Myocardial protection in the failing heart: I. Effect of cardioplegia and the beating state under simulated left ventricular restoration

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See related article on page 884.

Objective: Heart failure was induced by cardiac pacing to evaluate myocardial flow distribution of the open ventricle during delivery of either cardioplegia or in the beating state during simulated left ventricular restoration.

Methods: Studies included 5 (pacing-induced) failing pig hearts and 6 control hearts. Pacing-induced cardiac failure reduced fractional shortening by approximately 22%, increased left ventricular end-diastolic diameter by 34%, caused pulmonary hypertension (mean blood pressure increased from 12 to 35 mm Hg), and led to significant ascites. Global and regional coronary blood flow were measured with microspheres during cardiopulmonary bypass at 80 mm Hg perfusion pressure in either vented (collapsed) or open (exposure by traction for left ventricular restoration) left ventricles during continuous perfusion under either beating-heart or cardioplegic conditions.

Results: In control hearts, venting and exposure ventriculotomy did not affect flow. In failing hearts decompressed by venting, coronary flow was lower during the beating and cardioplegic delivery than during control conditions at the same perfusion pressure of 80 mm Hg. Mean cardioplegic flow during ventricular decompression by venting exceeded beating flow by 97%. Conversely, traction to increase the ventricular radius during exposure ventriculotomy reduced endocardial cardioplegic coronary blood flow by 64% (from 0.97 to 0.59 mL/[min · g]), whereas the beating state raised endocardial flow by 95% (from 0.40 to 0.78 mL/[min · g]). Changing ventricular shape changed coronary vascular resistance in failing hearts during beating or cardioplegic delivery.

Conclusions: Coronary blood flow alterations occurred only in failing hearts when geometry was changed from closed to open state. The beating method provided more endocardial flow than cardioplegic delivery during ventricular exposure for restoration. Vascular remodeling raised coronary vascular resistance in failing hearts, thereby requiring higher pressure for similar blood flows.

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Supported in part by Edwards Life Sciences and by the National Institute of Health-National Heart, Lung, and Blood Institute Grant 2 R01 HL055554-06. G.B. reports consulting fees from Sorin Biomedical, Inc, Irvine, Calif.

Received for publication Oct 11, 2005; revisions received March 1, 2006; accepted for publication March 21, 2006.

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J Thorac Cardiovasc Surg 2006;132:875-83
0022-5223/\$32.00

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doi:10.1016/j.jtcvs.2006.03.067

Surgical ventricular restoration is currently used to treat severe dilated cardiomyopathy.^{1,2} This is an effective procedure that reduces LV wall stress by decreasing ratio of LV diameter to wall thickness³ while reshaping the failing spherical chamber towards a normal (elliptical shape), which improves pump

Abbreviations and Acronyms

CPB = cardiopulmonary bypass
LV = left ventricular

performance.² Restoration is possible in both ischemic and nonischemic dilated cardiomyopathy.⁴⁻⁶ Selection of myocardial protective strategies that avoid intraoperative damage is an important consideration, because operative risk is high in patients with advanced heart failure.

Evaluation of protective strategies requires studies in models that simulate the disease state,⁷ as well as regulating the size and shape conditions that prevail during restoration. For example, venting to collapse the heart is not done during restoration, because the ventricle must be open during restoration, and this configuration has not yet been studied. Traction on the edges of the ventricle causes a more normal radius of curvature in the open heart, thereby simulating the normal full heart architecture. To date, studies have not tested whether the open configuration avoids the subendocardial underperfusion that may accompany collapse of the ventricular cavity during venting.^{8,9}

Dilated cardiomyopathy is susceptible to inadequate myocardial protection because increased regional myocardial work and oxygen demand may not be matched by sufficient regional myocardial perfusion. Blood cardioplegia is the preferred cardioprotective strategy in the United States for nonrestoration procedures¹⁰ and is usually accompanied by intermittent periods of ischemia. An alternative is to allow the heart to beat during the restoration procedure to avoid ischemic episodes.¹¹

This study compared the magnitude and distribution of perfusion during blood cardioplegic and beating methods of protection in normal and failing hearts after pacing induced cardiomyopathy. Ischemia was avoided, and the influences of shape in closed vented hearts (used for coronary artery bypass grafting procedures) and the open ventricle (used during restoration) were evaluated during continuous coronary perfusion of either warm noncardioplegic blood or warm blood cardioplegic solution.

