Warm nondepolarizing adenosine and lidocaine cardioplegia: Continuous versus intermittent delivery

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Objective: Continuous infusion of warm to normothermic cardioplegia may limit the surgeon's visual field, increase coronary vascular resistance, and lead to potassium-exacerbated ischemia-reperfusion damage. Our aim was to examine the versatility of a new normokalemic, nondepolarizing adenosine-lidocaine cardioplegia during continuous or intermittent infusion at 33°C and compare it with lidocaine cardioplegia.

Methods: Isolated, perfused rat hearts ($n = 6$ each group) were arrested at 33°C for 40 or 60 minutes with 200 μm of adenosine and 500 μm of lidocaine in Krebs-Henseleit buffer (10 mmol/L glucose, pH 7.6-7.7 at 37°C) or 500 μm of lidocaine in Krebs-Henseleit buffer for 60 minutes delivered at 60 mm Hg.

Results: Times to arrest were 7 to 10 seconds for the adenosine-lidocaine groups and 102 seconds for the lidocaine group ($P < .05$). Total cardioplegia volumes for intermittent (2 minutes every 18 minutes) and continuous deliveries were 122 to 159 mL and 699 to 922 mL for the 40- and 60-minute adenosine-lidocaine arrest protocols, respectively, and 136 mL for the 60-minute intermittent lidocaine group. In the last 2 minutes of the 40- and 60-minute arrest protocols, the coronary vascular resistance was not significantly different for the hearts arrested with adenosine and lidocaine (0.27–0.32 megadyne/sec/cm⁻⁵). Significantly higher coronary vascular resistance was found in the lidocaine cardioplegia group (0.38 megadyne/sec/cm⁻⁵). No significant differences were found between the continuous or intermittent adenosine-lidocaine delivery protocols. Hearts arrested with adenosine and lidocaine recovered 88% to 89% of aortic flow and 109% of coronary flow at 60 minutes of reperfusion after 40-minute arrest, and 77% to 86% of aortic flow and 98% to 109% of coronary flow at 60 minutes of reperfusion after 60-minute arrest. Lidocaine cardioplegia led to significantly lower aortic and coronary flows after 60-minute arrest compared with the intermittent adenosine-lidocaine group.

Conclusions: We conclude that adenosine-lidocaine cardioplegia can be delivered intermittently or continuously with similar functional recoveries after a 40- or 60-minute arrest at 33°C. Hearts receiving lidocaine cardioplegia took a significantly longer time to arrest, showed higher coronary vascular resistance, and achieved lower functional recovery than the 60-minute adenosine-lidocaine cardioplegia groups. Intermittent or continuous delivery of adenosine-lidocaine cardioplegia may offer an alternative to current surgical hyperkalemic cardioplegia at warm to normothermic temperatures.

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Part of the study was supported by the National Heart Foundation of Australia Grant G 05B 2034 (G. P. D.).

Received for publication Oct 20, 2006; revisions received Dec 6, 2006; accepted for publication Dec 18, 2006.

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J Thorac Cardiovasc Surg 2007;133:1171-8
0022-5223/\$32.00

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doi:10.1016/j.jtcvs.2006.12.058

For more than 3 decades, hypothermia has been widely accepted as an important component of myocardial protection during cardiac surgery.¹ Traditionally, the main reason for selecting hypothermia has been to decrease myocardial oxygen demand beyond the reduction achieved with electrochemical arrest induced by high potassium concentrations. Oxygen consumption during arrest at 11°C is 0.135 mL O₂/min per 100 g myocardium (>97% reduction from rest at

Abbreviations and Acronyms

AL = adenosine and lidocaine
CVR = coronary vascular resistance

37°C) compared with 1.1 mL O₂/min per 100 g myocardium when arrested at 37°C (90% reduction).² Although hypothermic arrest is still widely used, it has been increasingly associated with myocardial ischemia and stunning.³⁻⁵ The hypothermic heart, for example, is more susceptible to arrhythmias during “reanimation” and often requires electrical cardioversion to achieve normal sinus rhythm.⁵

In the early- to mid-1980s, Rosenkranz and associates⁶ and Teoh and colleagues⁷ challenged the underlying principles of hypothermic arrest and showed that induction of arrest with normothermic blood cardioplegia was superior to cold blood cardioplegia in functional recovery in the canine model. A few years later, Salerno and colleagues⁸ and Lichtenstein and colleagues^{9,10} proposed warm heart surgery with systemic normothermia as an alternative to hypothermic methods. Studies investigating normothermia have reported improved tissue distribution of oxygen and equivalence or improvement in postischemic functional outcomes, including cognitive functions.^{5,11-14} Nondepolarizing cardioplegia, using lidocaine alone as the arresting agent, has also shown protective properties at normothermic temperatures in animal models.¹⁵⁻¹⁷

