Superior myocardial protection with nicorandil cardioplegia

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Abstract

Objective: The ATP-sensitive potassium channel (K\textsubscript{ATP}) activator nicorandil used as cardioplegic agent may protect the left ventricle during cardiac arrest. Nicorandil in cold blood was compared with standard hyperkalemic blood and crystalloid cardioplegia.

Methods: Twenty-one pigs were randomly assigned to three groups: (1) cold hyperkalemic crystalloid (n = 7); (2) cold hyperkalemic blood (n = 7); and (3) nicorandil as cardioplegia in cold blood (n = 7). Left ventricular mechanical performance, pressure-volume area (PVA) and myocardial oxygen consumption (MVO\textsubscript{2}) were measured before and at 1 and at 2 h after 60 min of cold global ischemia on cardiopulmonary bypass using intraventricular pressure-volume conductance catheters, coronary flow probes and O\textsubscript{2}-content difference.

Results: The slope (M\textsubscript{w}) of the stroke work end-diastolic volume relationship, the preload recruitable stroke work relationship, was unchanged after ischemia in the nicorandil group, but was reduced to averaged 62.5% (standard deviation 14) of baseline values in both hyperkalemic perfusions (P < 0.05). The slope of the MVO\textsubscript{2}-PVA relationship was unchanged after nicorandil cardioplegia while the slope after hyperkalemic blood and crystalloid cardioplegia increased with 33% (P < 0.02) and 52% (P < 0.02) of baseline values, respectively.

Conclusions: Nicorandil as sole cardioplegic agent in cold blood given intermittently preserves left ventricular contractility and myocardial energetics significantly better than traditional forms of cardioplegia after cardiac arrest.

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Keywords: Cardioplegia; Energetics; Myocardial protection; Nicorandil

1. Introduction

For short-lasting cardiac surgery the heart may be adequately protected by standard hyperkalemic cardioplegia. For patients with limited cardiac reserve, or after long cross-clamp times, the present cardioprotective regimen still involves considerable risk of myocardial damage [1]. Patients at high risk of low cardiac output syndrome need better intraoperative myocardial protection [2]. Many attempts to improve these methods have been suggested, including substrate enhancement and changing cardioplegic vehicle, temperature and mode of delivery. Warm blood cardioplegia should theoretically provide sufficient oxygen and substrates to the myocardium to obtain infinite survival of the heart and complete avoidance of postcardioplegic dysfunction. However, previous work has shown a marked reduction of cardiac function immediately after warm, continuous antegrade blood cardioplegia [3]. The underlying mechanisms for this dysfunction are not fully understood but a contribution may be potassium induced calcium overload of the myocytes [4].

The use of ATP-sensitive potassium channel (K\textsubscript{ATP} channel) openers as cardioplegic agents have shown improved myocardial protection in several experimental studies. In the intact animal, the K\textsubscript{ATP} channel opener pinacidil has shown preserved postcardioplegic left ventricular function [5,6]. Two K\textsubscript{ATP} channel subtypes exist in the myocardium, one in the sarcolemma and the other in the inner mitochondrial membrane (mitoK\textsubscript{ATP}) [7]. Activation of surface K\textsubscript{ATP} channels in the myocyte have been proposed to produce cardioprotection via a shortening of the cardiac action potential and membrane hyperpolarisation, both of which would lead to reduced calcium overload during ischemia or reperfusion and a preservation of ATP [8]. The mitoK\textsubscript{ATP} channel is central in cardioprotection during ischemia or reperfusion [9] but the mechanisms for this protection are still unknown [10].

Nicorandil is a nitrate and a K\textsubscript{ATP} channel opener [11] and it activates both sarcolemmal and mitochondrial K\textsubscript{ATP} channels. It is approved for use in humans and has been

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shown to protect the myocardium against ischemic- and reperfusion injury as an additive to cardioplegia [9,12,13]. Nicorandil in Krebs-Henseleit solution has been shown in isolated rabbit hearts to give an effective cardioplegia [14] and has been shown in a rat model to mimic the cardioprotective effects of preconditioning [15].

Nicorandil was in this study used as sole cardioplegic agent and compared with the two more traditional forms of cardioplegia, cold hyperkalemic crystalloid and cold hyperkalemic blood cardioplegia. By exchanging potassium with the $K_{\text{ATP}}$ channel opener nicorandil we hypothesised improved preservation of myocardial efficiency in oxygen to mechanical work transfer after cardioplegia.