Methods

Eleven Yorkshire or Hanford-Yorkshire mix pigs weighing 38 to 89 kg were studied in accordance with National Institute of Health guidelines for the humane care and use of laboratory animals in research and in compliance with American Association for the Accreditation of Laboratory Animal Care and the animal subjects committee of the University of California, San Diego, where the studies were performed. Six animals were used as control subjects and 5 had heart failure induced by rapid ventricular pacing.

Heart Failure Preparations

After sedation with ketamine (24 mg/kg) and atropine (4 mg), anesthesia was induced with halothane (3%-5%) by mask. A mixture of oxygen and nitrous oxide (1:1) and halothane was used for ventilation after intubation. The heart was exposed through a sterile fourth interspace left thoracotomy, and the left hemiazygous vein was ligated. Two platinum screw electrodes were implanted in the lateral LV free wall, and left atrial pacing wires were placed for echocardiographic dimensional studies. The left pulmonary artery silicone elastomer catheter was placed to monitor progression of heart failure. Pacing was initiated 1 week later by modified protocol of Hintze and colleagues¹² (210-220 beats/min for 1 week, and 190-220 beats/min for an additional 2-3 weeks, depending on the status of the heart). Twice a week, the left atrium was briefly paced at 150 beats/min, and fractional shortening (2-dimensional echocardiography) and pulmonary arterial pressure were determined to compare fractional shortening and end-diastolic dimension at the same heart rate. Animals were killed after 4 to 6 weeks of pacing, and fractional shortening was determined 1 day before death.

Acute Study Surgical Preparation

Anesthesia was induced in control animals with ketamine (24 mg/kg) and atropine (4 mg), and then maintained with halothane after tracheostomy. To minimize hemodynamic effects, heart-failure animals had anesthesia induced with etomidate (4-8 mg/kg intravenously) and then maintained with isoflurane. Control and heart-failure pigs had similar anesthetic management with the onset of cardiopulmonary bypass (CPB), consisting of intravenous mixture of propofol (10 mg/mL) and Ketamine (0.8 mg/mL) that was infused at 0.5 mL/min. Diphenhydramine (300-400 mg) was administered subcutaneously, and hourly supplements of diazepam (5 mg) and buprenorphine (0.3 mg) were also administered.

Systemic perfusion was performed by femoral artery cannulation, and the aorta was cannulated with an 18F aortic perfusion catheter (APC-018; Baxter Healthcare Corporation CardioVascular Group, Irvine, Calif). Jugular and femoral veins were cannulated for anesthetic and fluid administration, and the aortic pressure was monitored from the left carotid artery. After median sternotomy, a dual-drainage venous-return catheter (Baxter TR-3240-0) was advanced from right atrial appendage to inferior vena cava, and a 14F antegrade perfusion catheter (Baxter ATC-014) was placed in the aortic root for coronary perfusion. CPB was achieved with a Baxter Spirogold membrane oxygenator and reservoir and Sarns (3M Health Care, Ann Arbor, Mich) roller pumps.

Antegrade coronary perfusion was carried out with a Sorin pump system (Sorin Biomedical, Inc, Irvine, Calif) and a Buckberg BCD (Sorin) heat exchanger and bubble trap. Cardioplegia maintenance solution contained 20 mEq potassium ion and was delivered at a 4:1 blood cardioplegic ratio. The initial oxygenator prime consisted of 1500 to 2000 mL Plasma-Lyte electrolyte solution with 125 mg methylprednisolone, 12.5 g mannitol, 500 mg calcium ion, 50 ml 50% dextrose, and 20 units insulin. Furosemide was administered if plasma potassium levels exceeded 5.0 mEq/L. Electrolytes were measured with i-STAT (Abbott Laboratories, Abbott Park, Ill) during and after the cardioplegic sections of the protocol. CPB was initiated at a flow of 40 to 60 mL/(min · kg), which was usually sufficient to maintain a systemic pressure

Beating Heart Shape and Thickness

Figure 1. Geometric configuration of LV during closed state, as chamber is vented, and when ventricular radius is expanded during traction to simulate open heart exposure needed during ventricular restoration.

greater than 55 mm Hg. The core temperature was maintained at 32°C, and the coronary perfusion temperature was held at 37°C.

