Blood Cardioplegia Delivery

Deleterious Effects of Potassium versus *Lidocaine*

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Delivery of cardioplegic (CP) solutions to all regions of the myocardium is critical for optimal myocardial protection during cardiac surgery. However, there are little data regarding the effects of CP agents upon coronary vascular resistance (CVR) and CP delivery. Accordingly, we evaluated blood CP (Hct 30) delivery and CVR during 75 minutes of multi-dose hypothermic blood CP arrest in an *in vivo* isolated dog heart preparation. Three groups of dogs were studied: K(K^+ = 30 mEq/L; n = 6), L (Lidocaine = 400 mg/L; K^+ = 4 mEq/L; n = 6), and KL (K^+ = 30 mEq/L, Lidocaine 400 mg/L; n = 6) during total cardiopulmonary bypass and moderate systemic hypothermia (28 C). Basal CVR was calculated by measuring total coronary flow (HR 120/min; mean aortic pressure = 80 mmHg) in the empty beating heart. After aortic cross-clamping, the blood CP solution was infused into the aortic root at a constant pressure (80 mmHg) and constant temperature (16 ± 2 C) for 60 seconds at 15 minute intervals for a total arrest time of 75 min. Total CP flow, CVR, O_2 consumption, lactate extraction/production, and K^+ balance during 75 minutes of arrest and 30 minutes of reperfusion were determined. The distribution of the CP solution in the left ventricle was measured with radioactive microspheres (9 ± 1 μ). Biopsy specimens were taken to measure wet to dry ratios. Values are mean ± SEM. Data were analyzed by BMDP-P2V. During the first CP infusion, after aortic cross-clamping, no differences in CVR or CP distribution were found among the three groups. However, CVR was increased significantly in the K group during the second CP infusion (0′: 0.98 ± 0.20 mmHg/ml/min/100 g; 15′: 2.66 ± 0.82; $p < 0.001$). The CVR remained high for the remainder of the arrest period. Moreover, total, epi- and endocardial flow decreased significantly (54%, $p < 0.001$). In groups L and KL, no significant changes in CVR were seen. Groups K and KL showed a significant K^+ extraction during the first CP infusion. During the early reperfusion period, K^+ washout occurred in these two groups, which was not seen in the L group. There was no significant difference between the three groups in myocardial O_2 consumption, lactate metabolism, and water content during the arrest and the reperfusion period. In conclusion, high concentrations of K^+ (30 mEq/L) can markedly increase CVR and impair blood CP delivery and distribution. These effects can be prevented by lidocaine. These findings warrant reassessment of the various additives to CP solutions and their effects on CVR and CP distribution during multi-dose hypothermic CP arrest.

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SUBENDOCARDIAL NECROSIS continues to be a major finding in patients who die following open-heart surgery.[1,2] Despite all attempts to protect the myocardium, ischemic damage may occur during the arrest period.

Potassium in concentrations ranging from 20 to 40 mEq/L is the most frequently used cardioplegic (CP) agent both in blood and crystalloid solutions. Several physiologic studies[3–5] have demonstrated that high K^+ concentrations enhance Ca^{++} uptake by smooth muscle cells, resulting in increased smooth muscle tone. Recently, Chiavarelli[6] demonstrated that isolated helical strip bovine coronary arteries incubated in a high potassium medium increased smooth muscle tone. Little attention, however, has been paid to the effect of potassium as a cardioplegic agent on coronary vascular resistance (CVR) and distribution of the CP solution. Recent data[7] from our laboratory have demonstrated that multi-dose hyperkalemic hypothermic crystalloid cardioplegia produces an increase in CVR during 75 minutes of arrest. This deleterious effect was ameliorated by the addition of lidocaine to the CP solution.

Recent studies[8,9] suggest that blood CP may be superior to crystalloid CP. This work has stimulated renewed interest in clinical hypothermic, hyperkalemic blood CP. A potential disadvantage of the hypothermic blood CP solution is the higher viscosity compared to crystalloid CP.

Presented at the Annual Meeting of the American Surgical Association, May 12–14, 1983, Boca Raton, Florida.

