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Continuous Addition of Adenosine with a Micropump System Improves Warm Whole Blood Cardioplegia

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ABSTRACT

Background: Micropump additive systems allow for continuous modification of cardioplegia composition during heart surgery. Although the use of such systems in warm heart surgery is theoretically desirable, the role of the systems has been clinically limited by coronary vasoreactivity with higher potassium concentration and unreliable mechanical arrest at lower potassium concentration. Adenosine, a potent coronary vasodilator and arresting agent, has the potential to reduce the potassium concentration required for arrest and to improve distribution of cardioplegia. However, clinical use of adenosine has been limited by a short half-life in blood and difficulty in titrating the dose. This study tested the hypothesis that continuous addition of adenosine with an in-line linear micropump system would facilitate whole blood hyperkalemic perfusion for cardiac surgery.

Methods: Canine hearts (n = 9) were randomized to 20 minutes of arrest with whole blood cardioplegia or cardioplegia with adenosine at either low (0.5 μM) or high (8 μM) concentration. Potassium was supplemented at an arresting dose (24 mEq/L) for 5 minutes and then at a maintenance dose (6 mEq/L) for an additional 15 minutes. Coronary flow was held constant (4 mL/kg per minute), and aortic root pressure was measured. Myocardial performance was assessed by measurement of the end-diastolic pressure to stroke volume relationship at constant afterload. Myocardial tissue perfusion was evaluated with colored microspheres.

Results: During the initial period of high-concentration potassium arrest, coronary resistance rose progressively regardless of adenosine addition. Coronary resistance remained elevated during the period of low potassium perfusion, except when high-concentration adenosine was added. With addition of 8 μM adenosine, coronary resistance returned to baseline, and left ventricular endocardial perfusion was augmented. Electromechanical quiescence improved with adenosine perfusion and was complete with high-dose adenosine addition. Function was preserved in all hearts.

Conclusion: Use of a modern micropump system allowed for continuous addition of adenosine and potassium to whole blood cardioplegia. Adenosine minimized potassium-induced coronary vasoconstriction and improved endocardial perfusion and mechanical quiescence. These findings supported addition of adenosine to the perfusate during warm whole blood cardioplegia.

INTRODUCTION

Several investigators have accumulated evidence supporting the theoretical advantage of warm continuous whole blood cardioplegia over other techniques of myocardial protection [Follette 1980, Lichtenstein 1990]. Compared with crystalloid cardioplegia, continuous whole blood warm cardioplegia has greater oxygen-carrying and oxygen-extraction capabilities, excellent buffering potential due to blood protein histidine groups, superior rheologically mediated microvascular flow, and better preservation of myocardial ultrastructure [Guyton 1995].

Untoward effects of use of near-continuous cardioplegia are resulting metabolic abnormalities, such as hyperglycemia [Hearse 1978], hyperkalemia [Tyers 1975], hyponatremia, and hemodilution [Latouff 1995, Rescigno 1998]. Because these drawbacks are due in part to the use of 5% dextrose in water (D_5W)-based solution, some surgeons have based cardioplegia on one-half normal saline solution or have mixed less crystalloid with warm whole blood (ie, 1:8 instead of 1:4), a modification of the original description of this technique [Lichtenstein 1991]. Adding smaller volumes of concentrated cardioplegia enhanced the ability to accurately control potassium level, minimized hemodilution, and decreased metabolic imbalances [LeHouerou 1992, Satyanarayana 1992, Menasche 1996].

Because of the apparent benefits, whole warm blood cardioplegia has become the method of myocardial protection preferred by several cardiac surgeons at Massachusetts General Hospital, especially in the care of high-risk patients. These patients include those with poor ventricular function or active ischemia and those undergoing complex operations (ie, combined valve and bypass operations) that require longer cross-clamp times.

A commercially available device, the Microplegia Protection System (MPS) (Quest Medical, Allen, TX, USA), can

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continuously infuse microliter quantities of potassium and other supplements to whole blood while maintaining the ability to modify the concentration of the additive and to regulate cardioplegia temperature during perfusion. It was hypothesized that this device would minimize the unwanted metabolic effects of continuous cardioplegia by eliminating use of hyponatremic solution containing potassium and glucose crystalloid. However, in our experience (unpublished), adding only potassium and magnesium to warm whole blood resulted in an increase in coronary resistance and less satisfactory recovery of myocardial electrical and mechanical function than with the 4:1 blood-to-crystalloid approach.

The established effect of hyperkalemia on coronary vascular resistance [Le Houerou 1992] can be countered by the use of adenosine, a potent coronary vasodilator [Berne 1980]. The ability of adenosine to reduce time to arrest, when used as an additive to hyperkalemic cardioplegia, may lessen the amount of potassium required for arrest [Schubert 1989, Willem de Jong 1990]. Furthermore, adenosine has been shown to improve cardiac function during reperfusion as an adjunct to hyperkalemic cardioplegia [Ledingham 1990, Willem de Jong 1990]. Unfortunately, clinical use of adenosine has been limited by its potency and its short half-life, estimated to be on the order of 10 seconds in human blood [Claude 1983, Soderback 1987, Moser 1989].

