde delivery of cardioplegic solution through the coronary sinus has been proposed to be a superior method of myocardial protection¹⁻³; however, capillary perfusion may be inadequate.⁴⁻⁷

Hypothermia (10° C) may provide additional protection but may prevent the resuscitation of the ischemic myocardium.⁷ Warm (37° C) blood cardioplegia, delivered either antegradely or retrogradely, permits earlier recovery of ventricular function,⁸ but results in greater anaerobic myocardial metabolism. Interruptions in the delivery of warm blood cardioplegia may lead to normothermic myocardial ischemia.⁹ We have recently shown that tepid (29° C) blood cardioplegia, given either antegradely or retrogradely, reduced anaerobic lactate and acid release during cardioplegic arrest and preserved ventricular function compared with either warm or cold cardioplegia.¹⁰ However, tepid retrograde cardioplegia resulted in a significant accumulation of

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lactate and hydrogen ions, the products of anaerobic metabolism.

An integrated approach to myocardial protection with both antegrade and retrograde delivery has been used to optimize cardioplegic perfusion.¹¹⁻¹⁶ We found that alternating retrograde perfusion with intermittent antegrade infusions into the aortic root effectively washed out lactate and acid that accumulated during retrograde delivery.¹⁴ Retrograde perfusion with simultaneous antegrade infusions into each completed vein graft resulted in similar protection to the alternating technique and was technically easier.¹⁶

We found that increasing normothermic retrograde flow rates from 50 to 200 ml/min decreased anaerobic lactate production.¹⁷ Further increases in flow to 300 or 500 ml/min increased the shunt flow without decreasing lactate production. This study was designed to compare delivery of tepid retrograde cardioplegia with simultaneous antegrade infusions into completed vein grafts at *high* flow (200 ml/min) versus *low* flow (100 ml/min). We hypothesized that tepid retrograde cardioplegia alone would result in less accumulation of potentially toxic lactate and hydrogen ions than warm retrograde cardioplegia. The addition of antegrade vein graft infusions may wash out any accumulated metabolites, and increasing the flow rate from 100 to 200 ml/min may further improve cardioplegic delivery to the ischemic myocardium.

Material and methods

Patient population. Twenty patients scheduled for isolated coronary artery bypass grafting by one surgeon agreed to participate in a study of alternative cardioplegic techniques. All patients signed a consent form approved by the Human Experimentation Committee. One patient in the *low* flow group was excluded intraoperatively because of an inability to insert a retrograde coronary sinus cannula. The preoperative characteristics of the remaining 19 patients are displayed in Table I.

Operative technique. Cardiopulmonary bypass was established using an ascending aortic cannula and a single, two-stage right atrial cannula. During bypass the hematocrit was between 20% and 25%; pump flows were between 2.0 and 2.5 L/min per square meter; and the mean arterial pressure was maintained between 50 and 60 mm Hg, with the administration of sodium nitroprusside or phenylephrine hydrochloride as required. Systemic perfusion was not actively cooled or warmed, but the body temperature was allowed to drift to $34^{\circ} \pm 1^{\circ}$ C. Rewarming to 38° C was begun during the construction of the proximal anastomoses, which was performed during a single prolonged crossclamp period. A left internal thoracic artery graft was anastomosed to the left anterior descending coronary artery as the last distal graft in all patients.

Table I. Patient demographics

	Low flow (%)	High flow (%)	<i>p</i> Value
No. patients	9	10	
Age (yr)	61 $\pm$ 8	58 $\pm$ 8	0.422
Triple-vessel disease	6 (67)	10 (100)	0.087
Double-vessel disease	3 (33)	0 (0)	
LV ejection fraction			
>60%	1 (11)	3 (30)	0.326
40%-59%	8 (89)	6 (60)	
20%-39%	0 (0)	11 (10)	
<20%	0 (0)	0 (0)	
Left main disease	0 (0)	2 (20)	0.474
Diabetes mellitus	6 (67)	4 (40)	0.370
Peripheral vascular disease	0 (0)	1 (10)	0.330
Hypertension	4 (44)	4 (40)	0.845