Despite an increasing number of investigators advocating warm surgery, there remain legitimate concerns with cardioplegic arrest at tepid to warm (33°C-37°C) heart temperatures. One problem confronting surgeons is the fine balance between the need to interrupt cardioplegia delivery to perform surgery and the need to continuously infuse to protect the heart at these higher temperatures. Lichtenstein and others¹⁰ suggested that a reasonable margin of safety exists if single interruptions are less than approximately 13 minutes. However, the safe period for intermittent delivery and total crossclamp times have not been established.^{5,10,12,18-20} In addition to obscuring the operating field, continuous delivery has been associated with potassium-induced injury to myocytes and the coronary vasculature,²¹ increased vascular resistance with prolonged crossclamp times leading to higher pump delivery pressures,²²⁻²⁴ and postoperative left ventricular dysfunction.²⁵

Accordingly, the aim of the present study was to examine the efficacy of a new normokalemic, nondepolarizing cardioplegia delivered at 33°C using both continuous and intermittent delivery protocols in the isolated working rat heart. An arrest temperature of 33°C was chosen on the basis of the studies of Engleman and colleagues²⁶ and Guyton and colleagues,²⁵ who reported that tepid temperatures provided optimal myocardial recovery and brain pro-

tection during cardiac surgery. Previously we showed in the rat heart that a crystalloid formulation of adenosine and lidocaine (AL) cardioplegia conferred greater protection at 22°C to 29°C compared with St Thomas' hospital number 2 solution delivered intermittently during 2 to 4 hours of arrest.²⁷ More recently we showed in the canine model of cardiopulmonary bypass that functional recovery after intermittent delivery of normothermic AL blood cardioplegia was equivalent to hypothermic potassium arrest; however, continuous delivery at normothermic temperatures was not studied.²⁸ In the present study we report that AL cardioplegia can be delivered continuously or intermittently at 33°C with no significant differences in postarrest functional recovery. We also report that lidocaine only cardioplegia was not as effective as AL cardioplegia in the time to arrest, maintenance of coronary artery vascular resistance, or functional recovery during reperfusion.

Materials and Methods**Animals**

Male Sprague-Dawley rats (370-450 g) from James Cook University's breeding colony were fed ad libitum and housed in a 14:10-hour light:dark cycle. Rats were anesthetized with an intraperitoneal injection of thiopentone sodium (100 mg/kg body weight), and hearts were rapidly excised.²⁷ Rats were handled in compliance with James Cook University Guidelines (Ethics Approval Number A759) and the “Guide for Care and Use of Laboratory Animals,” published by the National Institutes of Health (publication 85, revised 1985). Adenosine (A9251 > 99% purity) and other chemicals were obtained from Sigma Chemical Co (Castle Hill, NSW). Lignocaine hydrochloride (lidocaine) was purchased as a 2% solution (ilium) from the local Pharmaceutical Supplies (Lyppard, Queensland).

Composition of Buffers and Arrest Solutions

Krebs-Henseleit perfusion buffer. Isolated rat hearts were perfused in the Langendorff (nonworking) and working mode with a modified Krebs-Henseleit buffer containing 10 mmol/L glucose; 117 mmol/L NaCl, 5.9 mmol/L KCl, 25 mmol/L NaHCO₃, 1.2 mmol/L NaH₂PO₄, 1.12 mmol/L CaCl₂ (free Ca²⁺ = 1.07 mmol/L), 0.512 mmol/L MgCl₂ (free Mg²⁺ = 0.5 mmol/L), pH 7.4 at 37°C.²⁷ The perfusion buffer was filtered using a 1-μm membrane and then bubbled vigorously with 95% O₂/5% CO₂ to achieve a Po₂ greater than 600 mm Hg. The perfusion buffer was not recirculated.

Adenosine and lidocaine arrest solution. Adenosine (200 μm) plus lidocaine (500 μm) cardioplegia (AL) was freshly prepared in normokalemic Krebs-Henseleit buffer containing 10 mmol/L glucose at pH 7.7.²⁷ The AL arrest solution was filtered using a 0.2-μm filter and delivered at 33°C. The arrest solution was not actively bubbled with 95% O₂ and 5% CO₂.

Lidocaine arrest solution. Lidocaine (500 μm), in an otherwise identical normokalemic Krebs-Henseleit buffer containing 10 mmol/L glucose, was filtered using a 0.2-μm filter and maintained at 33°C. The arrest solution was not actively bubbled with 95% O₂ and 5% CO₂.