The LV was incised midway between the anterior and posterior papillary muscles from the apex to within 1.5 cm of the circumflex artery. Incised epicardial coronary branches were ligated. **Figure 1** shows the geometric differences in ventricular size and shape that were used to create the closed and open states that were evaluated in this study. Six transmurals stay sutures (three on each side) were placed 5 mm back from the incision, and pulling each side apart widened the LV radius and allowed sufficient traction to simulate the exposure used during ventricular restoration. The epicardial edges of the incision were loosely reapproximated during the closed-heart portion of the protocol. This collapsed, vented configuration reflected the decompressed heart shape used during coronary artery bypass grafting and valve replacement or repair.

Experimental Protocol

The experimental protocol was designed to examine the effects of three antegrade perfusion techniques each with and without the edges of the incised LV under traction under the following six experimental conditions (done in random sequence): 1, open heart, beating, whole blood perfusion; 2, open heart, nonpulsatile perfusion with warm blood cardioplegia; 3, open heart, pulsatile perfusion with warm blood cardioplegia; 4, closed heart, nonpulsatile perfusion with warm blood cardioplegia; 5, closed heart, pulsatile perfusion with warm blood cardioplegia solution; and 6, closed heart, beating, whole blood perfusion.

Before each experimental condition, a steady state of aortic pressure, perfusion pressure, and coronary artery blood flow was established for at least 3 minutes. Nonpulsatile, continuous cardioplegic perfusion was carried out at pressure of 80 mm Hg. The cardioplegic perfusion was switched to a pulsatile mode with a Stockert-Shiley pulsatile roller pump (Stockert-Shiley Inc, Irvine, Calif), with mean pressure kept at 80 mm Hg but phasic perfusion pressure varying from 60 to 100 mm Hg. Data were then collected

TABLE 1. End-diastolic dimension and fractional shortening in heart-failure pigs left atrially paced at 150 beats/min

Pig	End-diastolic dimension (cm)		Fractional shortening	
	Initial	Failure	Initial	Failure
400	4.9	6.57	0.36	0.22
418	3.9	5.99	0.37	0.17
412	3.86	4.46	0.42	0.14
408	3.73	5.2	0.45	0.31
304	4.22	5.54	0.47	0.28
Mean $\pm$ SD	4.12 $\pm$ 0.47	5.55 $\pm$ 0.8	0.41 $\pm$ 0.05	0.22 $\pm$ 0.072

in the following sequence. Phasic coronary blood flow was recorded after a 3-minute period to achieve steady state, coronary blood flow was measured by microsphere injection, and aortic pressure, perfusion pressure, and Sorin pump flow were recorded. Fluorescent microspheres (15 μ m diameter) were used to measure myocardial perfusion according to the method described by Glenny and coworkers.¹³ The microspheres were injected into a side port within the arterial line, where they underwent mixing, were distributed (Y-connector) into the arterial line of the blood¹³ cardioplegic device, and then were delivered into the heart by the aortic cannula. The aorta was clamped during all flow measurements. The coronary perfusion was through the aortic cardioplegic line, which also recorded mean and phasic pressures.

This report (part I), contrasts the effects of conventional methods of beating-heart and cardioplegic management in the normal and failing heart (conditions 1, 2, 4, and 6) to provide an experimental backdrop for conventional clinical methods used during surgical ventricular restoration. It is followed by part II, which presents a novel method of pulsatile cardioplegia delivery (conditions 1, 2, and 3) to determine whether pulsation of conventional cardioplegic delivery enhances protection.

No late studies were done for recovery because of the multiple studies (six conditions) needed and prolonged duration of the experiment (approximately 4-hour CPB time). Once the study was completed, each animal was killed with an overdose of sodium pentobarbital. The heart was excised, and microsphere measurements were made according to the method of Glenny and coworkers.¹³

Data and Statistical Analysis

The flow resistance was computed as the quotient of the pressure difference within the coronary circulation and the flow. Arterial pressure was set at 80 mm Hg, and the vented heart was set at zero pressure to determine the flow resistance computation at 80 mm Hg/flow/100 g tissue. Data were analyzed with the SPSS statistical program (SPSS Inc, Chicago, Ill) and expressed as mean $\pm$ SEM.

Results

Heart Failure Model

Studies were completed in 6 control animals (55 $\pm$ 12 kg). Ten animals entered the pacing protocol, but 5 died before the CPB study. **Table 1** shows data from the 5 successful heart-failure preparations. Flow data for 1 of the 5 heart-failure animals in the closed state had values that were more

Figure 2. Mean transmural flows for closed and open states in beating heart with whole blood perfusion and nonpulsatile perfusion cardioplegia in control (A) and congestive heart failure (B) hearts. Resistances to flow are similarly shown for control (C) and congestive heart failure (D) hearts. CHF, Congestive heart failure.

than 2 SD outside the mean. This animal was considered to represent an outlier and was excluded from analysis. The heart-failure flow data for the open and closed states therefore correspond to 5 and 4 animals, respectively.