Supported in part by USPHS Grant No. HL 26215-04.

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Submitted for publication: May 16, 1983.

0003-4932/83/0900/0266 $01.15 © J. B. Lippincott Company

The combination of increased viscosity[10] and possible increases in smooth muscle tone may result in impaired CP delivery and distribution. The purpose of this study was to investigate the effects of multi-dose, hyperkalemic, hypothermic blood CP on CVR and CP distribution in the isolated intact canine heart and to determine the effects of the addition of lidocaine to the blood CP vehicle.

Material and Methods

Adult mongrel dogs, weighing 22 to 45 kg, were anesthetized with sodium-pentobarbital (30 mg/kg body weight [BW]; IV); anesthesia was maintained with sodium-pentobarbital or gallamine triethiodide (Flaxedil). All dogs were intubated and placed on a volume-cycled respirator (Harvard Apparatus). A polyvinyl catheter was placed in the left femoral artery and connected to a Statham-Gould pressure-transducer to measure systemic pressure. An IV line was inserted in the left femoral vein for the administration of drugs. ECG (lead II) was monitored continuously. After systemic heparinization (300 U/kg BW, IV), each dog was placed on cardiopulmonary bypass with aortic perfusion through a cannula in the right femoral artery and venous return through separate vena caval cannulas (Fig. 1). Throughout each experiment, the perfusion pressure was kept constant (80 mmHg). The extracorporeal system (BOS-5S, Bentley Lab.) was primed with donor blood and the Hct maintained at ±30 throughout each experiment. The azygos vein was ligated and tapes placed around the venae cavae to assure total bypass. The pulmonary hili were snared to eliminate bronchial blood flow and the main pulmonary artery was ligated. A No. 32 Argyle catheter was inserted through the right atrial appendage and lead into the right ventricle for sampling and measurement of coronary sinus blood flow. After the sinus node was crushed, atrial pacing was instituted at 120 beats/minute. (Cordis Synchrocor II). A metal cannula was inserted into the left ventricular cavity through the left ventricular apex and the left ventricle continuously vented (−5 cm H_2O). A No. 20 cannula was inserted into the brachiocephalic artery for the infusion of the cardioplegic solution. A Thermistor gauge was placed in the anterior intraventricular septum to measure myocardial temperature. A No. 14 Angiocath was placed in the ascending aorta and connected to a Statham-Gould pressure-transducer to measure the infusion pressure of the cardioplegic solution. Pressures and ECG were recorded on a Hewlett-Packard recorder. Donor blood was used as the CP vehicle and the Hct adjusted to 30%, if necessary, with Ringers lactate. The solution was oxygenated with 100% O_2 with a separate oxygenator (BOS-5S, Bentley Lab.) and the temperature kept constant at