An adenosine control group was not included in this study because adenosine in Krebs–Henseleit buffer at 200 μM does not maintain arrest in the isolated rat heart at 32°C to 33°C ($n = 2$) or at 22°C to 29°C ($n = 6$) (unpublished data, Sloots, BSc [Hons], 2006).

Isolated–perfused (Langendorff and working) rat heart preparation. Hearts were rapidly removed from anesthetized rats and immediately placed in an ice-cold Krebs–Henseleit buffer. Excess tissue was removed, and the heart was connected through the aorta to a standard Langendorff apparatus and perfused in a retrograde fashion with a perfusion pressure of 80 cm H₂O (60 mm Hg).²⁷ The pulmonary artery was cannulated for collection of coronary venous effluent. After tying off the pulmonary veins and superior and inferior vena cava to minimize leaks (<1 mL/min), the atrium was cannulated and the preparation was then switched to working mode. The preload (inflow of buffer into the left atrium) was set at 10 cm H₂O (7.6 mm Hg), and the afterload was set at 100 cm H₂O (76 mm Hg). Hearts were stabilized for 10 minutes before converting back to Langendorff (nonworking) mode to administer the arrest solution. Heart rate, aortic pressure, coronary flow, aortic flow, inflow and coronary venous oxygen content, and oxygen consumption were measured before, during, and after arrest as reported previously.²⁷ Rate–pressure product, an index of oxygen demand,²⁹ was calculated from the heart rate $\times$ peak systolic pressure.

Aortic pressure was measured continuously using a pressure transducer (UFI Instruments, Morro Bay, Calif) coupled to a MacLab 2e (ADI Instruments, Sydney, Australia). Systolic and diastolic pressures and heart rate were calculated from the pressure trace using MacLab software. Inflow and coronary venous perfusate Po_2 and PCO_2 , pH, and ion concentrations (Ca^{2+} , Cl^- , K^+ , and Na^+) were measured using a Bayer 865 blood gas analyzer (Bayer Diagnostics, Queensland, Australia). Coronary venous flow and aortic flow were measured in volumetric cylinders. The initial criteria for exclusion of working hearts during the 10-minute equilibration period was a heart rate less than 250 beats/min, systolic pressure less than 110 mm Hg, and coronary flow less than 10 mL/min. No pacing or cardiac massage was used during the recovery phase in the working mode. The heart's surface temperature was measured during arrest using a Cole-Palmer Thermistor Thermometer (8402-20) (Cole-Palmer Instrument Co, Vernon Hills, Ill), which was tucked under the left auricle.

Mode of Cardioplegic Delivery and Experimental Protocol

Rats were randomly assigned to 5 groups for delivery of cardioplegia solution: (1) 40-minute arrest with continuous AL solution ($n = 6$); (2) 40-minute arrest with intermittent AL solution ($n = 6$); (3) 60-minute arrest with continuous AL solution ($n = 6$); (4) 60-minute arrest with intermittent AL solution ($n = 6$); (5) 60-minute arrest with intermittent lidocaine cardioplegia ($n = 6$). Surgical tepid temperature was maintained by placing a thermostatically regulated water-perfused jacket around the heart when required to yield a heart surface temperature of 32°C to 33°C.

Forty-minute Arrest Protocol

Continuous. The cardioplegia was administered through the aorta at 33°C and a constant pressure of 60 mm Hg with the heart

in the Langendorff mode for 40 minutes. At 18 and 38 minutes the cardioplegia flow rate and volume were measured and used to estimate coronary vascular resistance (CVR) during arrest.

Intermittent. A strategy of 20-minute intervals for delivery of cardioplegia was used. A 50-mL induction dose of cardioplegia solution was administered at 33°C, and the aorta was crossclamped using a plastic nontraumatic clip for 18 minutes. The clip was then released to deliver a 2-minute infusion pulse of cardioplegia solution, and the clamp was reapplied. A terminal cardioplegia infusion was given at 38 minutes for 2 minutes. The cardioplegia flow rate and volume at 18 and 38 minutes were measured to estimate CVR.

Sixty-minute Arrest Protocol

Continuous. The arrest solution was administered in Langendorff mode for 60 minutes per the 40-minute protocol, with cardioplegia volume measured at 18, 38, and 58 minutes of arrest.

Intermittent. A 50-mL induction dose was administered per the 40-minute protocol, with 2-minute pulses of cardioplegia solution at 18 and 38 minutes, and a terminal infusion for 2 minutes after 58 minutes of arrest. The cardioplegia volume at 18, 38, and 58 minutes was measured for estimating CVR.

After arrest, all hearts were switched to working mode and reperfused with oxygenated Krebs–Henseleit buffer containing glucose at 37°C, and the function was monitored for 1 hour of reperfusion.