2. Material and methods

2.1. Preparation

2.1.1. Anaesthesia

Domestic pigs of either sex with mean weight 47 (standard deviation, SD 5) kg were fasted overnight and premedicated with 20 mg/kg ketamine (Parke-Davis, Scandinavia AB, Sweden) and 2 mg atropine (Hydro Pharma, Norway). Anaesthesia was induced with intravenous infusion of 10 mg/kg pentobarbital (Nyxemed Pharma, Norway) and 0.02 mg/kg fentanyl (Janssen-Cilag, Belgium) and maintained with 0.02 mg kg$^{-1}$ h$^{-1}$ fentanyl, 0.3 mg kg$^{-1}$ h$^{-1}$ midazolam (Roche, Switzerland) and 4 mg kg$^{-1}$ h$^{-1}$ pentobarbital. The pigs were tracheostomised and ventilated on a volume-cycled ventilator (FiO$_2$ = 0.6, Servo 900, Elema-Schönander, Sweden). Glucose enriched sodium chloride (1.25 g glucose/l sodium chloride) was given for basal fluid replacement (10 mg kg$^{-1}$ h$^{-1}$). Body temperature was recorded from a rectal probe and urine was drained through a cystostoma. Catheters were placed in the femoral arteries and jugular veins for pressure monitoring and blood sampling. Animals were killed after the experiment with intracardiac injection of KCl. The local steering committee of the Norwegian Animal Experiments Authority approved the study protocol and animals received care in compliance with the European Convention on Animal Care.

2.1.2. Instrumentation

After a median sternotomy, the pericardium was incised and the left hemiazygos vein was ligated to avoid systemic blood into the coronary sinus. Ultrasonic transit-time probes (Cardio-Med CM-4000, Medi-Stim AS, Norway) were placed on the pulmonary artery and on the right, the left anterior descending and the circumflex coronary arteries for cardiac output (CO) and myocardial blood flow (MBF) measurements. Cardiac venous blood samples were obtained from a 16 G catheter in the coronary sinus. To transiently reduce left ventricular preload, a 7 F balloon catheter (Sorin Biomedical, Italy) was placed in the inferior caval vein. A 7 F, 12 electrode, dualfield combined microtip and conductance catheter (Sentron, CD Leycom, The Netherlands) for continuous measurements of left ventricular pressures and volumes was introduced into the left ventricle through the left carotid artery. A 22 G catheter was placed in the pulmonary artery for monitoring of mean pulmonary artery pressure and injection of hypertonic saline for parallel volume measurements. A blood prime of fresh porcine blood from a cross-matched donor pig and 15 000 IU/L Heparin was circulated at 37°C in a membrane oxygenator (Monolyth, Sorin Biomedical, Italy) using a centrifugal pump (Biomedicus, MN). After baseline measurements, biopsies, blood collection and full heparinisation (activated clotting time >480 s), the left brachiocephalic artery was cannulated and venous drainage obtained from a cavoatrial cannula. A cardioplegic cannula with a side branch for pressure monitoring was placed in the ascending aorta. The conductance catheter was temporarily withdrawn and cardiopulmonary bypass (CPB) initiated. The aorta was cross-clamped for 60 min and the left ventricle vented through the apex. The myocardial temperature was measured with a myocardial probe connected to a thermistor (COM-1, American Edwards Laboratories, CA). Cardiac biopsies were taken at baseline and at the end of the experiment (14Ga Tru-Cut Biopsy Needle, Pharmaseal, IL) and analysed for water content using the microgravity method described by Mehlhorn [16].

2.2. Protocol

2.2.1. Experimental protocol

After baseline measurements 29 pigs were randomised to receive standard potassium-magnesium crystalloid cardioplegia or two sorts hypothermic blood cardioplegia, either hyperkalemic blood cardioplegia, or blood cardioplegia in which the ATP-sensitive potassium channel opener nicorandil replaced the potassium. All forms of cardioplegia were given antegrade through the aortic root cannula and intermittently, cardiac arrest was initiated with 500 ml followed by 200 ml cardioplegia every 20th min. The infusion pressure measured at the aortic root was kept between 50 and 80 mmHg.

Blood cardioplegia was cooled to 10°C on a separate blood cardioplegia system (Shiley BCD, Phizer, CA), and administered antegrade. Cardioplegic solutions were added using an infusion pump (STC 521, Therumo, Japan). The compositions of cardioplegic solutions are outlined in Table 1. Hyperkalemic blood cardioplegia was prepared as described by Menasché [17]. Topical hypothermia was applied when necessary to maintain myocardial temperature below 18°C. The hearts underwent 60 min of ischemic arrest before the aortic cross-clamp was released. Weaning from CPB was tried 20 min after cross-clamp release. If necessary, animals were allowed another 20 min of support before CPB was terminated. The first set of postplegic measurements was sampled 60 min after cross-
Output from the conductance catheter. The pressure-volume
relationship was avoided by disconnecting the respirator during
clamp release. The last set of measurements was sampled
following another hour of reperfusion off pump. Only pigs
that were successfully weaned from CPB without use of
inotropic agents were included in the study.