This study tested the hypothesis that continuous addition of adenosine with an in-line micropump system would facilitate normothermic whole blood hyperkalemic cardioplegia.

MATERIALS AND METHODS

Experimental Preparation

These studies were performed in accordance with the *Guide for the Care and Use of Laboratory Animals* published by the National Institutes of Health (NIH publication 85-23, revised 1985).

Nine mongrel dogs of either sex weighing 27 to 38 kg were anesthetized with intravenous α-chloralose (75-150 mg/kg) and urethane (0.75-1.5 g/kg). After endotracheal intubation, the animal was ventilated with oxygen-enriched room air. The heart was exposed through a median sternotomy and supported in a pericardial cradle prior to ligation of the azygos vein. Aortic pressure was continuously monitored, and right-heart bypass was established with cannulation of the aorta and pulmonary artery to allow control of left-heart preload and afterload as previously described [Daggett 1967]. Cardiac output was controlled with a calibrated roller pump, which infused the cannulated pulmonary artery with warm oxygenated blood from the cardiotomy reservoir. A second calibrated roller pump regulated aortic pressure by infusing or withdrawing warm oxygenated blood through a cannula in the left subclavian artery. A catheter implanted in the aortic root enabled simultaneous monitoring of aortic root pressure and infusion of cardioplegic solution at 4 mL/kg per minute. Left ventricular (LV) pressure measurements and venting at a pressure of 5 cm H_2O during cardioplegia were accomplished with a cannula placed in the apical dimple of the LV. After crushing of the sinoatrial node, heart rate was held constant by pacing with wires sewn to the right atrium. An electrocardiogram was produced by a right ventricular epicardial lead. All pressures were measured with strain-gauge transducers (Viggo Spectramed DTX, Oxnard, CA, USA) and recorded with the electrocardiogram on a multichannel polygraph (Marquette, Milwaukee, WI, USA).

Arterial P_{CO_2} and P_{O_2}, pH, body temperature, anticoagulation therapy, and continuous anesthesia were regulated or administered as previously described [Geffin 1987].

Protocol

An initial myocardial function curve (control) was established for each heart prior to 2 20-minute arrest periods induced by hyperkalemic antegrade warm blood cardioplegia followed by 20-minute recovery intervals (Figure 1). In each arrest interval, the potassium concentration for the first 5 minutes was 24 mEq/L (high dose), and for the remaining 15 minutes it was 6 mEq/L (low dose). Animals were randomly assigned to 1 of 3 groups. Canines in each group underwent 2 arrest periods so that the maximum benefit from each animal could be gained and to allow each heart to be used as its own control, thereby reducing interanimal variability.

The first group received cardioplegia without adenosine followed by cardioplegia with a low concentration (0.5 μM) of adenosine. The second group was identical to the first with the exception that the order of administration of the adenosine and adenosine-free cardioplegia was reversed. The third group received cardioplegia with a high concentration (8 μM) of adenosine followed by adenosine-free cardioplegia. Measurements of myocardial function performed during right-heart bypass were made immediately after both arrest periods. Regional myocardial blood flow distribution was evaluated with colored microspheres (BioPal, Worcester, MA, USA) prior to both aortic cross-clamp intervals and during the fifth and 20th minutes of cardioplegic arrest.

After the first 20-minute arrest period, the cross clamp was removed, atrial pacing was resumed, and reperfusion with normokalemic blood at 37°C was started. The heart was allowed to beat while vented for 20 minutes at a mean aortic pressure of 70 mm Hg.

At the end of the first recovery period, the LV vent was closed, right-heart bypass was resumed, and cardiac output was gradually raised to its baseline value of 2090 mL/min. When hemodynamics were stable, cardiac function and myocardial blood flow evaluations once again were performed at constant aortic pressure as described below. The second arrest and recovery periods were performed in a similar fashion.

Myocardial Function

LV performance was measured by increasing preload while afterload was kept constant with independent pumps for right-heart bypass as described previously [Berne 1980]. Pacing was established at a rate of 150 to 160 beats/min, and a mean aortic pressure of 70 mm Hg was maintained. Five measurements of LV peak and end-diastolic pressures were made while flow through the pulmonary artery (preload) was varied incrementally from 1190 to 3540 mL/min.