Coronary Vascular Resistance

CVR in megadynes/second/centimeters⁻⁵ was calculated during cardioplegia delivery by dividing delivery pressure (millimeters of mercury) by flow (milliliters/second) from equation 1.

$$\text{CVR} = \frac{1333 \times \text{mm Hg}}{(\text{mL/sec})} \times 10^{-6} \quad (1)$$

where 1 mm Hg = 1333 dynes cm^{-2} and 10^{-6} is a conversion factor from dynes to megadynes.²⁷

Statistical Analysis

All results are expressed as mean $\pm$ standard error of the mean. Data from the 40- and 60-minute protocols were analyzed separately. Two-way analysis of variance for repeated measures was used to compare discrete variables (eg, aortic flow, systolic pressures) over multiple time points between the treatment groups, with a Bonferroni post hoc test to show where the differences existed.

Results

Arrest Times, Cardioplegia Solution Volumes, and Coronary Vascular Resistance

Arrest times are shown in Table 1. No significant differences were found between the different AL arrest protocols, which ranged from 7.2 ± 0.8 seconds to 10.0 ± 1.8 seconds ($n = 24$). Hearts receiving lidocaine cardioplegia took 102 ± 27 seconds to arrest ($P < .01$), with values ranging from 25 to 200 seconds (Table 1). In addition, ventricular arrest occurred before atrial arrest in 2 hearts receiving

TABLE 1. Arrest time and delivered cardioplegia volumes during 40-minute or 60-minute arrest (Langendorff mode) using continuous or intermittent delivery of adenosine and lidocaine or lidocaine only cardioplegia at 32°C to 33°C (n = 6)

Cardioplegia delivery regimen	Arrest time (sec)	Induction volume (mL)	Cardioplegia volumes (2 min at 18 min) (mL)	Cardioplegia volumes (2 min at 38 min) (mL)	Cardioplegia volumes (2 min at 58 min) (mL)	Total cardioplegia volume (mL)	Time to first beat (min)	Time to aortic flow (min)
AL 40 min continuous	10.0 ± 1.8	N/A	35.6 ± 1.6	34.3 ± 1.2	N/A	699.4 ± 0.5	1.7 ± 0.6	4.0 ± 0.8
AL 40 min intermittent	8.2 ± 0.8	50	37.0 ± 1.9	34.5 ± 1.7	N/A	121.5 ± 0.6	1.8 ± 0.5	7.5 ± 1.3
AL 60 min continuous	8.0 ± 0.4	N/A	31.7 ± 1.4	30.7 ± 1.1	30.0 ± 1.0	922.1 ± 0.3	2.5 ± 0.2	6.1 ± 0.7
AL 60 min intermittent	7.2 ± 0.8	50	37.3 ± 2.2	37.0 ± 2.1	35.3 ± 2.4	159.3 ± 0.8	3.5 ± 0.6	10.0 ± 2.0
Lidocaine 60 min intermittent	102 ± 27*	50	31.7 ± 2.1	29.0 ± 2.1	25.5 ± 1.4†	136.1 ± 0.7	3.3 ± 1.3	11.7 ± 2.7

AL, Adenosine and lidocaine; N/A, not available. For methods of the different deliveries see "Materials and Methods." * $P \leq .01$ lidocaine group arrest time with all other groups. † $P \leq .01$ lidocaine group cardioplegia volume at 58 minutes compared with 18 minutes (paired-samples *t* test), and lidocaine group cardioplegia volume at 58 minutes compared with AL intermittent group cardioplegia volume at 58 minutes.

lidocaine cardioplegia, and heart escape beats occurred for 2 minutes before full electrochemical arrest was achieved in 1 heart receiving lidocaine.

The total volume of cardioplegia solution delivered to hearts during the 40-minute arrest period was 699.4 ± 0.5 mL during continuous delivery and 121.5 ± 0.6 mL during intermittent delivery (Table 1). For the 60-minute arrest protocol, the total cardioplegic volume was 922.1 ± 0.3 mL for continuous flow and 159.3 ± 0.8 mL for intermittent delivery. There was a slight (<5%) decrease in AL cardioplegia volume per minute delivered during the 40- and 60-minute arrest periods, but this was not significant. The volume of lidocaine cardioplegia delivered per minute during the 60-minute arrest period decreased significantly from 31.7 ± 2.1 mL/min to 25.5 ± 1.4 mL/min ($P < .01$).