Cardioplegic technique. Patients were randomly assigned to either *high* or *low* flow cardioplegic delivery before operation with a computer-generated randomization table. All patients received a tepid (29° C) blood cardioplegic solution that was prepared by mixing four parts of oxygenated blood with one part of a crystalloid solution¹⁸ and delivered with the Buckberg system (Sorin Inc., Irvine, Calif.). Cardiac arrest was achieved with an antegrade infusion of 500 ml of high-potassium (30 mEq/L) cardioplegic solution given at a flow rate between 200 and 400 ml/min sufficient to maintain the aortic root pressure at 70 mm Hg. After this infusion, the aortic root was vented and retrograde delivery of cardioplegic solution began through an autoinflatable coronary sinus cannula (Research Medical, Midvale, Utah). Coronary sinus pressures were monitored continuously by a separate pressure-monitoring line and maintained at less than 40 mm Hg throughout the procedure. The initial retrograde flow rate in all patients was 100 ml/min. After completion of the distal anastomosis of the vein graft to the right coronary artery, biochemical measurements were obtained at a retrograde flow rate of 100 ml/min. Retrograde perfusion was then modified to include simultaneous antegrade infusions into the completed right coronary artery graft, first at a flow rate of 100 ml/min and then at 200 ml/min in all patients. After a 1-minute timed perfusion at each flow rate, simultaneous retrograde and vein graft infusions were continued at the flow rate specified by the randomization table. This protocol discriminated the effect of retrograde cardioplegia alone, the addition of a single vein graft at a flow rate of 100 ml/min, and the effect of increasing the flow rate to 200 ml/min. Timed collections of the effluent from the aortic root were also measured as indicated in Fig. 1.

Measurements of myocardial metabolism. Arterial and coronary sinus blood samples were assayed to estimate the myocardial consumption of oxygen and production of lactate or acid. During periods of retrograde perfusion, effluent from the aortic root was used as a source of coronary venous blood. Oxygen content (O_2 Con) was calculated from the formula:

Fig. 1. Study protocol for comparing flow rates. After antegrade arrest by way of the aortic root, continuous retrograde delivery was instituted through the coronary sinus at a flow rate of 100 ml/min. Cardioplegic flow was interrupted whenever necessary to visualize the distal anastomosis. After completion of the first distal anastomosis, the cardioplegic solution was delivered both retrogradely and antegradely into the vein graft at a flow rate of 100 ml/min for 1 minute, then at 200 ml/min for 1 minute. Simultaneous antegrade and retrograde delivery of the cardioplegic solution was then given at either *low* (100 ml/min) or *high* (200 ml/min) flow for the remainder of the procedure. *XCL*, Aortic crossclamp; *CPB*, cardiopulmonary bypass; *LITA*, left internal thoracic artery.

$$O_2Con = 1.39 \text{ Hgb} \times SaO_2 + 0.0031 \times Po_2$$

where Hgb is the hemoglobin concentration, SaO_2 is the oxygen saturation, and Po_2 is the partial pressure of oxygen. Myocardial oxygen extraction (O_2Ex) was calculated as the arterial or cardioplegic oxygen content minus the coronary effluent oxygen content and myocardial oxygen consumption (MVO_2) determined after correcting for coronary flow ($MVO_2 = O_2Ex \times \text{flow}$). Measurements were made at 37° C and then corrected to the cardioplegic temperature at the time of sampling.

Blood lactate concentration was determined with the use of a commercially available assay (Rapid Lactate Stat Pack kit, Calbiochem-Behring, La Jolla, Calif.). Lactate extraction (LEx) was calculated as the difference between arterial and coronary effluent lactate content. Negative lactate extraction is expressed as net lactate release. Lactate consumption or production (MVL) was determined after correcting lactate extraction for coronary flow.

The concentration of hydrogen ion [H^+] in blood was determined by converting the measured pH value to [H^+] by the formula: [H^+] = Antilog (−pH). Measurements were made at 37° C and corrected to the myocardial temperature at the time of sampling. Myocardial acid production was calculated as the difference in H^+ concentration between arterial and coronary effluent blood corrected for coronary flow.