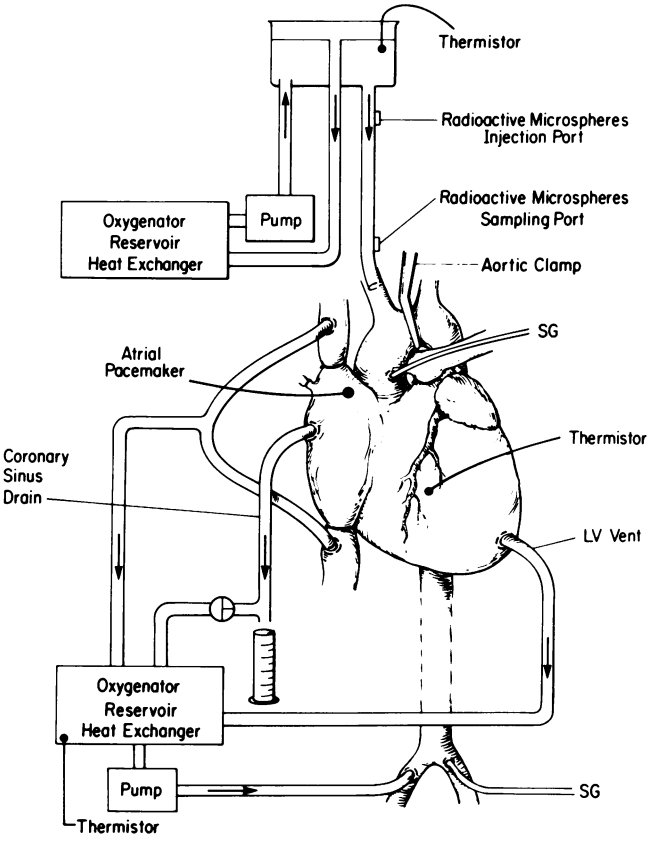

FIG. 1. Experimental preparation used for the experiments. SG = strain gauge.

16 ± 2 C with a separate heat exchanger. The pH was kept constant at 7.8. Multiple infusions of the CP solution were made at an infusion pressure of 80 mmHg. Arterial blood gases and electrolytes were measured every 15 minutes and maintained within the physiologic range.

Experimental Protocol (Fig. 2)

After allowing 10 minutes for stabilization of the preparation in an empty beating state at 38 C, the volume of the coronary sinus blood flow was measured with a calibrated cylinder during 1 minute. Samples from arterial and coronary sinus blood were taken to measure myocardial O_2 consumption, myocardial lactate extraction/production, and potassium extraction/production. After obtaining these measurements, each dog was cooled systemically to 28 C. Allowing another 10 minutes for stabilization, the volume of coronary sinus blood flow was measured again and samples were taken from arterial and coronary sinus blood to measure myocardial O_2 consumption, lactate extraction/production, and potassium extraction/production. The aorta was then cross-clamped between the brachiocephalic artery

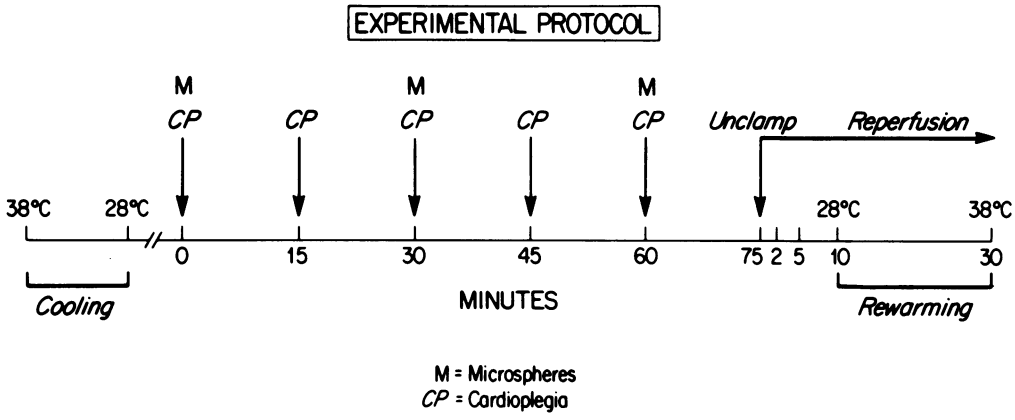

FIG. 2. Experimental protocol.

and the left subclavian artery. The blood CP solution was then immediately infused directly into the aortic root (pressure, 80 mmHg; temperature, 16 ± 2 C) during 60 seconds. The volume of the coronary sinus flow during the same period was measured directly. This represented total CP flow with each injection. Samples were obtained from the CP solution and the coronary sinus flow to measure O_2 consumption, lactate extraction/production, and K^+ extraction/production. The total coronary sinus flow volume was discarded. Additional CP infusions were performed at 15-minute intervals for a total arrest time of 75 minutes. The volume of the coronary sinus flow was measured during each injection. After 75 minutes of arrest, the aortic cross-clamp was removed and the heart was reperfused at a mean pressure of 80mmHg. The temperature was kept constant at 28 C for 10 minutes. Coronary sinus flow was measured and samples were taken at 2 minutes, 5 minutes, and 10 minutes after reperfusion. If necessary, defibrillation was performed 5 minutes after reperfusion. Atrial pacing was reinstituted in all animals (heart rate, 120/min). The temperature was then increased gradually over 15 minutes to 38 C. Thirty minutes after reperfusion, the last set of measurements and samples were taken and the experiment was terminated.