CVRs are shown in Figure 1. At 18 minutes of arrest there was no significant difference in CVR between the continuous and the intermittent AL arrest groups (data not shown), or at 38 minutes (0.28 ± 0.01 megadyne/sec/cm⁻⁵) for both 40-minute arrest groups (Figure 1, A), or at 38 minutes for the two 60-minute AL arrest groups (0.32 ± 0.01 vs 0.27 ± 0.02 megadyne/sec/cm⁻⁵ (Figure 1, A). Similarly, there was no significant difference at 58 minutes for the continuous and intermittent AL groups (0.32 ± 0.01 megadyne/sec/cm⁻⁵ vs 0.27 ± 0.02 megadyne/sec/cm⁻⁵, respectively) (Figure 1, B). In contrast, CVR in the 60-minute intermittent lidocaine group was significantly different from the 60-minute intermittent AL group after 38 minutes of arrest (0.34 ± 0.03 megadyne/sec/cm⁻⁵) ($P < .05$) and during the terminal delivery of cardioplegia after 58 minutes of arrest (0.38 ± 0.02 megadyne/sec/cm⁻⁵) ($P < .01$) (Figure 1, B).

The time for the hearts to spontaneously recover electrical activity after arrest is shown in Table 1. There were no significant differences between the AL groups or the lidocaine group, although the time to achieve aortic flow varied from 4.0 ± 0.8 minutes for the AL 40-minute continuous

group to 11.7 ± 2.7 minutes for the lidocaine 60-minute intermittent group. However, this difference was not significant because of the range in data within both the 60-minute intermittent AL and lidocaine groups (Table 1).

Functional Profiles Before Arrest and During Recovery

During the pre-arrest period there was no significant difference in the functional parameters measured among the 5 groups tested in the 40- and 60-minute arrest protocols (Tables 2 and 3). Heart rate, developed pressures, aortic flow, coronary flow, and rate-pressure product during the recovery period for the 40-minute arrest groups are shown in Table 2. Percentage recovery of aortic flow and coronary flow during reperfusion are shown in Figure 2, A and B. Hearts arrested with continuous AL for 40 minutes recovered $89\% \pm 6\%$ of heart rate, $85\% \pm 5\%$ of pre-arrest aortic flow, and $100\% \pm 7\%$ of pre-arrest coronary flow after 15 minutes of reperfusion. Hearts arrested with intermittent AL for 40 minutes recovered $91\% \pm 4\%$ of heart rate, $82\% \pm 3\%$ of pre-arrest aortic flow, and $106\% \pm 10\%$ of pre-arrest coronary flow after 15 minutes of reperfusion. After 30 minutes of reperfusion, the flows had increased to a maximum of $105\% \pm 7\%$ of pre-arrest aortic flow and $108\% \pm 4\%$ of pre-arrest coronary flow in the continuous group, and $94\% \pm 3\%$ of pre-arrest aortic flow and $99\% \pm 3\%$ of pre-arrest coronary flow in the intermittent group. There was a subsequent slight decrease in aortic flows by 60 minutes of reperfusion, but there was no significant difference in heart rate, aortic flow, coronary flow, or rate-pressure product between groups during the recovery period.

Functional parameters during recovery in hearts arrested for 60 minutes are shown in Table 3 and Figure 2, A and B. By 15 minutes of reperfusion, heart rate recovered to $82\% \pm 4\%$ and $88\% \pm 5\%$ of pre-arrest values in hearts arrested with AL continuous and AL intermittent methods,

Figure 1. CVR measured after 38-minute arrest (A) and 58-minute arrest (B) in hearts arrested for 40 or 60 minutes with continuous or intermittent delivery of AL or lidocaine cardioplegia. (* $P \leq .05$ lidocaine group compared with AL intermittent group after 38-minute arrest; ** $P \leq .01$ lidocaine group compared with AL intermittent group after 58-minute arrest.) For the method of CVR calculation, see "Materials and Methods." AL, Adenosine and lidocaine; CVR, coronary vascular resistance; Cont, continuous; Int, intermittent.

respectively, and $68\% \pm 11\%$ of pre-arrest value in hearts arrested with lidocaine. There were no significant differences between these groups in heart rate or rate-pressure product during the recovery period. After 15 minutes of reperfusion, hearts arrested with AL solution had recovered $77\% \pm 4\%$ of pre-arrest aortic flow and $98\% \pm 5\%$ of pre-arrest coronary flow in the continuous group and $77\% \pm 7\%$ of pre-arrest aortic flow and $104\% \pm 8\%$ of pre-arrest coronary flow in the intermittent group, compared with $54\% \pm 12\%$ recovery of aortic flow and $75\% \pm 15\%$ recovery of coronary flow in the lidocaine group. There was a significant difference in recovery of aortic flow between the 60-minute intermittent lidocaine arrest group and the

60-minute intermittent AL arrest group ($P < .01$) and AL continuous group ($P < .05$). Recovery of coronary flow was also significantly different between the intermittent lidocaine group and the AL intermittent group ($P < .01$).