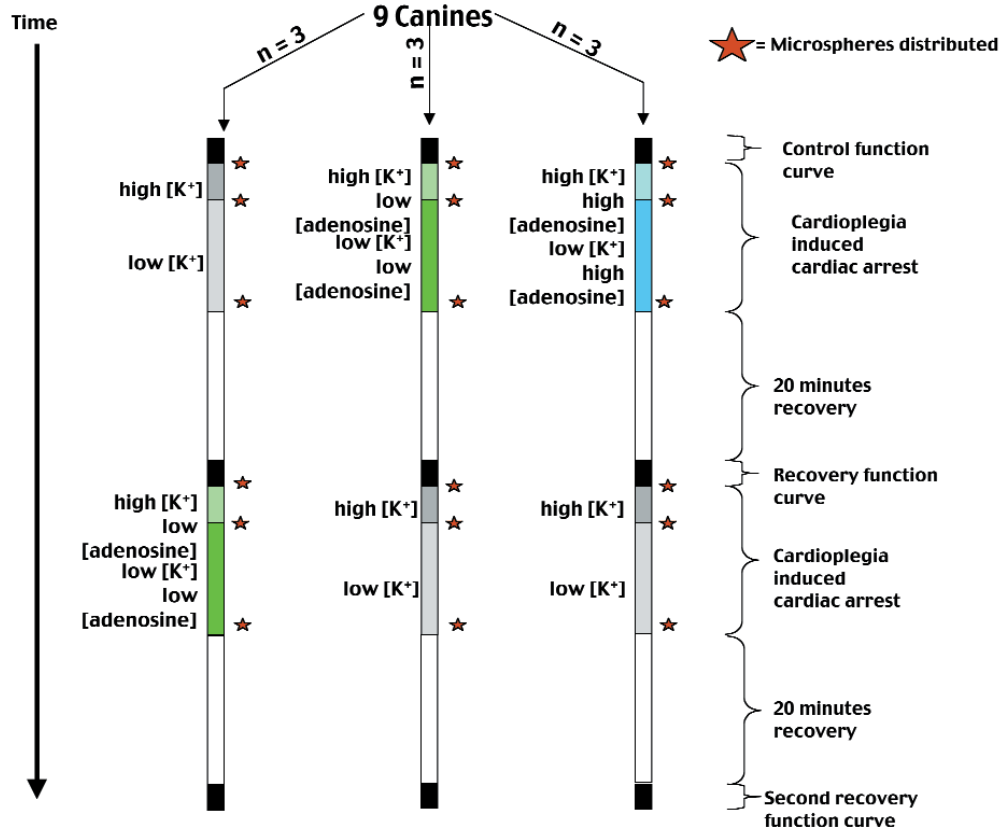

Figure 1. Experimental protocol. After performance of an initial myocardial function curve, canines were randomized to 3 experimental groups. Each animal underwent 2 arrests, once with cardioplegia with adenosine (0.5 or 8 μM) and once without adenosine addition (control). For each arrest interval, the potassium concentration was 24 mEq/L for the first 5 minutes (high [K^+]) and 6 mEq/L for the remaining 15 minutes (low [K^+]). After a 20-minute recovery period, the myocardial function of each heart was assessed. Microspheres were introduced before and 5 and 20 minutes after cross-clamping.

Cardioplegia Delivery and Electromechanical Quiescence

Total cardiopulmonary bypass was instituted, pacing was discontinued, and the LV was vented at a pressure of 5 cm H_2O through an apical cannula. Aortic pressure was decreased to 50 mm Hg, and the aorta was cross clamped. Blood from the cardiopulmonary bypass machine was pumped to the MPS, where potassium (24 mEq/L or 6 mEq/L), magnesium sulfate (2.5 mEq/L), and, optionally, adenosine (0, 0.5 μM, or 8 μM) were added. The MPS pumps used stock solutions of potassium, adenosine, and magnesium at concentrations of 2 mEq/mL, 3 mg/mL, and 4.06 mEq/mL, respectively, as additives for the whole blood cardioplegia solution. Anterograde cardioplegia was delivered through the aortic root at a constant flow of 4 mL/kg per minute and at a temperature of 37°C. Thus because cardioplegia flow was held constant, coronary resistance was directly related to aortic root pressure.

The time from clamping of the aorta to cardiac arrest was recorded. If the heart contracted while perfused with low-potassium cardioplegia, the potassium concentration was increased to 24 mEq/L for 1 minute. From the onset of arrest to the end of cardioplegia delivery, all disruptions in electromechanical quiescence were recorded.

Regional Myocardial Blood Flow

For determination of regional perfusion prior to cross clamping, at the fifth and at the 20th minutes of arrest, colored microspheres were introduced into the coronary circulation. Measurements of coronary blood flow made prior to cross clamping were performed during right-heart bypass by introduction of microspheres into the left atrium. Approximately 10 million 10- to 12-μm–diameter colored microspheres were suspended in 3 mL normothermic saline solution and steadily flushed into the left atrium by 20 mL of warm saline solution over 20 seconds. Over the following 2 minutes, blood was withdrawn from the ascending aorta with a small roller pump and placed into preweighed vials to serve as a reference sample. This pump had been started prior to microsphere injection.

Regional myocardial blood flow measurements during the fifth and 20th minutes of cardioplegic arrest were performed by introduction of microspheres into the aortic root through the cardioplegia line. A suspension comprising 500,000 microspheres in 0.2 mL saline solution was steadily flushed into the aortic root through the cardioplegia line with 2 mL warm saline solution over 5 seconds while cardioplegia solution was flowing. Coronary perfusion pressure was not appreciably perturbed by this injection.