At the acute study, pulmonary arterial pressure roughly doubled after 28 days of pacing (range 24-38), increasing from a control average of approximately 19 mm Hg to approximately 42 mm Hg. Fractional shortening declined approximately 50% during failure, reaching an average of 22% (as low as 14% in one animal). LV end-diastolic dimensions increased an average of 34% with failure (Table 1), with ascites averaging 1.0 L (range 0.5-2.5 L). Each heart-failure pig had a dilated, thin-walled heart, with all chambers appearing grossly enlarged; however, ratios of LV weight to body weight were similar in control and heart-failure animals.

Studies on Myocardial Blood Flow during CPB

To assess the stability of each preparation, the closed heart beating condition was repeated at the beginning and end of each study. There was no difference in the total coronary blood flow measured at a perfusion pressure of 80 mm Hg, and there was no effect of the perfusion sequence on the

change in blood flow with time in studies done in random fashion. An entire experimental sequence lasted 2.5 hours. There was an average of 4 hours total time on CPB.

Figure 2 shows the average transmural myocardial blood flows in both control (Figure 2, A) and heart-failure (Figure 2, B) animals. During control conditions, cardioplegic flow exceeded beating flow by 29% and 62% in the closed (vented) and open states ($P < .02$), respectively, so that altering shape by traction on the edges of the ventriculotomy did not change this relationship. Conversely, ventricular shape had a major effect on flow distribution in failing hearts. Opening the ventricle by traction increased transmural blood flow 103% (0.38 to 0.77 mL/[min · g], $P < .03$) in the beating state. In contrast, cardioplegia lowered perfusion by 18% (0.75 to 0.64 mL/[min · g]), thereby reaching levels below beating perfusion.

The mean transmural flow resistance values in Figure 2 (C and D) demonstrate that heart failure raised resistance in both the beating and cardioplegic states. In contrast to the control state, in which ventricular traction reduced resistance during cardioplegia, vascular resistance during cardioplegia increased markedly during traction in failing

Figure 3. Mean endocardial (*Endo*) flows for closed and open states in beating heart with whole blood perfusion and nonpulsatile perfusion cardioplegia in control (A) and congestive heart failure (B) hearts. Resistances to flow are similarly shown for control (C) and congestive heart failure (D) hearts. CHF, Congestive heart failure.

hearts ($P < .05$). The effect of traction in whole blood beating heart was negligible in control hearts, but increased flow (decreased resistance) nearly significantly in failing hearts ($P < .051$).

The changes in average blood flow across the wall were similar in the endocardium. cardioplegic flow exceeded beating flow by 43% ($P < .01$) during control conditions in the closed (vented) state, signifying less perfusion (higher resistance) with whole blood beating perfusion versus cardioplegia, as shown in Figure 3. In the open state, the cardioplegic flow was even greater than the beating flow (68%). Furthermore, traction had no significant effect on endocardial blood flow in either the cardioplegic or beating state during control conditions.

In failing hearts, endocardial flow decreased by 132% and 38% ($P < .01$) during cardioplegic and beating perfusion in the vented state (Figure 3, B), with cardioplegic flow continuing to exceed beating flow (0.97 vs 0.40 mL/[min · g]). During failure, endocardial perfusion showed a significant and opposite effect of traction during the beating and cardioplegic states: blood flow increased by 94% (lower resistance) to the endocardium with traction in the beating heart ($P < .03$) yet decreased by 64% when the vented heart was opened and placed under traction during cardioplegic infusion.

There were no significant effects of perfusion technique on the ratio of epicardial to endocardial blood flow (Figure 4),

although there was preferential endocardial perfusion during cardioplegia during control conditions (endocardial/epicardial ratio of 1.3 vs 1.0) in the vented state. During failure, the flow ratio for cardioplegia in the traction state became more uniform (1.1, $P = .018$), but no significant interaction existed between the site of blood flow measurement and the perfusion technique.