When data from AL groups were compared, there was a trend in the intermittent group toward increased coronary flow and lower CVR during arrest, and improved recovery of aortic flow and coronary flow during the recovery period compared with the continuous group, but these differences did not reach statistical significance.

Discussion

Although hypothermic cardioplegia seems to remain the most popular method of myocardial protection,^{1,23,30} the use of tepid and warm cardioplegia is increasingly being investigated to establish the safe temperature and optimal procedure for protecting the heart and brain during cardiac surgery.^{13,24,28,31,32} The main goal of the present study was to investigate the effect of intermittent delivery of a new normokalemic, nondepolarizing AL cardioplegia at 33°C and compare the results with continuous delivery in the isolated rat heart model. On the basis of functional outcomes (CVR, aortic flow, coronary flow, systolic and diastolic pressures, and heart rate), we report that protection of the myocardium and coronary vasculature seems to be equivalent with intermittent and continuous infusion of AL cardioplegia during 40 minutes and 60 minutes of arrest at 33°C . We further report that intermittent delivery of lidocaine cardioplegia was not as effective as intermittent AL cardioplegia. The presence of adenosine with lidocaine led to faster arrest times and conferred greater protection during and after cardioplegic arrest.

Warm Intermittent Versus Warm Continuous Delivery

The present study demonstrated that intermittent AL cardioplegia was equivalent to continuous AL cardioplegia, despite the fact that total cardioplegia volume for the intermittent group was less than 20% of the continuous infusion group (Table 1). This shows that greater cardioplegia volume does not improve outcome in this model. In addition, there was no significant difference in CVR between the intermittent and continuous AL groups, with values ranging from 0.27 ± 0.02 megadyne/sec/cm⁻⁵ to 0.32 ± 0.02 megadyne/sec/cm⁻⁵ (Figure 1, A and B). Changes in CVR may be related to autoregulation (smooth muscle constriction or relaxation), extravascular compression (caused by systolic and diastolic mechanics and tissue edema), or particulate embolization in the microvessels. A relatively constant CVR indicates that there were no differences in smooth muscle reactivity, vascular endothelial function, or extravascular compression from edema during 40 or 60 minutes of global ischemic arrest between the AL groups. In contrast, in pigs undergoing cardiopulmonary bypass, Eric-

TABLE 2. Functional parameters of isolated rat hearts during pre-arrest and reperfusion (working mode), using continuous or intermittent delivery of adenosine and lidocaine cardioplegia for 40-minute arrest at 32°C to 33°C (n = 6)

Arrest protocol	40-minute cardioplegia delivery regimen	Heart rate (beats/min)	Systolic pressure (mm Hg)	Diastolic pressure (mm Hg)	Aortic flow (mL/min)	Coronary flow (mL/min)	Rate pressure product (mm Hg/min)
Pre-arrest	Continuous	297 ± 18	140.8 ± 0.8	65.0 ± 3.4	60.3 ± 0.5	20.8 ± 1.2	41,733 ± 2339
	Intermittent	313 ± 16	136.7 ± 3.1	63.3 ± 2.1	57.7 ± 2.9	19.2 ± 1.0	42,700 ± 1835
Reperfusion 15 min	Continuous	263 ± 20	140.0 ± 2.2	65.0 ± 2.6	51.3 ± 2.9	20.8 ± 1.9	36,600 ± 2623
	Intermittent	282 ± 11	133.3 ± 6.3	61.7 ± 4.0	47.8 ± 3.9	20.0 ± 1.5	37,425 ± 1799
Reperfusion 30 min	Continuous	281 ± 15	137.5 ± 2.1	65.8 ± 3.3	53.8 ± 1.1	22.3 ± 1.2	38,513 ± 1713
	Intermittent	321 ± 14	127.5 ± 5.3	63.3 ± 4.0	54.0 ± 1.9	19.0 ± 1.3	40,783 ± 2013
Reperfusion 45 min	Continuous	300 ± 17	133.3 ± 2.5	65.0 ± 3.4	54.2 ± 0.4	23.2 ± 1.2	39,913 ± 1940
	Intermittent	325 ± 12	126.7 ± 5.1	65.0 ± 5.0	52.8 ± 1.8	21.0 ± 1.7	41,021 ± 1658
Reperfusion 60 min	Continuous	306 ± 13	133.3 ± 2.5	65.0 ± 3.4	53.3 ± 0.7	22.7 ± 0.9	40,729 ± 1594
	Intermittent	322 ± 8	127.5 ± 4.6	66.0 ± 4.9	51.0 ± 1.7	20.7 ± 0.9	40,958 ± 1607