Creatine kinase measurement. An antibody inhibition technique was used to measure the MB isozyme of creatine kinase (CK-MB). Sequential CK-MB measurements were performed at 2, 4, 8, 16, 24, and 48 hours after the removal of the aortic crossclamp. Integration of the area under the concentration-time curve for CK-MB within the first 48 hours postoperatively allowed calculation of the total CK-MB release, expressed as units ($IU \times hr$). We have previously found that this assessment correlates with infarction as assessed by technetium pyrophosphate scan.¹⁹

Hemodynamic measurements. Heart rate, mean arterial pressure, and mean pulmonary artery pressure were measured preoperatively and postoperatively. Cardiac output was measured in triplicate via a thermodilution technique by an independent individual who was unaware of the cardioplegic technique used. Derived hemodynamic indices were calculated:

$$CI = CO/BSA \text{ (L/min/m}^2\text{)}$$

$$SI = CI/HR \text{ (ml/min/m}^2\text{)}$$

$$LVSWI = SI \times (MAP - PCWP) \times 0.0316 \text{ (gm} \cdot \text{m/m}^2\text{)}$$

$$SVRI = (MAP - RAP) \times 80/CI \text{ (dyne} \cdot \text{sec/cm}^5\text{)}$$

where *CI* = cardiac index, *BSA* = body surface area, *SI* = stroke index, *LVSWI* = left ventricular stroke work index, and *SVRI* = systemic vascular resistance index.

These hemodynamic variables were measured before initiation of cardiopulmonary bypass and at 2, 4, 8, and 24 hours after removal of the aortic crossclamp. Postoperative preload and afterload were optimized by individuals who were unaware of the cardioplegic technique used.²⁰

Statistical analysis. Statistical analysis was performed using the SAS program (SAS Institute, Cary, N.C.). Categorical variables were analyzed with χ^2 or Fisher's exact test as appropriate. Continuous variables were analyzed using analysis of variance (ANOVA) or paired *t* tests as appropriate. A two-way ANOVA was used to simultaneously evaluate the effect of time and flow rate between groups. When the *F* statistic of the two-way ANOVA was significant, differences between groups were specified by Duncan's multiple range test. Statistical significance was assumed at *p* < 0.05.

Results

Table II presents the operative data. No significant differences were found in the number of grafts constructed, the aortic crossclamp time, or the total cardiopulmonary bypass time. All 10 patients in the *high* flow group received an initial saphenous vein graft to the right coronary artery or one of its branches compared with eight of nine patients in the *low* flow group. Despite an increased flow rate in the *high* flow group, the total volume of cardioplegic solution delivered did not differ between groups (*p* = 0.749). Similarly, the volume of effluent in the aortic root measured during the last 1-minute timed collection was not different between groups. The volume of effluent in the aortic root did not increase significantly when the flow rate was increased to 200 ml/min (*low* 85 ± 19 ml vs *high* 116 ± 45 ml, *p* = 0.217). When the volume of cardioplegic solution delivered was adjusted for the aortic crossclamp time, total cardioplegic delivery was higher in the *high* flow group (114 ± 22 ml/min vs *low* 84 ± 18 ml/min, *p* = 0.005). Similarly, cardioplegic delivery per bypass graft was also higher in the *high* flow group (1677 ± 365 ml/graft vs *low* 1264 ± 239 ml/graft, *p* = 0.01). Ischemic time expressed as the percentage of the crossclamp period during which no cardioplegic solution was given was not different between groups. Minimum cardioplegic temperatures were similar in both groups (*low* 34° ± 0.5° C vs *high* 35° ± 0.1° C, *p* = 0.616 by two-way ANOVA).

No deaths, strokes, or perioperative myocardial infarctions occurred in this low-risk study population. One patient in the *high* flow group had low cardiac output syndrome because he required ino-