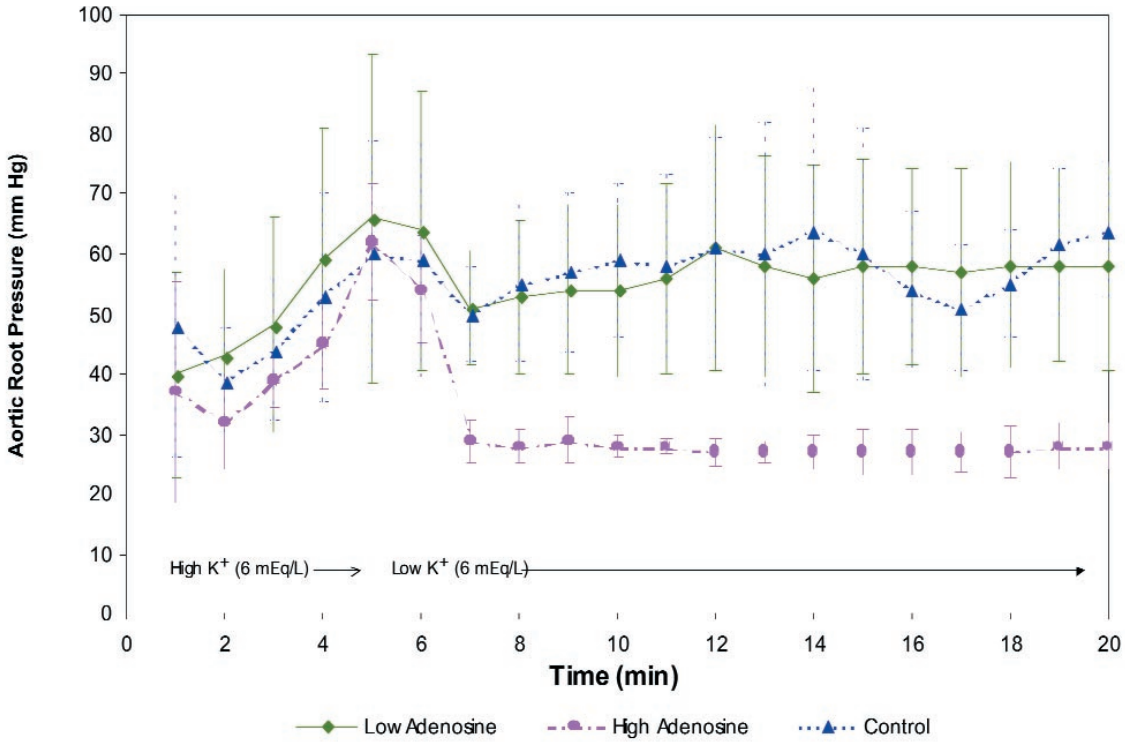

Figure 2. Aortic pressure at constant cardioplegic flow starting from the onset of the cross-clamp period. Mean pressure for the groups receiving high-dose adenosine (n = 3) and low-dose adenosine (n = 5) and the control group (n = 8) and the standard deviation for each group are graphed. Addition of high-dose adenosine reduced coronary resistance to baseline level, but only when cardioplegia with a low potassium concentration was used.

At the conclusion of the experiment, the heart was excised and sectioned. The LV papillary muscles were removed. The interventricular septum was divided into anterior and posterior segments, which were sectioned into right ventricular subepicardial, midmyocardial, and LV subendocardial layers. The LV free wall was divided into anterior and lateral segments, which were separated into basal, equatorial, and apical portions and subsequently sectioned into subepicardial, midmyocardial, and subendocardial layers. Colored microspheres in reference blood samples and in myocardial tissue samples were subsequently sent for activation and counting (BioPal).

Statistical Analysis

Data analysis was conducted on a desktop personal computer with SAS software (release 8.01; SAS, Cary, NC, USA) in a Windows-NT environment (Microsoft, Redmond, WA, USA). *P* values for the differences between continuous values were computed with the unpaired *t* test, and the χ^2 method was used for binary variables.

RESULTS

Three groups, each comprising 3 canines, were used in the experiment. However, data from 1 of the 6 hearts subjected to cardioplegia with low-dose adenosine were rejected from the study, because the MPS pump had been improperly set. One heart, which had uneventfully undergone cardioplegia with low-dose adenosine, developed sudden and severe aortic valve insufficiency and thus could not subsequently undergo cardioplegia. Thus the control group was reduced to a total of 8 hearts.

Coronary Resistance

Figure 2 depicts aortic root pressure during delivery of cardioplegia at a constant rate (4 mL/kg per minute) starting at the time of cross clamping. Initial root pressure was similar in the high-adenosine, low-adenosine, and control groups. During the initial 5-minute period of high-potassium arrest, root pressure, a proportional measure of coronary resistance, rose progressively regardless of adenosine addition. After 5 minutes, potassium concentration was dropped to the lower dosage, and, subsequently, resistance decreased in all hearts over a 2-minute interval. The high-adenosine group had the largest reduction (33 ± 6 mm Hg) compared with the low-adenosine group (11 ± 22 mm Hg) and with the control group (11 ± 16 mm Hg).

During the rest of the arrest period, coronary resistance in the high-adenosine group was significantly lower than resistance in both the low-adenosine and the control groups ($P < .001$). After 20 minutes of arrest, the aortic root pressure was 28 ± 4 mm Hg in the high-adenosine group compared with 58 ± 17 mm Hg for the low-adenosine group and 64 ± 11 mm Hg in the control group.

