1. Introduction

In myocardial protection during heart surgery, cardioplegia is an important factor. Hearse et al. [1], reported potassium cardioplegia, which has been the main process of cardioplegia for 40 years. But depolarizing potassium cardioplegia does not act perfectly in protecting myocardium. Extracellular hyperkalemia induced abnormal transmembrane ion fluxes. Fast-sodium channels are inactivated and sodium-calcium changes occur. But the sodium, calcium ‘window’ current will lead to increased intracellular \([Ca^{2+}]\) concentration. Decreasing of adenosine triphosphate (ATP) in myocardium continues during arrest.

Other agents for cardioplegic solution have been investigated. Locking the ion channel in a closed state will maintain the transmembrane electrical potential in a polarized state. Adenosine triphosphate-sensitive potassium channel opening (PCO) agents (e.g. pinacidil, nicorandil, or aprikalim) achieve polarized or hyperpolarized arrest, so these agents have the potential to be superior in depolarizing potassium cardioplegia. But some reports of animal models indicated increasing problematic post-ischemic arrhythmias and systemic hypotension. PCO agents could not be adopted for clinical use.

Fast-sodium channel blocker, lidocaine, and magnesium crystalloid cardioplegia achieve polarized arrest, and have been adopted clinically. This combination of agents indicated better results in preservation of myocardial ATP and post-ischemic LV function compared to potassium cardioplegia.

Blood cardioplegia has advantages in buffer-effect, and \(O_2\) consumption, compared to crystalloid cardioplegia.

We designed lidocaine-magnesium blood cardioplegia and examined the effects in canine hearts.

2. Material and methods

Thirteen adult dogs (12–21 kg) were studied in cardiopulmonary bypass models. All animals were premedicated with morphine sulfate (4 mg/kg). Anesthesia was induced with intravenous administration of sodium pentobarbital (20 mg/kg) and maintained with intermittent boluses (3 mg/kg). The animals were endotracheally intubated and placed on a volume ventilator. Femoral artery pressure was monitored. Limb leads were placed for recording electrocardiogram.

A right parasternotomy allowed canulation of the right subclavian artery for inflow from the cardiopulmonary bypass (CPB). Venous return to the pump was through bicaval cannulation. An ascending aortic cardioplegia delivery cannula was placed and secured. The main pulmonary artery was clamped. The left ventricle was vented through left atrium, and systemic cooling was maintained at 30 °C. CPB flow was about 100 ml/kg. Global myocardial ischemia was then initiated by crossclamping the ascending aorta.

One of the two types of cardioplegia was administered (100 ml per min, every 20 min for 5 min, 28 °C, antegrade...
delivery). Group A was administered potassium blood cardioplegia, which was used in our institute (Table 1). Group B was lidocaine blood cardioplegia. Global ischemia was maintained for 60 min. The animals were rewarmed to systemic normothermia when the cross-clamp was removed. Direct-current defibrillation was successful for those hearts that did not resume a spontaneous organized rhythm.

Twenty minutes after cross-clamp removal, the hearts were kept in a vented non-working state on CPB. If hemodynamic was stable, CPB was tapered. LV function data were gathered 60 min after tapering CPB (Table 1).

All animals received humane care in compliance with the ‘Principle of Laboratory Animal Care’ formulated by the National Academy of Sciences and published by the National Institute of Health (NIH publication No. 85–23, revised 1985).

Hemodynamic data were gathered using conductance catheter (Millar Instruments, Texas, USA) by inserting through the LV apex. The catheter connected to the heart was a volume and pressure measuring device and analyzing computer (PC9821t13 NEC, Tokyo). The program generated pressure-volume loops.

Time-varying left ventricular volume, \( V(t) \), followed from the measured conductance in the left ventricular through the following formula:

\[
V(t) = (1/\alpha) (L^2/\sigma_b) G(t) - \text{Vc},
\]

in which \( \alpha \) is a dimensionless constant, \( \sigma_b \) is the specific conductivity of blood measured by a calibrating cuvette for each experiment, and \( G(t) \) was the sum of the conductance. \( \text{Vc} \) is a correction term caused by the conductance each experiment, and \( G(t) \)

The slope of the end-systolic pressure volume relation (ESPVR), \( E_p \) (\( \text{Emax} \)), was calculated by the linear regression of the end-systolic pressure-volume points obtained during IVC occlusion. To quantify the magnitude of the measured change in a contractile state, we compared the ratio of \( \text{Emax} \) obtained during IVC occlusion at pre- and post-global ischemia (%\( \text{Emax} \)) [5]. Data were indicated as relative value of pre- and post-general ischemia.