Studies on Variance in Myocardial Blood Flow

The coefficient of variance (the SD divided by the mean) for blood flow data was determined for each heart. Figure 5 shows the coefficient of variance data for control and heart-failure pigs. The data show a perfusion effect ($P < .03$), whereby less variance of flow occurred in the beating state than with cardioplegia, which showed more heterogeneous perfusion in the control and failure states. This was independent of the vented or traction cardiac shape.

Discussion

The experimental model showed changes similar to clinical heart failure, as signified by increased diastolic dimension, reduced shortening, increased pulmonary pressure, and ascites. Studies of transmural and subendocardial flows in the normal and failing ventricle were done in both vented and open geometries (to simulate restoration), with the beating and cardioplegic methods of perfusion simulating conditions used during clinical ventricular restoration. Although

Figure 4. Epicardial to endocardial (Epi/Endo) blood flow ratio in closed and open states in beating heart with whole blood perfusion and nonpulsatile perfusion cardioplegia in control (A) and congestive heart failure (B) hearts. CHF, Congestive heart failure.

shape change from the collapsed to the open position did not alter perfusion in normal hearts, failing hearts showed significant reduction of perfusion to the vulnerable subendocardial area¹⁴ during cardioplegic delivery. Conversely, subendocardial flow increased during traction in failing hearts and exceeded cardioplegic flow.

This observation confirms our hypothesis that the effects of traction and conventional cardioplegic distribution may differ between normal and failing hearts as a result of the changes in the vascular and myocardial architecture. During failure, traction expanded ventricular radius, and this change in geometry raised vascular resistance to reduce cardioplegic perfusion. Conversely, endocardial perfusion improved during the beating state when flows were tested during the open architecture. Perhaps the reduced contractile force in failing hearts exerted less compressive force on the intramural vessels. This may account for improvement in perfusion when traction restores the normal curvature, thereby returning coronary anatomy to a more natural size and form. This return to the natural perfusion conditions of the ventricular curvature of the full heart may underscore the effect of contraction on vessel-muscle interaction.

The adequacy of flow must be related to demand. That is, the highest requirement is in the dilated working heart, falling to 10 mL/(100 g · min) in the normal working ventricle, diminishing during decompression to approximately 3 mL/(100 g · min) in the vented state on CPB, and becoming lowest at 1 mL/(100 g · min) during normothermic cardioplegia,¹⁵ as shown in Figure 6. No change of demands exists during CPB in the empty heart, because it remains decompressed whether it is collapsed during venting or remains open during traction for simulated restoration.

The flow and resistance changes in the failure model represent vascular remodeling. Flows in the failing heart at a mean perfusion pressure of 80 mm Hg were lower than control levels during the empty state with beating and cardioplegic perfusion. Diminution of endocardial flow was most prominent when traction was added to cardioplegic perfusion, with a 64% reduction of perfusion occurring in the failing open heart (Figure 3). These were steady-state observations during continuous perfusion to avoid ischemia. These observations imply that more marked underperfusion may follow intermittent ischemic intervals, which are commonplace during blood

Figure 5. Coefficient of variance of blood flow in closed and open states in beating heart with whole blood perfusion and nonpulsatile perfusion cardioplegia in control (A) and congestive heart failure (B) hearts. CHF, Congestive heart failure.

Figure 6. Myocardial oxygen requirements in dilated heart during failure, in normal working ventricle during beating empty state at 37°C, during CPB, and during 37°C blood cardioplegia.

cardioplegic delivery.¹⁶ This hypothesis remains to be tested. In contrast, endocardial flow increased by 100% when the ventricular radius was increased by traction in the beating state (0.77 vs 0.38 mL/[min · g], $P < .05$).

The influence of flow distribution during beating may relate to how myocardial compression of coronary vessels is changed when ventricular geometry is transformed from the decompressed vented state to the stretched heart during traction. Streeter and associates¹⁷ have demonstrated a more oblique cleavage plane direction as chamber widening occurs. Studies by LeGrice and coworkers¹⁸ suggest that such shape and size alteration may alter cleavage planes and result in less transmural shear on coronary vessels surrounded by myocardial muscular components. Such diminished compression of oblique fibers on intraluminal vessels may allow more perfusion during systole and diastole, especially because the emptiness of the beating heart offsets flow opposition from interventricular blood pressure.