Electromechanical Quiescence

The times from cross clamping to electromechanical arrest in hearts perfused with high-adenosine, low-adenosine,

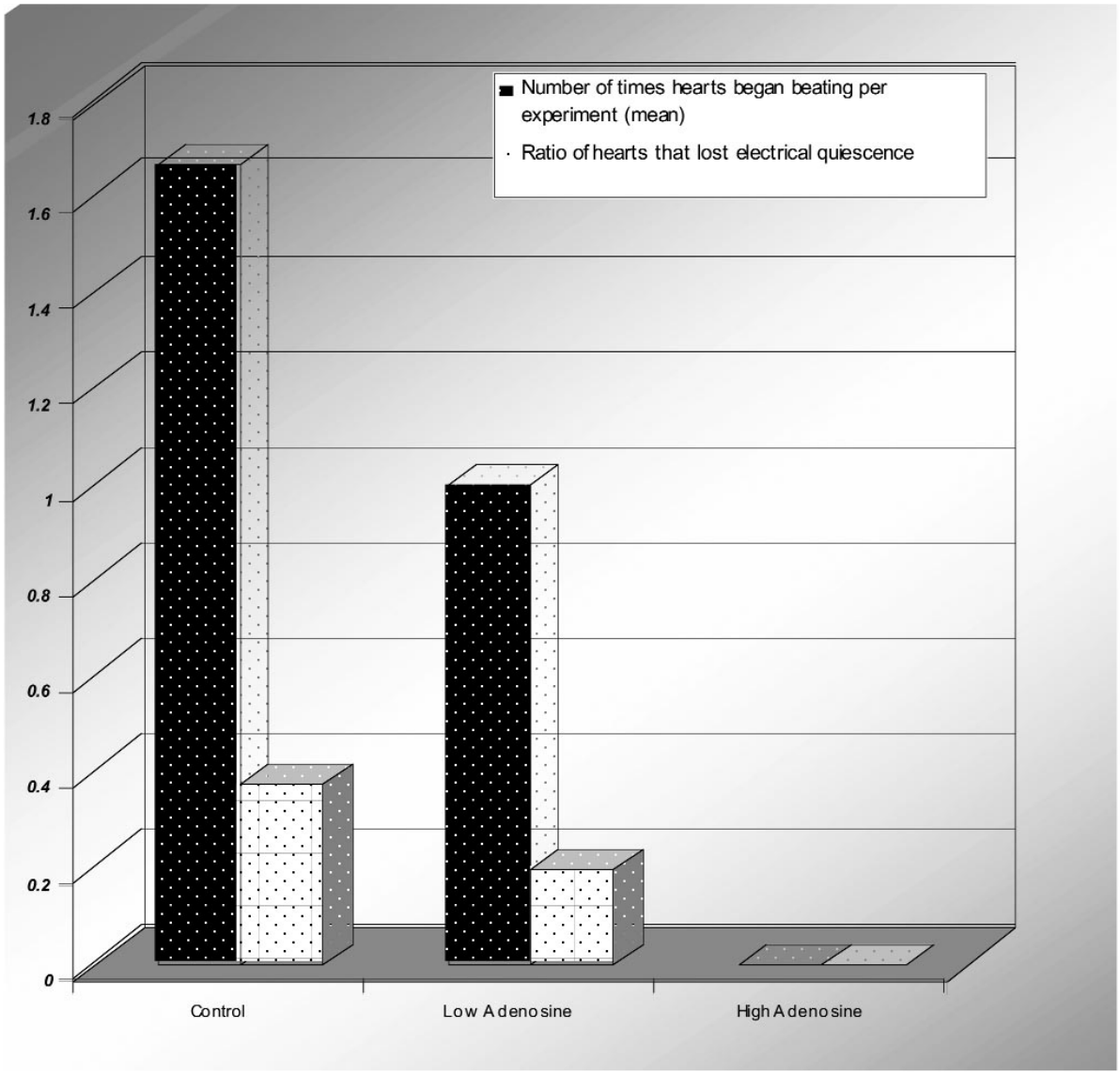

Figure 3. Failures in electromechanical quiescence in 3 cardioplegia groups. The vertical axis represents either the average number of times the hearts began beating (white dots on black) or the ratio of hearts with failure of quiescence (black dots on white). The 3 groups tested were control (no adenosine addition), low adenosine (0.5 μM), and high adenosine (8 μM). Adenosine addition improved quiescence ($P < .05$).

and control cardioplegia were 80.3 ± 13, 74.8 ± 9, and 96 ± 26 seconds, respectively ($P < .05$ for control versus high- and low-adenosine groups combined).

Electromechanical quiescence was maintained in the high-adenosine group, and the low-adenosine group was significantly more quiescent ($P < .05$) than the group receiving adenosine-free (control) cardioplegia (Figure 3). During the period of low-potassium cardioplegia, electromechanical activity was observed in both the low-adenosine group and the control group. One heart of the 5 subjected to cardioplegia with adenosine addition began beating during the arrest period. Three of the 8 hearts studied as controls had 1 or at most 2 failures of quiescence. A total of 5 failures were observed in this group.