The coronary resistance (CVR) was calculated as follows:

Coronary resistance

= mean aortic root pressure/total coronary flow.

The CP flow and distribution was determined with radioactive microspheres[11] (9 ± 1 μ; New England Nuclear Co.) labelled with 113 Sn, 103 Ru and 46 Sc. The microspheres were injected during the first 15 seconds of the first (0'), third (30') and fifth (60') injection of the CP solution through a port in the CP infusion system. Reference samples were taken from a port 30 cm distal of the injection site at a constant rate (6.8 cc/min; Holter pump, Extracorporeal). After termination of the experiment, the dog was killed with an overdose of sodium-pentobarbital. The heart was excised *in toto* and weighed. The free wall of the left ventricle was removed, weighed, and divided in endocardial and epicardial regions. Total and regional flow and endo/epi ratio were calculated with a multi-channel auto-gamma counter with Kennedy-tape drive (Packard Instrument Co.) at appropriate window settings. The spill correction was performed automatically by computer (VAX-11, Digital Equipment Co.).

O_2 content was analysed with a Lex-O_2-Con (Lexington Instrument Co.) and O_2-consumption expressed as cc/100 g/min.

Myocardial lactate extraction/production was determined by the enzymatic method[12] with a Gilford UV-Spectro-photometer and expressed as μmol/100 g/min. Potassium extraction/production was measured and expressed as mEq/100 gm/min.

Full thickness myocardial biopsy specimens were taken from the right ventricular free wall at control time (38 C), after the first, third, and fifth CP infusion, and 5 minutes (28 C) and 30 minutes (38 C) after reperfusion. Water content was calculated after drying the sample to a constant weight at 110 C. Myocardial temperatures were measured just before and after CP-infusion.

The dogs were divided in three experimental groups: group K: blood CP solution + KCl (30 mEq/L) (n = 6); group L: blood CP solution + Lidocaine (400 mg/L) (n = 6); and group KL: blood CP solution + KCL (30 mEq/L) + lidocaine (400 mg/L) (n = 6).

Statistics

After collecting the data, all variables were examined for apparent skewed error distribution and for inhomogeneous variances. It was found that logarithmic transformation of resistance values was required to remove skew from its error distribution, and thus statis-

tical test were performed upon log (resistance). This transformation also stabilized variances of the resistances. Other variables did not require transformation. All estimated means (group and for different times) were compared within the context of a repeat measures analysis of variance using the BMDP-P2V program.[13,14] All values are expressed as mean ± SEM. A p value less than 0.05 was considered significant.

The National Research Council's guide for the care and the use of laboratory animals was followed.

Results

Coronary Vascular Resistance

As can be seen in figure 3, there were no differences between the three groups when the control measurements were taken at 38 C (K: 2.14 ± 0.31 mmHg/ml/min/100 g; L: 2.27 ± 0.16; KL: 1.9 ± 0.24). Moderate hypothermia (28 C) caused a significant decrease in the CVR in all three groups (K: 1.07 ± 0.16; L: 1.02 ± 0.16; KL: 0.90 ± 0.07) ($p < 0.001$). During the first CP infusion, the CVR in the K group did not change significantly (0.98 ± 0.20). However, in the L group and in the KL group, a further significant decrease in CVR occurred (L: 0.64 ± 0.10; $p < 0.025$; KL: 0.48 ± 0.03; $p < 0.025$). During the second and subsequent CP infusions, a very large and highly significant ($p < 0.001$) increase in CVR was seen in the K group only (15′: 2.66 ± 0.82; 30′: 2.26 ± 0.52; 60′: 2.04 ± 0.39). The CVR in the two other groups did not change significantly. Upon reperfusion, the CVR in the K group fell sharply to the level of the CVR in the two other groups at 2 minutes off reperfusion. However, at 5 minutes after reperfusion, there was an increase in CVR in the K group which was not seen in the L or the KL group. Thirty minutes after reperfusion, the CVR in the three groups was the same but significantly lower than the control value at 38 C.