Ensuring endocardial perfusion of the open ventricle may be especially important in dilated failing hearts, because subendocardial under perfusion in vented hearts remains the main source of damage after hypertrophy¹⁹ or ischemia.²⁰ Subendocardial vessels become distorted when venting produces the collapsed heart, and this phenomenon is improved when traction restores the normal radial curvature. Simultaneously, the surrounding intravascular compression is reduced in failing hearts because of lessened shortening and reduced wall thickness. Conversely, there was marked impairment of endocardial perfusion (falling from 0.78 to 0.40 mL/[min · g]) in the

beating empty state, paralleling the early observations of Sapsford and associates⁸ in the beating heart during aortic valve replacement in hypertrophied hearts.

The decrease in flow or increase in vascular resistance in the failing hearts reflects the remodeling of the coronary vasculature, so that a higher pressure is needed to ensure perfusion during both the beating and cardioplegic states. Future studies must be done to determine whether this is due to alteration in the length, the number of vessels, or the vascular cross-sectional area.²¹ Furthermore, pacing-induced congestive heart failure diminishes myocardial blood flow reserve.¹⁷ This is perhaps due to defective endothelial control¹⁸ that occurs without physical luminal obstruction,^{1,17,22} as suggested by Krombach²³ and supported by our findings.

Our measurements reflect baseline flow relative to metabolic needs, and these demands were low in bypassed hearts, so continuous flow likely matches energy requirements. The autoregulatory mechanisms were not changed pharmacologically, so local tissue vasoactivity was responsible for flow delivery. Perhaps the reduced coefficient of variability (Figure 5) in the beating heart reflects how intermittent contraction aids in the spatial effects of homogeneous perfusion. This may limit the “twinkling type” perfusion relative to cardioplegic delivery, in which no myocardial contractile factors are available to ensure more homogeneous distribution.^{22,24,25}

Clinical Implications

Guidelines for perfusion of the open ventricle of dilated failing hearts undergoing restoration may evolve from these data. These are the first measurements of failing hearts under traction to simulate the open configuration used in clinically enlarged hearts with increased volume. This experiment did not measure either biochemical evidence of the adequacy of perfusion (lactate production) or postoperative function to evaluate the safety of these perfusion methods. Baseline flow in the beating closed state always returned to control levels, implying the absence of ischemia because compensatory vasodilation from reactive hyperemia would be expected with previous underperfusion.

The avoidance of ischemia is standard practice when the beating heart is used,¹ but intermittent ischemic intervals are traditional when cardioplegia is used during restoration. In general, two to three doses are given each 15 to 20 minutes, especially with new surgeons who learn the restoration procedure. Our data emphasize the importance of ensuring a high perfusion pressure to aid flow distribution and thereby offset the vascular remodeling observed in this study. Conversely, the force of contraction during the beating state may be useful to gauge the adequacy of delivery. The vigor of twisting would be expected to decrease if

perfusion is inadequate, and this clinical sign has been used to stimulate increased perfusion pressure during restoration. Further testing is needed to clarify the usefulness of this sign.

A fundamental difference between the beating state and cardioplegia is that intentional ischemia is avoided with the beating method. To ensure optimal flow, it is essential that all distal and proximal grafts are completed with the beating method to allow improved flow beyond the stenosis during ventricular restoration. If cardioplegia is used, this consideration of grafting sequence is less important. However, time dependency (duration of restoration procedure) becomes a factor in protection if the cardioplegic method is used, because the duration of aortic clamping is prolonged. Conversely, with the beating state, perfusion is continued throughout ventricular restoration while the heart is under traction. Ischemic times are thereby eliminated, and the time dependency of cardioplegia becomes replaced with procedure dependency (the duration of the restoration procedure). During traction, continuous and augmented subendocardial perfusion occurs during use of the beating method, as opposed to relative hypoperfusion during intermittent blood cardioplegia delivery.

Conclusions

Myocardial protection remains an important goal during restoration in failing hearts. This study examines for the first time, the effect of geometry of the ventricle (open or closed) in failing hearts during beating and cardioplegic protection methods. A comparison between these methods of protection show that continuous perfusion during the beating state improved flow in the open ventricle as compared to relatively diminished perfusion during continuous cardioplegia delivery. Differences of perfusion between the vented and traction states in failing dilated hearts may provide a model for future studies, because the open model mirrors clinical events during ventricular restoration. The importance of perfusion pressure is emphasized, because flow decreases in failing hearts relative to control hearts perfused at the same pressure in the vented and traction states.

We acknowledge the contributions of staff at all three institutions, and in particular the surgical and administrative skills of Mr Richard Pavelec, without whose contributions these complex studies would not have been possible.

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