Myocardial Function

LV function was evaluated by measurement of systolic pressure to end-diastolic pressure relations at constant afterload. These results were graphically reviewed for all 9 hearts and demonstrated that there was no change in contractility and that the heart did not sustain any injury after cardioplegia. This finding was subsequently confirmed by statistical analysis that showed no appreciable change in performance between conditions before and after arrest (Figure 4).

Regional Myocardial Blood Flow

Endocardial to epicardial blood flow distribution in 6 distinct areas of the myocardium was estimated with colored microspheres (Figure 5). At the LV base ($P < .05$), there was a

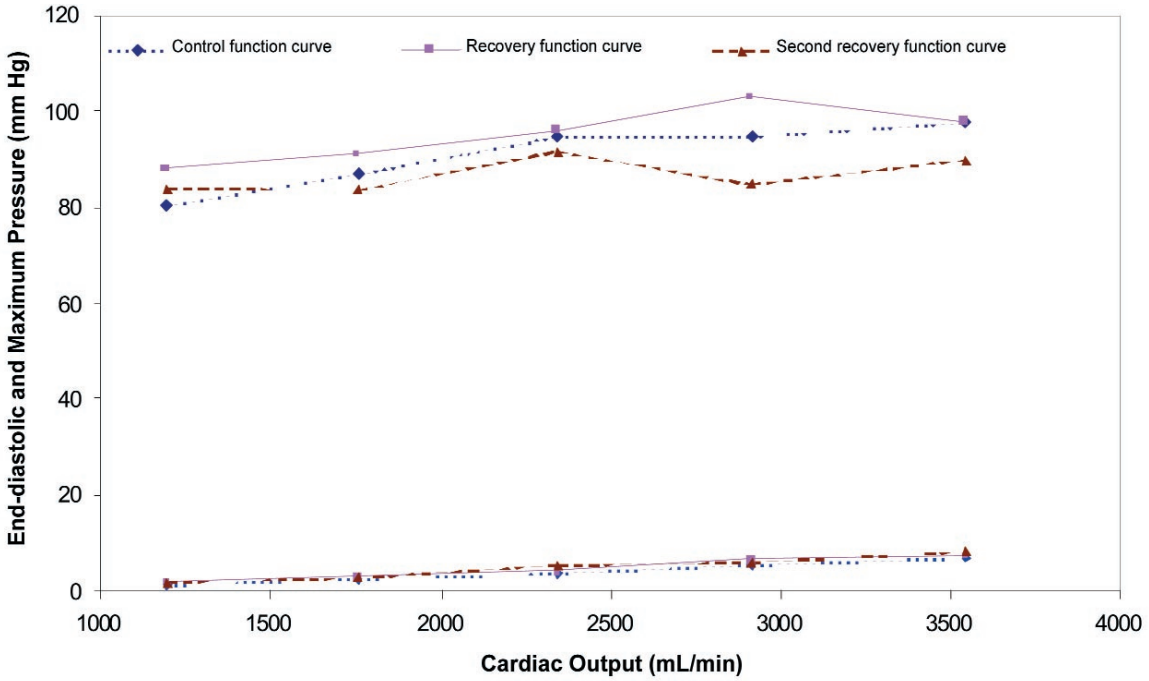

Figure 4. Left ventricular systolic pressure and end-diastolic pressure versus cardiac output. Left ventricular peak and end-diastolic pressures were obtained at increasing cardiac output while constant afterload was maintained. The data show preserved left ventricular function in all heats.

significant increase in ratio of endocardial to epicardial flow (at 20 minutes) between the group receiving high-dose adenosine (n = 3) and the adenosine-free group (n = 8). Perhaps because of the scatter of the data and the small sample size, the effects of adenosine in the other regions of the heart were not statistically significant.

The addition of high-dose adenosine to the cardioplegia solution enhanced endocardial perfusion, relative to the epicardium, when the flow distribution that existed prior to cardioplegia (t = 0) was compared with that after 20 minutes of cross clamping. Although this improvement occurred in several regions of the myocardium, the effect was most significant in the LV base ($P < .07$) and in the anterior portion of the LV. Adenosine-free cardioplegia, in contrast, did not discernibly alter endocardial to epicardial flow distribution in comparison with flow patterns prior to initiation of cardioplegia.

Endocardial to epicardial flow ratios at the 5-minute mark were comparable with those prior to cross clamping in each experimental group (not shown on graph). The scatter in microsphere counts, as well as the small sample size, contributed to the standard error graphically represented (Figure 5).

DISCUSSION

In the original description of application of continuous warm blood cardioplegia, whole blood was mixed with a high-potassium, hyponatremic, and hyperglycemic solution (5% dextrose one-half normal saline solution) in a 4:1 ratio. Continuous infusion of this solution can cause metabolic derangement and hemodilution during extended cross-clamp periods [Satyanarayana 1992]. Myocardial protection with continuous warm hyperkalemic whole blood has demonstrable advantages over hypothermic techniques that have led to its preferential use by some surgeons [Cannon 1994]. This study was aimed at refining the method of delivering continuous hyperkalemic warm whole blood cardioplegia.