Table II. Operative data

	<i>Low flow</i> (<i>n</i> = 9)	<i>High flow</i> (<i>n</i> = 10)	<i>p</i> Value
LIMA	9 (100%)	10 (100%)	1.000
Grafts			
Three	2 (22%)	0 (0%)	0.198
Four	2 (22%)	5 (50%)	
Five	5 (56%)	5 (50%)	
Pump time (min)	86 ± 15	85 ± 12	0.862
Crossclamp time (min)	66 ± 13	66 ± 12	0.989
Total cardioplegic solution delivered (ml)	5168 ± 1314	5550 ± 2879	0.749
Average cardioplegic return in aortic root (ml/min)	82 ± 20	89 ± 48	0.655
Percentage of cross-clamp time without cardioplegia	31 ± 6	33 ± 9	0.544
Area under the CKMB curve (IU · hr)	1747 ± 724	1331 ± 1198	0.475
Myocardial infarction	0	0	1.000
Low-output syndrome	0	1	0.330
Stroke	0	0	1.000
Operative mortality	0	0	1.000

tropic support for greater than 30 minutes in the intensive care unit to maintain systolic blood pressure greater than 90 mm Hg and a cardiac index of 2.1 L/min per square meter or greater. Perioperative myocardial injury estimated by the area under the CK-MB curve was not different between groups.

Metabolic data. Myocardial oxygen consumption, lactate, and acid production were similar in both groups after antegrade arrest. Table III illustrates myocardial oxygen extraction, lactate, and acid release before aortic crossclamping, after antegrade arrest, during the first retrograde dose (at a flow rate of 100 ml/min), and during reperfusion. No differences were demonstrated between groups.

Fig. 2 illustrates the change in myocardial oxygen consumption, lactate, and acid production after the completion of the right coronary artery graft. Tepid retrograde cardioplegia alone resulted in an accumulation of hydrogen ions that was washed out after the addition of simultaneous antegrade perfusion into the right coronary artery graft. Increasing the flow rate from 100 ml/min to 200 ml/min resulted in a further washout of lactate and hydrogen ions with a corresponding increase in myocardial oxygen consumption.

During the crossclamp period, *high* cardioplegic flows resulted in greater lactate release. Similarly, myocardial acid release was higher in the *high* flow

Table III. Perioperative metabolic data

	Low flow (n = 9)	High flow (n = 10)	p Value
Baseline			
Oxygen extraction (dl/ml)	2.9 (0.5)	3.1 (0.5)	0.836
Lactate extraction (mmol/ml)	-0.3 (0.3)	0.2 (0.1)	0.139
Acid release (Δ pH)	0.05 (0.01)	0.06 (0.01)	0.561
Antegrade arrest			
Oxygen extraction (dl/ml)	3.0 (0.7)	2.6 (0.4)	0.638
Lactate extraction (mmol/ml)	-0.1 (0.2)	-0.1 (0.2)	0.982
Acid release (Δ pH)	0.09 (0.03)	0.12 (0.02)	0.310
Initial retrograde (100 ml/min)			
Oxygen extraction (dl/ml)	0.3 (0.1)	0.2 (0.1)	0.665
Lactate extraction (mmol/ml)	-0.3 (0.2)	-0.6 (0.1)	0.187
Acid release (Δ pH)	0.01 (0.01)	0.05 (0.01)	0.003
Retrograde and first vein graft (100 ml/min)			
Oxygen extraction (dl/ml)	0.4 (0.4)	0.4 (0.4)	.522
Lactate extraction (mmol/ml)	-0.6 (0.3)	-0.8 (0.3)	.628
Acid release (Δ pH)	0.08 (0.01)	0.08 (0.01)	.961
Aortic crossclamp removal			
Oxygen extraction (dl/ml)	1.2 (0.3)	2.0 (0.5)	0.213
Lactate extraction (mmol/ml)	0.1 (0.1)	-0.2 (0.1)	0.144
Acid release (Δ pH)	0.03 (0.01)	0.05 (0.01)	0.317
Reperfusion (5 min)			
Oxygen extraction (dl/ml)	3.9 (0.5)	4.2 (0.5)	0.761
Lactate extraction (mmol/ml)	-0.1 (0.1)	-0.1 (0.1)	0.522
Acid release (Δ pH)	0.06 (0.01)	0.07 (0.01)	0.642
Reperfusion (10 min)			
Oxygen extraction (dl/ml)	5.5 (0.5)	5.0 (0.4)	0.466
Lactate extraction (mmol/ml)	0.1 (0.1)	0.1 (0.1)	0.991
Acid release (Δ pH)	0.05 (0.01)	0.07 (0.01)	0.148

group. Acid washout decreased throughout the crossclamp period, resulting in no significant differences between groups after completion of the fourth distal anastomosis. Similarly, myocardial oxygen consumption was higher in the *high* flow group, but this difference dissipated as additional vein grafts became perfused. Fig. 3 illustrates the difference in metabolite washout between the two groups.