sson and colleagues²³ demonstrated that CVR increased 1.7 times from approximately 0.33 mm Hg/min/mL⁻¹ at 5 minutes to 0.55 mm Hg/min/mL⁻¹ at 45 minutes; they suggested that this increase may have been linked to increased endothelial dysfunction or perivascular edema associated with warm continuous hyperkalemic cardioplegia. We did not test vascular reactivity for endothelial function and therefore cannot comment on potential differences in endothelial function between the groups. Using a canine model, Torchiana and colleagues²⁴ demonstrated that CVR increased slowly to a maximum of 2.5-fold in the last minute of receiving antegrade warm hyperkalemic blood

cardioplegia. They and others further postulated that the increased CVR was likely caused by the depolarizing potassium in the cardioplegia, an observation previously noted by Kucich in 1987,²² and that this effect of potassium may be more pronounced at higher temperatures.^{33,34} Furthermore, in 1991 Mankad and colleagues²¹ reported that high potassium levels in St Thomas' hospital solution or Bretschneider solution resulted in endothelial damage and that this deleterious effect of potassium was concentration dependent. Increased CVR during arrest from hyperkalemia may also compromise the distribution of the cardioplegic solution and increase the risk of ischemic injury.²³ For

TABLE 3. Functional parameters of isolated rat hearts during pre-arrest and reperfusion (working mode), using continuous or intermittent delivery of adenosine and lidocaine or lidocaine only cardioplegia for 60-minute arrest at 32°C to 33°C (n = 6)

Arrest protocol	60-minute cardioplegia delivery regimen	Heart rate (beats/min)	Systolic pressure (mm Hg)	Diastolic pressure (mm Hg)	Aortic flow (mL/min)	Coronary flow (mL/min)	Rate pressure product (mm Hg/min)
Pre-arrest	AL continuous	309 ± 10	126.7 ± 3.6	71.7 ± 4.0	56.7 ± 1.6	20.7 ± 0.8	39,025 ± 892
	AL intermittent	317 ± 14	140.0 ± 3.9	75.0 ± 3.2	61.0 ± 2.4	21.3 ± 1.7	44,275 ± 2155
	Lidocaine intermittent	339 ± 16	134.2 ± 2.7	70.0 ± 2.2	51.7 ± 0.8	19.8 ± 1.4	45,413 ± 1949
Reperfusion 15 min	AL continuous	254 ± 17	126.7 ± 4.2	72.5 ± 4.4	44.0 ± 3.1	20.3 ± 1.7	31,875 ± 1295
	AL intermittent	276 ± 12	135.0 ± 3.4	75.8 ± 2.7	46.8 ± 4.3	22.2 ± 2.3	37,292 ± 2124
	Lidocaine intermittent	226 ± 34	124.3 ± 14.0	70.0 ± 5.0	27.5 ± 6.2	14.2 ± 2.8	30,327 ± 5526
Reperfusion 30 min	AL continuous	288 ± 14	122.5 ± 4.6	74.2 ± 4.0	47.8 ± 2.5	20.7 ± 1.1	34,938 ± 966
	AL intermittent	304 ± 6	132.5 ± 3.6	76.7 ± 2.5	54.3 ± 2.1	20.7 ± 1.1	40,271 ± 1179
	Lidocaine intermittent	293 ± 17	127.5 ± 1.7	72.5 ± 3.1	37.2 ± 2.5	16.2 ± 0.9	37,329 ± 2242
Reperfusion 45 min	AL continuous	297 ± 18	120.8 ± 4.5	73.3 ± 4.4	46.3 ± 2.7	21.0 ± 1.8	35,496 ± 1331
	AL intermittent	310 ± 10	132.5 ± 4.2	75.8 ± 3.3	53.5 ± 2.0	22.8 ± 1.2	40,929 ± 1041
	Lidocaine intermittent	290 ± 13	126.7 ± 1.7	71.7 ± 2.8	37.5 ± 1.9	16.3 ± 0.9	36,817 ± 2042
Reperfusion 60 min	AL continuous	297 ± 16	119.2 ± 4.4	73.3 ± 4.4	43.5 ± 3.6	20.5 ± 1.9	35,008 ± 826
	AL intermittent	317 ± 12	132.5 ± 4.2	76.7 ± 2.5	52.6 ± 1.9	23.0 ± 1.1	41,854 ± 1538
	Lidocaine intermittent	302 ± 13	124.2 ± 1.5	70.8 ± 2.7	36.3 ± 2.2*	16.8 ± 0.7†	37,513 ± 1946

AL, Adenosine and lidocaine. *Significant difference in aortic flow between lidocaine intermittent group compared with AL intermittent group ($P \leq .01$) and AL continuous group ($P \leq .05$). †Significant difference in coronary flow between lidocaine intermittent group compared with AL intermittent group ($P \leq .01$).