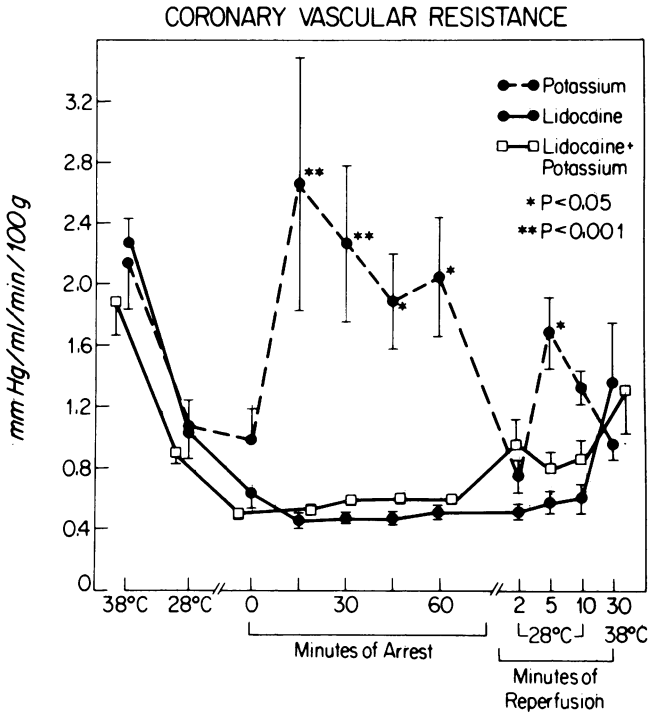

FIG. 3. Changes in coronary vascular resistance in potassium, lidocaine, and lidocaine plus potassium cardioplegia. p Values express significant differences comparing lidocaine or lidocaine plus potassium to potassium alone.

Cardioplegic Flow and Distribution

Figure 4 demonstrates that the total flow and epicardial flow was the same in the three groups during the first CP infusion. The endocardial flow in the L group was significantly lower than in the K group at the first infusion (K: 1.78 ± 0.25 cc/g/min; L: 1.40 ± 0.22; $p < 0.025$), and as a result, the endo/epi ratio was also lower in the L group at this time. During the third and fifth infusions of the CP solution, total flow, epicardial and endocardial flows decreased significantly in the K group (total flow: 0′: 1.51 ± 0.21; 30′: 0.70 ± 0.16; 60′: 0.74 ± 0.10; $p < 0.001$) (epicardial flow: 0′: 1.24 ± 0.17; 30′: 0.57 ± 0.53; 60′: 0.59 ± 0.07; $p < 0.001$) (endocardial flow: 0′: 1.78 ± 0.25; 30′: 0.82 ± 0.20; 60′: 0.77 ± 0.15; $p < 0.001$). The endo/epi ratio did not change. In the lidocaine group, the endocardial flow increased significantly ($p < 0.001$) (endocardial flow: 0′: 1.40 ± 0.22; 30′: 2.12 ± 0.24; 60′: 2.07 ± 0.21) without significant change in the epicardial flow. The endo/epi ratio increased also significantly ($p < 0.025$). In the KL group, no changes occurred.

Metabolic Data

Myocardial oxygen consumption. There was no significant difference in the O_2 consumption in the three groups during the arrest period. For every minute of arrest, between 0.02 and 0.03 ccO_2 per 100 g was consumed.

Lactate extraction/production. Throughout the arrest period, a minimal lactate production was noted. There were no significant differences between the groups.

Potassium extraction/production. During the first CP infusion, a significant amount of K^+ was extracted by the myocardium in the K and KL groups (Fig. 5) (K: 0′: 2.62 ± 0.51 mEq/100g/min; KL: 0′: 2.39 ± 0.19; $p < 0.001$). During subsequent infusions, the amount of K^+ extracted was significantly less ($p < 0.001$) (K: 30′: 0.62 ± 0.16; 60′: 0.38 ± 0.12; KL: 30′: 0.55 ± 0.22; 60′: 0.20 ± 0.07). In these groups, a significant K^+ washout occurred during the early reperfusion. No changes in K^+ balance were seen in the L group.