Hemodynamic data. Postoperative heart rate was increased compared with baseline, whereas the mean arterial pressure fell, but no differences were found between groups in heart rate or mean arterial pressure either before or after surgery. Fig. 4 displays the postoperative hemodynamic data obtained at 2, 4, 8, and 24 hours after the removal of the aortic crossclamp. Cardiac index and left ventricular stroke work index were higher in the *high* flow group 2 hours postoperatively at similar filling pressures ($p < 0.05$ by analysis of covariance [ANOCOVA]).

Discussion

Despite apparently adequate blood cardioplegic protection, sensitive measures reveal delayed recov-

ery of myocardial metabolism and ventricular function.^{7,8} This impairment may be due to inhomogeneous distribution of cardioplegic solution during either antegrade or retrograde cardioplegia alone.²¹ An integrated cardioplegic technique using both antegrade and retrograde delivery has been advocated by many authors.¹¹⁻¹⁶ However, the optimal flow rate required to improve myocardial perfusion when using integrated cardioplegia is not known. We previously found that a flow rate of less than 200 ml/min during normothermic (37° C) retrograde cardioplegia resulted in an accumulation of lactate and acid during the crossclamp period.¹⁷ Flow rates in excess of 200 ml/min did not result in further washout of toxic metabolites. However, flow rates of 200 ml/min may be detrimental if they result in high coronary sinus pressures. A coronary sinus pressure of greater than 40 mm Hg has been reported to result in perivascular hemorrhage and edema, as well as direct coronary sinus injury.²²

Lowering the temperature from 37° C to 29° C reduced myocardial oxygen consumption by almost 50%.¹⁰ Therefore a 50% reduction in flow rate from

Fig. 2. *Top panel*, Percent change in lactate and acid production and oxygen consumption after the addition of antegrade cardioplegic perfusion into the completed right coronary artery graft. *Bottom panel*, Percent change in lactate and acid production and oxygen consumption achieved by increasing the flow rate from 100 ml/min (*low*) to 200 ml/min (*high*). Myocardial oxygen consumption significantly increased as the flow rate increased. Similarly, increasing the cardioplegic flow rate significantly increased lactate and acid washout.

200 ml/min to 100 ml/min may not be detrimental at a myocardial temperature of 29° C. This study was undertaken to determine the optimal flow rate for integrated tepid (29° C) blood cardioplegia and is the first report to investigate flow rates with this increasingly popular cardioplegic technique.

At 29° C, retrograde flows of 100 ml/min were inadequate to maintain homogeneous myocardial perfusion. The addition of a single vein graft resulted in increased washout of lactate and acid. Most patients (18 of 19) received an initial graft to the right coronary artery or one of its distal branches. Increasing the flow rate from 100 to 200 ml/min resulted in a further washout of toxic metabolites. We believe that the increased flow rate led to improved myocardial perfusion. When perfusion was improved by additional antegrade infusions into completed vein grafts, the effect of flow rate was attenuated. Thus anaerobic metabolism was stimulated by *inadequate* myocardial perfusion that was prevented by either increasing

the flow rates or by the addition of simultaneous vein graft infusions.

We were able to deliver a flow rate of 200 ml/min in all 10 patients in the *high* flow group with a coronary sinus pressure less than 40 mm Hg. We used a single pump head to deliver cardioplegic solution into the coronary sinus cannula and the vein grafts simultaneously. Possibly, increases in coronary sinus pressure may have resulted in increased flow down the vein grafts. It is also possible that higher flow rates (in excess of 250 ml/min) may be better than our high-flow technique. We did not examine this possibility in our study. We did find, however, that the effluent in the aortic root during a 1-minute timed collection was not different between groups. The variability in this measurement likely reflects the variability in thebesian shunt flow. Thus increasing flow rates beyond 200 ml/min during integrated cardioplegic delivery may increase the shunt fraction as we observed with retrograde cardioplegia alone.¹⁷