Figure 2. Percentage of pre-arrest values of (A) aortic flow and (B) coronary flow recorded during the 60-minute reperfusion period in hearts arrested with ◇: 40 minutes of continuous AL, □: 40 minutes of intermittent AL, x: 60 minutes of continuous AL, Δ: 60 minutes of intermittent AL, and ■: 60 minutes of intermittent lidocaine. *Significant difference in aortic flow between the 60-minute intermittent lidocaine group compared with 60-minute AL intermittent group ($P \leq .01$) and 60-minute AL continuous group ($P \leq .05$), and *significant difference in coronary flow between the 60-minute intermittent lidocaine group compared with 60-minute AL intermittent group ($P \leq .01$).

many decades, high depolarizing potassium concentrations have been used in aortic ring studies and artery conduits to induce *maximum* vasoconstriction response when studying the effect of new drugs on coronary vasoreactivity.³⁵ AL cardioplegia may offer an alternative to the possible detrimental effects of high depolarizing potassium concentration on the microvasculature because potassium is kept at normal plasma values.²⁷

After global ischemic arrest, our study also showed that there were no significant differences in functional recovery after 40- and 60-minute arrest with AL (Tables 2 and 3). For example, hearts arrested for 60 minutes with intermittent or continuous AL recovered similar percentages of pre-arrest values in developed pressures, heart rate, aortic flow, coronary flow, and rate-pressure product after 60 minutes of

reperfusion (Table 3). These data suggest that the myocardium and coronary microvasculature were protected during the 40- or 60-minute arrest period using AL cardioplegia at 33°C. Although there was a trend for intermittent delivery of AL cardioplegia to improve functional recovery after 60 minutes of arrest, these differences were not significant.

Warm Intermittent Adenosine-Lidocaine Cardioplegia Versus Lidocaine Cardioplegia

Intermittent AL cardioplegia was also compared with intermittent lidocaine cardioplegia over a 60-minute arrest at 33°C. In this study, intermittent lidocaine cardioplegia was not as effective as intermittent AL cardioplegia, with variable and significantly longer arrest times (102 ± 27 seconds vs 7.2 ± 0.8 to 10.0 ± 1.8 seconds) (Table 1), significantly higher CVR during arrest ($\sim 20\%$ higher CVR measured at 38 and 58 minutes) (Figure 1, B), and significantly lower returns in aortic and coronary flows during reperfusion ($P < .01$) (Table 3). Lidocaine cardioplegia has been advocated as an alternative to K^+ depolarizing cardioplegia by a number of groups using Langendorff perfused rat and rabbit hearts.¹⁵⁻¹⁷ Although lidocaine at 500 μM arrests the rat heart faster than does clamping a heart receiving Krebs-Henseleit alone (1.7 ± 0.45 vs 10.7 ± 2.2 minutes ($n = 4$, unpublished data, Sloots, BSc [Hons], 2006), the key is to include 200 μM of adenosine, which arrests the heart faster and confers greater protection on the myocardium and coronary vasculature compared with lidocaine only cardioplegia (Figure 1, B; Table 3).

Conclusions

In the past, surgeons have been reluctant to adopt warm cardiac surgery presumably because of the effects of near-continuous delivery of depolarizing potassium cardioplegia on the heart and the potential deleterious effects of higher temperatures on brain function.^{5,10,19,20} In addition, there seems to be a lack of consensus concerning the safe period for interrupting the flow of cardioplegia to visualize the operative field and the length of crossclamp time.^{5,10,19,20} The possible clinical significance of developing nondepolarizing AL cardioplegia may relate to (1) reducing the need for high depolarizing potassium in cardioplegia; (2) offering the surgeon greater versatility over the visual field at higher temperatures; (3) providing lower CVR and greater uniformity of cardioplegia delivery to the myocardium; (4) protecting the myocardium and coronary vasculature from ischemic injury³⁶⁻³⁸; (5) providing greater control over the patient's serum K^+ levels and other related electrolytes, particularly in those patients with renal disease; and (6) having the benefits of potent anti-inflammatory properties.^{18,39,40} Although we acknowledge the strengths and limitations of using the perfused rat heart model and crystalloid cardioplegia in this study,⁴¹ further large animal studies and human safety trials are required to examine AL cardioplegia as an alternative to conventional K^+ -based cardioplegia practices.

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