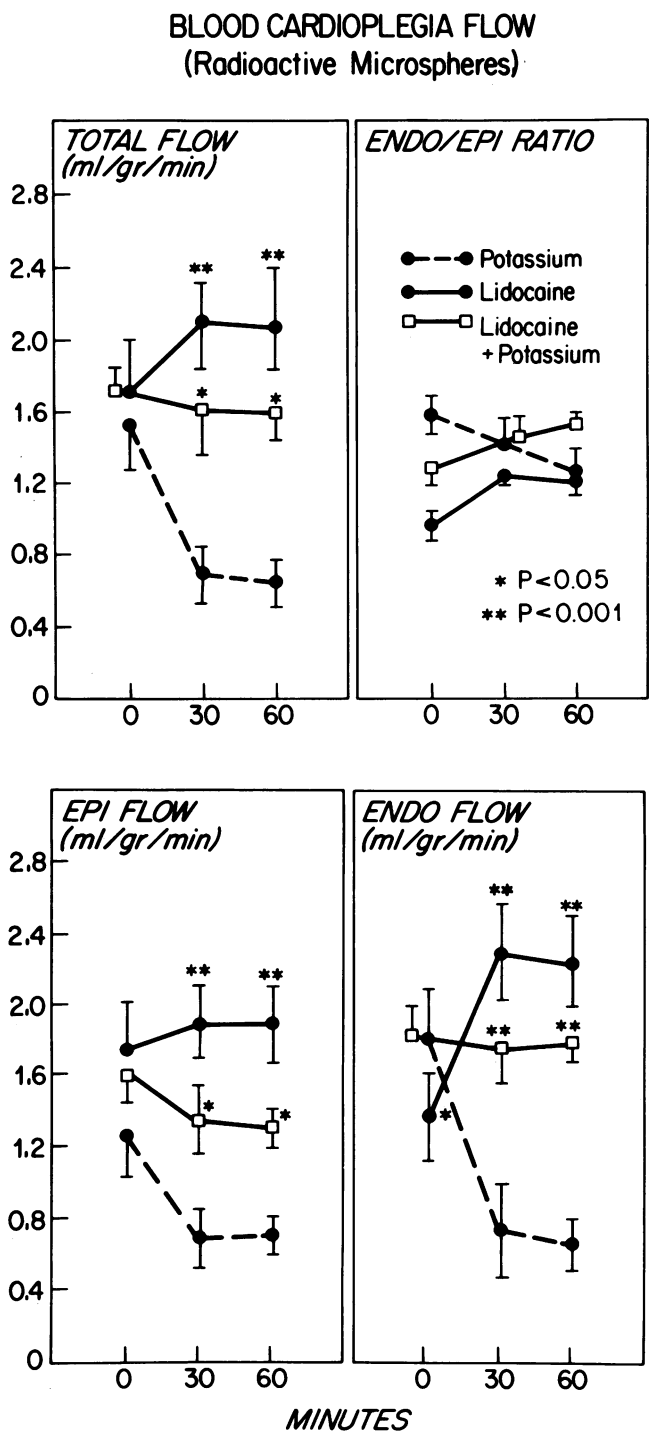

FIG. 4. Blood—cardioplegia flow and distribution during the arrest period. p Values indicate significant differences comparing lidocaine or lidocaine plus potassium to potassium alone.

Myocardial water content. No significant changes in water content were seen in any of the three groups.

Myocardial temperature. Mean myocardial temperature was 19.2 ± 1.5 C in the K group, 17.4 ± 0.06 in the L group, and 17.6 ± 0.7 in the KL group. This difference was not significant.

Discussion

Significant advances have been made in protecting hearts from perioperative myocardial damage; however, myocardial necrosis continues to be a significant clinical problem.[1,2] It has been assumed that the vulnerability of the myocardium during surgical cardioplegia was due to the effects of myocardial hypertrophy and coronary artery disease[2] limiting the delivery of cardioplegic agent.