Fig. 3. *Panel A*, Myocardial lactate release after completion of each distal anastomosis. Washout of accumulated lactate was higher in patients receiving *high* cardioplegic flow rates after the second distal anastomosis. The difference between *high* and *low* flow rates dissipated as additional vein grafts became perfused ($p = 0.088$ by two-way ANOVA). *Panel B*, Myocardial oxygen consumption after completion of each distal anastomosis. Oxygen consumption was higher in patients receiving *high* cardioplegic flow rates after the first distal anastomosis. This difference dissipated as additional vein grafts became perfused ($p = 0.158$ by two-way ANOVA). *Panel C*, Myocardial acid release after completion of each distal anastomosis. Washout of accumulated hydrogen ions was higher in patients receiving *high* cardioplegic flow rates ($p = 0.034$ by two-way ANOVA) (mean $\pm$ standard error of the mean).

The improved myocardial perfusion in the *high* flow group improved early postoperative hemodynamics. Fig. 4 illustrates that at a given preload (left ventricular end-diastolic pressure), cardiac index

and left ventricular stroke work index were higher in the *high* flow group. No differences were observed between groups in clinical outcomes. Our study population consisted of low-risk patients with excel-

Fig. 4. Panel A, Cardiac index at baseline (PRE), 2, 4, 8, and 24 hours postoperatively. Cardiac index was greater in the high flow group (hollow symbols; $p = 0.03$ by ANOCOVA). LVEDP, Left ventricular end-diastolic pressure (mm Hg). Panel B, Left ventricular stroke work index (LVSWI) at baseline (PRE), 2, 4, 8, and 24 hours postoperatively. LVSWI was greater in the high flow group (hollow symbols; $p = 0.05$ by ANOCOVA). PCWP, Pulmonary capillary wedge pressure (mm Hg).

lent collateral circulation and preserved left ventricular function, and clinical differences were not anticipated.

Study limitations. Coronary venous blood obtained from the aortic root during retrograde delivery of cardioplegic solution is contaminated by noncoronary collateral blood flow from the pulmonary veins. Contamination is further exacerbated by simultaneous vein graft perfusions that may deliver oxygenated blood cardioplegic solution into the

aortic effluent. These sources of contamination tend to decrease both lactate and acid concentrations while increasing oxygen tensions in the aortic effluent. Therefore our measurements of myocardial washout *underestimate* the true accumulation of lactate and acid in ischemic myocardium. Coronary blood flow during cardioplegic arrest was assumed to be equivalent to cardioplegic flow rate. Variability in the thebesian shunt fraction at different flow rates also confounds these measurements.

Despite these limitations, we were able to detect subtle differences in myocardial metabolism during cardioplegic arrest. Our ability to detect differences in metabolite washout despite significant contamination suggests an even larger difference between high- and low-flow groups. Furthermore, the significant improvement in left ventricular function 2 hours after crossclamp removal suggests that improved myocardial protection was achieved at higher flow rates.

Coronary blood flow was not measured during reperfusion. Therefore our inability to detect metabolic differences during reperfusion may be a result of differences in coronary blood flow that may have masked true differences in metabolic activity.

Our technique of "continuous" retrograde delivery of blood cardioplegic solution required interruption for more than 30% of the crossclamp period to adequately visualize the distal anastomosis. Maintaining "continuous" flow throughout the crossclamp period may have reduced the accumulation of toxic metabolites that we observed in this study. However, we believe that is more prudent to ensure a technically proficient distal anastomosis and continue to interrupt cardioplegic delivery whenever necessary. When interruptions are necessary, a flow rate of 200 ml/min is required to ensure adequate washout of the accumulated metabolites.

Summary

We conclude from this study that flow rates of 100 ml/min are inadequate when using an integrated, tepid blood cardioplegic approach to myocardial protection. We have previously demonstrated that subtle metabolic and hemodynamic differences of the magnitude found in this study correlate with differences in clinical outcomes in higher risk populations, such as those patients who require surgery for unstable angina.^{23, 24} Therefore in high-risk patients flow rates less than 200 ml/min may increase the incidence of postoperative morbidity and mortality. The possible benefits of increasing flow rates beyond 250 ml/min requires further investigation.

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