Use of whole blood with the addition of highly concentrated potassium (2000 mEq/L) and magnesium (240 mEq/L) would theoretically limit the adverse metabolic and volume overload effects. However, this study confirmed our clinical experience that such a strategy results in coronary vasoconstriction. The phenomenon of hyperkalemic, warm whole blood cardioplegia leading to coronary vasoconstriction has been documented previously and may originate from alteration of endothelium-dependent relaxation through a non–nitric oxide and noncyclooxygenase pathway [He 1996, Hearse 1975]. This phenomenon is largely absent with cold cardioplegia [Torchiana 2000].

The hypothesis of this study was that adenosine, a thoroughly studied coronary vasodilatory agent [Morrison 2002, Olsson 1976, Tyers 1975, Wilson 1990], would ameliorate the vasoconstrictive effects of hyperkalemic cardioplegia. Although adenosine was chosen for its ability to dilate the coronary arteries, this purine has many other cardioprotective properties, which may have contributed to rapid electromechanical quiescence and preservation of function in the adenosine-perfused hearts. These qualities include ability to induce conduction block in the atrioventricular and sinoatrial nodes [DiMarco 1983, Belardinelli 1988], to indirectly inhibit myocardial contractility [Dobson 1983], and to improve tolerance of the myocardium to ischemic arrest [Ely 1985]. The diverse and potent actions of adenosine enable it to minimize

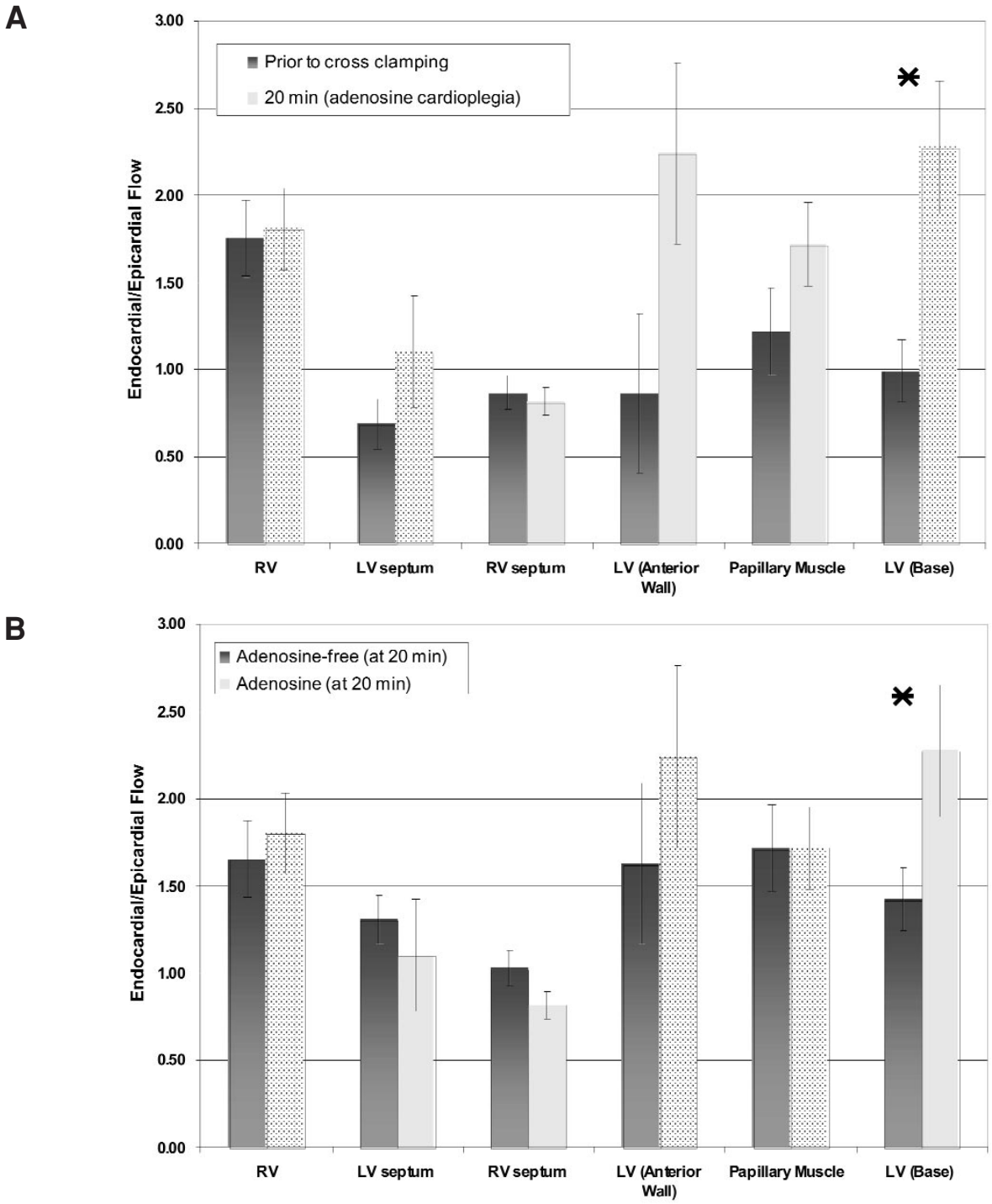

Figure 5. Endocardial to epicardial flow ratio as calculated with colored microspheres. A, Perfusion ratio prior to cross clamping and at 20 minutes in the high-adenosine group (8 μM) in indicated regions of the heart. B, Similar depiction comparing control (adenosine-free) and adenosine groups 20 minutes into the cross-clamp period. The ratio for the septum was calculated as endocardial flow versus midseptal flow. Data are shown ±SE. Asterisks indicate significant difference between groups; RV, right ventricle; LV, left ventricle.

myocardial injury when administered prior to [Lasley 1995], during [Bolling 1989], and after cross-clamp intervals [Ledingham 1990]. Furthermore, some surgeons have used a bolus of adenosine to aid in initiation of arrest [Maddali 2000].