This study has demonstrated that the presence of a high concentration of potassium in the cardioplegic vehicle can interfere with the delivery of the cardioplegic solution in the normal canine heart.

Hypothermia has been described[17] to decrease vascular smooth muscle tension. Profound hypothermia has been assumed to produce vasodilatation for adequate delivery of cardioplegic solutions.

High concentrations of potassium are known to alter calcium transport in vascular smooth muscle, resulting in increased smooth muscle tension.[3-5,18] The work of Chiavarelli et al.[6] demonstrated that increased potassium produces marked increases in isolated coronary artery smooth muscle tone. This study demonstrates that hyperkalemic hypothermic blood cardioplegia produces marked increases in coronary vascular resistance

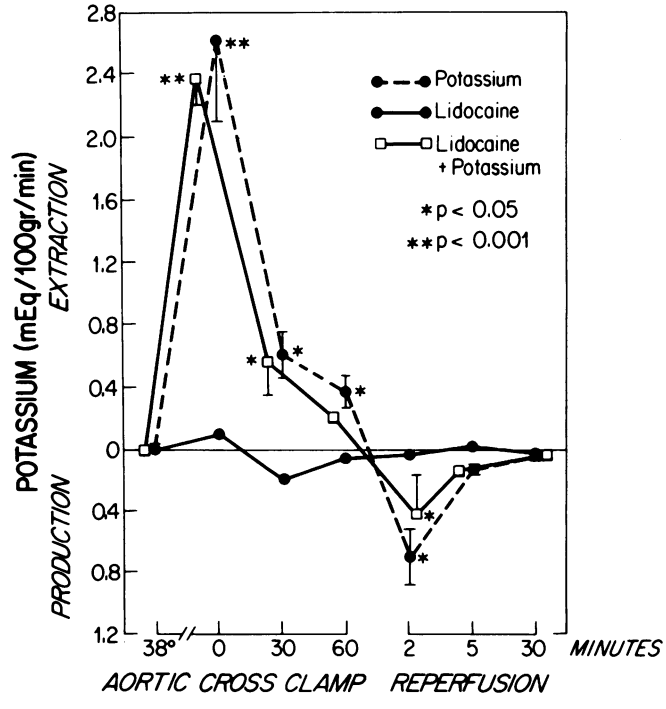

FIG. 5. Comparison of potassium—flux during cross-clamp and reperfusion. p Values indicate significant differences comparing potassium and potassium plus lidocaine to lidocaine alone.

during 75 minutes of cardiac arrest. The results of this study can be explained by these effects of potassium on coronary artery smooth muscle contraction. Thus, the findings of this study, in addition to the recent data regarding conduction abnormalities[15,16] in the postoperative period, highlight the problems of hyperkalemic cardioplegia.

In addition, this study has demonstrated that when lidocaine is added to the hyperkalemic blood cardioplegia solution or when it is used as the only cardioplegic agent, these changes in resistance and cardioplegia flow do not occur. A number of factors underlie the rationale for inclusion of lidocaine in cardioplegic solutions. It has the ability to induce cardiac arrest by inhibition of sodium influx and membrane depolarization.[19] Moreover, it has antidysrhythmic properties[20,21] that may reduce the incidence of rhythm disturbances during the early reperfusion period. Also, there is evidence that it inhibits cellular influx or intracellular release of calcium,[22] and by inhibiting phospholipase-A activity,[23] it could have a so called "membrane stabilizing" effect. In a recent study from our laboratory, Kyo[24] demonstrated in dogs during 90 minutes of hypothermic (28 C) arrest that lidocaine, when added to a crystalloid cardioplegic solution, had superior effects on myocardial functional recovery when compared to potassium. This study provides a rationale for the use of lidocaine in hypothermic hyperkalemic blood cardioplegia.