Myocardial water content was determined from samples of the left ventricle taken immediately after death, weighed, and placed in an oven for desiccation. The samples were weighed daily until a constant weight was obtained for two days. The percent of water content of the tissue was determined by the following equation [6].

\[
\text{Tissue % water content} = \frac{\text{(wet weight} - \text{dry weight})}{\text{wet weight}} \times 100.
\]

We studied the levels of serum troponin-T at pre CPB and proceeded with cross-clamp removal three hours later to see the degree of myocardial injury. The levels were measured by an enzyme-linked immunosorbent assay. Histologic examination was performed on transmural sections of the left ventricle taken from the LAD and circumflex coronary areas away from areas of instrumentation. These were then fixed in 10% buffered formalin. Sections were stained with hematoxylin and eosin and examined by a pathologist. Microscopic study was carried out. Each field examined the presence of interstitial edema, hypereosinophilia, and intramyocardial hemorrhage. Serum lidocaine concentration was studied in group B. The animal blood was taken after every cardioplegia injection, cross-clamp removal, and 30 min after reperfusion. Concentration of the drug was measured by using a fully automatic high performance liquid chromatography system (REMEDi-HS) [7].

2.1. Statistical analysis

All values are expressed as the mean ± the standard error of the mean. When comparisons were made in each group about cardiac function between pre- and post-CPB, the Wilcoxon single-rank test was used. When comparisons were made between the two groups, the Mann–Whitney U-test was used. In the comparison of spontaneous recovery rate after release of aortic cross-clamp, the Fisher’s exact test was used. A \( P \)-value < 0.05 was considered significant.

3. Results

All animals were tapered from CPB. During the working phase, adequate hemodynamics were maintained in all animals through the conclusion. Time required for cardiac arrest took 78 ± 3 s in group A and 89 ± 9 s in group B. There was no significant difference between the two groups.

Ventricular systolic performance was assessed using the percentage of maximum elastance relationship (%\( \text{Emax} \)) and was significantly better for lidocaine-magnesium cardioplegia compared with potassium cardioplegia (group A: 63 ± 3%, group B: 76 ± 4%) (Fig. 1a). The % LYSW was not significant between the two groups (group A: 76 ± 2%, group B: 79 ± 1%) (Fig. 1b). The percent of myocardial water content was significantly lower in group B (group A: 82.3 ± 4%, group B: 75.5 ± 2%) (Fig. 1c). The concentration of serum troponin-T was almost similar in both groups (group A: 3.5 ± 0.8 ng/ml, group B: 3.3 ± 0.7 ng/ml) (Fig. 1d).

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Final concentration of blood cardioplaufias. Cardiac functions of pre- and post-CPB</th>
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</thead>
<tbody>
<tr>
<td>Contents</td>
<td>Potassium</td>
</tr>
<tr>
<td>Na</td>
<td>135</td>
</tr>
<tr>
<td>K</td>
<td>20</td>
</tr>
<tr>
<td>Ca</td>
<td>8</td>
</tr>
<tr>
<td>Mg</td>
<td>4</td>
</tr>
<tr>
<td>Lidocaine</td>
<td>Induction</td>
</tr>
<tr>
<td>pH</td>
<td>7.4</td>
</tr>
<tr>
<td>Hematocrit</td>
<td>20</td>
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<tr>
<td>Cardiac function</td>
<td></td>
</tr>
<tr>
<td>Potassium</td>
<td>HR (beat/min)</td>
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<tr>
<td>PreCPB</td>
<td>141 ± 26</td>
</tr>
<tr>
<td>PostCPB</td>
<td>128 ± 18</td>
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<tr>
<td>Lidocaine-Mg CP</td>
<td></td>
</tr>
<tr>
<td>PreCPB</td>
<td>146 ± 18</td>
</tr>
<tr>
<td>PostCPB</td>
<td>132 ± 24</td>
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</tbody>
</table>

Lid-Mg: Lidocaine-magnesium. CPB: Cardiopulmonary bypass.
Lidocaine-magnesium cardioplegia produced higher spontaneous recovery. Defibrillation occurred in three dogs in group A but not in group B.

In the pathological findings, interstitial edema tended to be more prominent in group A (Fig. 2).

Serum concentration of lidocaine in group B was measured. It was highest after initiation of first administration of cardioplegia and decreased slowly. It was under normal therapeutic level 30 min after removal of cross-clamping (after first injection 19.6 g/ml, second injection 17.4 g/ml, third injection 13.1 g/ml, reperfusion 10.4 g/ml, 30 min later reperfusion 4.6 g/ml) (Fig. 3).

4. Discussion

This study compared depolarizing potassium blood cardioplegia to polarizing lidocaine-magnesium blood cardioplegia in canine heart hypothermic models.

Calcium overload at reperfusion damages mitochondria of myocardial cell and decreases mitochondria ATP, and induces hyperoxidization, which destroys cell membrane. Lidocaine inhibits influx of sodium and calcium and stabilizes electrical potential of cell membrane, and will avoid calcium overload [8].

In general the effects of sodium channel blocker rely on the concentration of extracellular sodium. The lower the level of sodium, the higher the effect of the drug. On the contrary, Hearse et al. reported that the lack of sodium diminished the working of the sodium-calcium exchange system. Sunamori et al. reported lidocaine magnesium crystalloid cardioplegia. This cardioplegia was superior to potassium cardioplegia in canine hearts for reducing myocardial edema [9]. Our result was similar with them about water content. Sodium concentration of the solution was 70 mEq/l. While planning to produce blood lidocaine cardioplegia, we installed a circuit to mix blood and reduce the concentration of sodium. The final concentration of our solution was about 100 mEq/l.