Regardless of the potential clinical utility of adenosine, use of this agent has been limited by its systemic potency and short half-life. Injected intraarterially into isolated perfused hearts, adenosine produced maximum dilation at 10^{-5} M

concentration [Schrader 1977]. In human blood, the half-life of adenosine is thought to be less than 10 seconds [Lichtenstein 1991, Rescigno 1998]. If mixed in a cardioplegia reservoir with blood, adenosine would be metabolized over a very brief time, and its concentration in the solution perfusing a patient's heart would be unpredictable. Use of the MPS system allowed for continuous and precise addition of adenosine directly into the cardioplegia line, minimizing the time between addition to blood and perfusion of the heart.

At the beginning of the study, the dosage of adenosine required to keep resistance near baseline was unknown. Because of the effectiveness of the drug as a vasodilator, too high a dose could result in a very low aortic root pressure with the possibility of regional malperfusion or systemic effects. One clinical trial investigating use of adenosine in warm blood cardioplegia avoided high dosages of the nucleotide because of systemic hypotension [Cohen 1998]. The dose ultimately selected was a reflection of work done by other investigators [Latouff 1995] as well as pilot studies that assessed a wide range of concentrations [Fremes 1996].

Addition of adenosine had no effect on the progressive rise in coronary resistance during infusion of the hearts with the arresting (high) dose of potassium. However, in the period of maintenance (low) potassium perfusion that followed, coronary resistance dropped significantly, relative to control and low adenosine groups, in hearts infused with high-dose adenosine ($P < .001$). Resistance promptly returned to baseline and remained low throughout the cross-clamp period. The low-adenosine dosage had no demonstrable effect on coronary resistance.

Adenosine used as a supplement to crystalloid hyperkalemic cardioplegia has been shown to shorten time to arrest. The results of this study supported this finding and demonstrated that adenosine had a similar effect when used with hyperkalemic normothermic whole blood cardioplegia. In addition, we showed that adenosine suppressed electromechanical activity in a dose-dependent fashion. Thus this study demonstrated the advantage of adding adenosine to warm whole blood cardioplegia at the onset of cardioplegia and throughout the arrest period. Furthermore, microsphere data, which showed that adenosine acts as a vasodilatory agent preferentially in the endocardium, suggested that addition of adenosine will enhance the cardioprotective effects of warm cardioplegia by improving endocardial perfusion.

Although this work demonstrated that some of the limitations of adenosine, such as its short half-life, may be overcome by use of a microplegia system, the optimum dose of adenosine remains to be determined. Because adenosine slows the activity of the sinoatrial pacemaker through adenosine triphosphate–sensitive potassium channels but increases cardiac perfusion through the adenosine A_2 receptor [Yoneyama 1999], it is possible that the concentration of adenosine needed in initiating cardioplegia may be different from that used to maintain cardioplegic arrest. The microplegia system used allows for titration of adenosine concentration during the clamp period and could be used to test dosages experimentally.

Myocardial function was assessed during right-heart bypass by variation of preload while constant afterload was maintained. Minor damage to the myocardium, such as that which might be caused by changes in endocardial flow during cardioplegia, would not be detected with this method, because the damage would not be severe enough to cause a measurable change in cardiac performance. However, it can be assumed that this method provides a reasonable measure of global function, because each heart was repeatedly subjected to multiple periods of arrest and returned to baseline functioning.

This study has important potential clinical implications in the delivery of warm cardioplegia. Although it did not impact high-potassium–induced coronary resistance (arresting dose), adenosine did improve resistance during maintenance infusion. Further studies are necessary to determine whether a shortened period of high potassium delivery, or a higher concentration of adenosine, would prevent the steep elevation in resistance observed initially. The myocardial stress in this study was insufficient to damage the hearts in any group. Additional studies are needed to characterize the impact of this therapy on myocardial performance after long ischemic intervals.

CONCLUSION

The recent introduction of micropump systems for selective delivery of cardioplegic additives to whole blood at varying doses and time intervals enables novel permutations of cardioplegic solutions. In this experiment micropump technology was used to deliver adenosine, an unstable compound, in a continuous manner at discrete periods to coincide with periods of high or low potassium delivery. This study demonstrated that high-dose addition of adenosine to hyperkalemic whole-blood cardioplegia effectively decreases potassium-mediated coronary resistance and improves electromechanical quiescence during the low-potassium maintenance period. Adenosine was found to act preferentially on the endocardium, where it decreases vascular resistance. The findings suggested that clinical use of adenosine may overcome some of the clinical limitations of warm whole blood cardioplegia.

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