Coronary artery bypass graft surgery is the most common cardiac surgical procedure performed today, and hyperkalemic solutions are most commonly used to induce cardiac arrest. The delivery of cardioplegic solutions to all segments of the myocardium is essential for adequate myocardial protection.[2,25,26] The difficulty of achieving this goal in patients with coronary artery disease is well known.[27-29] This study demonstrates that high potassium concentrations can decrease cardioplegic delivery in hearts with normal coronary arteries. Hyperkalemic cardioplegia may be even more deleterious in hearts with obstructed coronary arteries.

The results of this study suggest the need for a reassessment of the use of potassium cardioplegia.

Acknowledgments

The authors are grateful to John Newell for statistical analysis, Ted Gardner, Michael Hennessey, Edmund Fisher, and Alvin Denenberg for technical assistance, and Miss Linda Sclafani for the preparation of the manuscript.

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Discussion

DR. LARY ROBINSON (Durham, North Carolina): In collaboration with Drs. Hearse and Brainbridge in London, we too have been interested in the effects of various cardioplegia components on coronary vascular resistance, and have evaluated the dose-response characteristics of potassium chloride when infused into isolated rat hearts at a fixed pressure.

(Slide) This slide shows the various potassium concentrations along the abscissa. Coronary flow rate is drawn on the ordinate to your right, and depicted by the squares. The ordinate on the left, and the circles, depict heart rate. Within the concentration range of 10 to 20 millimoles (mmol) of potassium, there was no significant effect on coronary flow, but cardiac arrest was complete. In contrast, in the range of 25 to 50 mmol of potassium, there was a precipitous drop in coronary flow rate, and therefore a rise in coronary vascular resistance, probably as a consequence of potassium-induced increase in left ventricular resting tension. The concentration of 30 mmol/l in this area, used in Dr. Derkac's study, therefore predictably led to an increase in coronary vascular resistance.

In another study, we found particulate matter in cardioplegic solution caused a steady decline in coronary flow rate, and therefore a progressive rise in coronary vascular resistance, continuously infused into isolated rat hearts at a fixed pressure.

(Slide) in this slide, coronary flow rate, measured every minute, is shown along the ordinate. Duration of infusion is along the abscissa. The circles show a dramatic decline in coronary flow rate in unfiltered solution, whereas this effect is negated by filtration with an 0.8 micron filter, the boxes.

(Slide) Adding nifedipine to the cardioplegic solution, the circles, partially overcomes this apparent coronary vasoconstriction, compared to filtered solutions, the boxes. Procaine gives even better results, and we suspect lidocaine, as used in Dr. Derkac's study, will give similar positive effects. The studies described were done in crystalloid cardioplegia. However, we suspect these findings apply to blood cardioplegia as well.

Therefore, we would ask the authors two questions. First, have you looked at experimental groups of dogs, using lower potassium concentrations, to see if these coronary flow abnormalities are eliminated, as might be expected from Dr. Hearse's previous work? And, second, since at least part of your results may be related to coronary vasoconstriction induced by particulate contamination of cardioplegic solutions which lidocaine might act to eliminate, could small-porosity filtration of these solutions for all three groups help remove some contamination, and perhaps act to eliminate this factor that might have influenced your overall results?

DR. FELIX THEODOSIUS RAPAPORT (Stony Brook, New York): I was wondering if the authors of this very elegant presentation have any hypothesis for the differences in the intracellular effects of potassium lidocaine in explaining this result.

DR. WAYNE M. DERKAC (Closing Discussion): In response to Dr. Robinson's question, we are currently evaluating lower potassium solutions. No information is available at the present time from these studies.

Although I think that the issue of filtration of cardioplegic solution is a good one and that perhaps some of the vasoconstriction may be attributable to particulate debris in the cardioplegic solution, I must say that even from Dr. Robinson's data it is apparent that filtration will not alter all of the adverse effects of potassium cardioplegia on coronary vascular resistance.

In response to Dr. Rappaport's question, I would like to say that it has been hypothesized that potassium, by enhancing calcium uptake by smooth muscle cells, accounts for an increase in smooth muscle tone. Conversely, lidocaine inhibits calcium influx into smooth muscle cells. Presumably, this may account for the effects on coronary vascular resistance seen with these two agents.