We designed different concentrations of lidocaine-magnesium cardioplegia to obtain rapid arrest at induction. In the beginning of this study, we administered lidocaine with 0.43 mM/l, but mechanical and electrical arrest could not be achieved. We increased the concentration of lidocaine gradually. The final concentration of lidocaine for induction was designed at 1.3 mM/l. The time to arrest became almost the same with potassium blood cardioplegia. Joel et al. conducted an adenosine-lidocaine blood cardioplegia study of canine hearts in 2004. Concentration of lidocaine was lower (0.75 mM/l) than our solution [10]. But their solution took longer to arrest (over 2 min) and needed extra lines to deliver adenosine. Our circuit line was simple and easy to handle. We reduced the concentration of lidocaine to 0.43 mM/l from the second administration to avoid toxic effects. We measured serum lidocaine concen-
Hypothermic cardioprotective techniques have been a mainstay for intraoperative myocardial protection for most cardiac surgeons. Myocardial metabolism is passive in low temperatures, encouraging energy conservation as well as blood cardioplegia coronary blood flow and oxygen supply decreasing in low temperatures. Lichtenstein et al. reported warm induction with blood cardioplegia in 1989 [13]. Warm induction cardioplegia theoretically avoids many of the potential problems associated with cold cardioplegia by allowing the heart to continue using oxygen and substrate for energy production and maintenance of normal cellular metabolism. However, the warm cardioplegia presents some problems. These relate to continuous injection of cardioplegia, for example, hyperkalemia causes inadequate visualization. Optimal myocardial temperature varied depending on delivery systems. We administered the solution for antegrade intermittent method. Hayashida et al. reported tepid hypothermic antegrade blood cardioplegia, reduced anerobic lactate and acid release during arrest and preserved cardiac function [14]. We designed the temperature in this study for tepid hypothermia. The temperature of cardioplegia was 28 °C in both groups.

Cardiac function was assessed by time-varying elastance models. Quantification and comparison are based on the slope of this linear relationship, Emax. This methodology has been validated as a correlate of myocardial contractility or systolic function over the range of physiologic preload and afterload [15]. In this study, lidocaine-magnesium blood group exceeded potassium blood group.

Myocardial water content was less in lidocaine-magnesium blood group. This result indicated myocardial edema decrease in lidocaine group. Same results were found in pathologic study.

In conclusion, lidocaine-magnesium blood cardioplegia was superior to potassium blood cardioplegia in systolic left ventricular function and reduced myocardial edema in canine heart.

References

[8] Hauser H, Dawson RMC. The displacement of calcium ions from phos-


ICVTS on-line discussion A

Title: The safety of using millimolar doses of lidocaine as cardioplegia
Authors: Hazem B. Fallouh, Cardiac Surgery Department, St. Thomas’ Hospital, London SE1 7EH, United Kingdom; David J. Chambers

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eComment: We read with interest the paper by Yamaguchi and colleagues [1] that studies the effect of lidocaine-magnesium blood cardioplegia in an in vivo canine model. The interest of this study lies in the fact that it addresses the safety issue of infusing millimolar doses of lidocaine as a cardioplegic agent. This is done by measuring the serum concentration throughout the procedure, but particularly around the time when cardiopulmonary bypass will be discontinued. There appeared, however, to be a very narrow margin of safety because it took 30 minutes for lidocaine to reach safe levels and this will be largely dependent on the renal clearance of the drug, which could be less effective during cardiopulmonary bypass. In reference 10 (incorrectly cited!) Corvera and colleagues [2] used lower lidocaine concentrations in combination with adenosine. Thus, it is possible that, in this study, the use of a higher magnesium concentration (possibly closer to the concentration used in the St. Thomas’ Hospital cardioplegia of 32 mEq/L (16 mmol/l), which would act to block the L-type calcium channels) may have allowed a reduction in their lidocaine concentration. However, serum concentrations of lidocaine were not measured in the study by Corvera and coworkers.

Another point of interest is the formulation of the potassium cardioplegia used at the authors’ institute; the calcium concentration stated is considerably higher than most cardioplegic solutions, at 8 mEq/L (4 mmol/l)! What was the reason behind this? In addition, why were the sodium and potassium concentrations in the Lidocaine-Mg solution so low? Moreover, there are numerous errors of fact throughout the manuscript. For example, the lidocaine concentration used in the maintenance infusion is cited as 0.65 mmol/l in Table 1 and 0.43 mmol/l in the discussion text. The lidocaine serum concentration is cited as µg/ml in Fig 3 and g/ml in the text. It is also surprising that statements made in the Introduction are not supported by references. These, and many other points, should have been brought to the attention of the authors by the reviewers so that they could be corrected or explained.

References