2.2.2. Data acquisition

The conductance catheter was reinserted and contractile
indices measured at one and at 2 h after cross-clamp
release. Pressure and conductance signals were relayed to a
conductance conditioner (Sigma 5DF, CD Leycom, The
Netherlands). Sampling rate of the signals was set to 200 Hz
and real time signals were displayed using the software
Conduct PC, CPC V3.15 (CD Leycom). Blood resistivity
(ρ) was measured using a cuvette designed for the
conductance equipment. Parallel volume was calculated
by plotting values of end-systolic parallel conductance
ductances, using the formula:

\[ V_{\text{t}} = \frac{1}{\alpha} \times (L^2/\rho) \times (G_{\text{t}} - G_{\rho}) \]

Where \( \alpha \) is the slope factor relating conductance volume to
an independent volume estimation, \( L \) is the interelectrode
distance, \( \rho \) is blood resistivity, \( G_{\text{t}} \) is the sum of segmental
conductances and \( G_{\rho} \) is parallel conductance. The slope
factor \( \alpha \) was calculated by comparing cardiac output from
the pulmonary artery transit-time flow probe with cardiac
output from the conductance catheter. The pressure-volume
calculations were done by the analysis software of the
Conduct PC package after examination of the pressure-
volume loops. Left ventricular contractility was assessed by
the slope (\( M_w \)) of Preload Recruitable Stroke Work
(PRSW), which serves as a load- and heart rate independent
index of myocardial contractility. The correlation coeffi-
cient for all \( M_w \) was 0.94 (SD 0.1) and at least ten
consecutive beats were recorded during vena cava occlu-
sions (VCO). End-diastolic stiffness was quantified by the
end-diastolic pressure-volume relationship, according to the
equation: \( P_{\text{ed}} = \alpha \times e^{(\beta x V_{\text{es}})} \), where \( \beta \) describes diastolic
stiffness. Diastolic function was also assessed by the
derivative of pressure decay with respect to time and the
time constant of relaxation, tau, both calculated by the CPC
software. In this software, tau is calculated as the time from
d\( P_{\text{dmin}} \) until pressure reaches half the value at d\( P_{\text{dmin}} \).
Pressure-volume area (PVA, in mmHg * ml) represent the
total mechanical work as described by Suga and colleagues
[19] and was calculated as: PVA = \[ SW + (P_{\text{es}} \times (V_{\text{es}} - V_0)/2) - (P_{\text{ed}} \times (V_{\text{es}} - V_0)/2)] \times 1.33 \times 10^{-4} J \ mmHg^{-1} \ ml^{-1} \] where \( P_{\text{es}} \) and \( V_{\text{es}} \) is end systolic pressure and
volume, respectively. The \( V_0 \) was calculated from the
extrapolated x-intercept from the curvilinear slope of the
end-systolic pressure-volume relationship (\( E_{\text{es}} \)) during
VCO, and \( P_{\text{ed}} \) is end diastolic pressure. Left ventricular
coronary blood flow (LVCFB) was estimated as left
ventricular weight/heart weight times coronary blood flow.
Left ventricular oxygen consumption was calculated by
MVO \(_2 \) = (LVCFB * avdO \(_2 \) * Hb * 1.39)/HR * 20.2, where
MVO \(_2 \) is left ventricular myocardial oxygen
consumption, avdO \(_2 \) is difference between aortic and
myocardial venous oxygen saturation, Hb is haemoglobin
in g/ml, 1.39 is a constant in ml O\(_2\)/g Hb, HR is heart rate
and 20.2 is a constant in Joule/ml O\(_2\). MVO \(_2 \) relates to PVA
in a linear way and the y-intercept is assumed to be
equivalent to directly determined Unloaded MVO \(_2 \) [19].

2.3. Statistics

All results are expressed as mean ± 1 SD. Normality of
data was analysed with normal score plots of residuals. Data
were analysed using analysis of variance for repeated
measures (RANOVA). Delta values, calculated as the
difference between baseline and later measurements, were
used as the response. In analysis of ventricular energetics

<table>
<thead>
<tr>
<th>Component</th>
<th>Crystalloid cardioplegia</th>
<th>Hyperkalemic blood cardioplegia</th>
<th>Nicorandil cardioplegia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potassium (mmol)</td>
<td>16</td>
<td>24</td>
<td>0</td>
</tr>
<tr>
<td>Magnesium (mmol)</td>
<td>16</td>
<td>4.5</td>
<td>15</td>
</tr>
<tr>
<td>Procaine (mmol)</td>
<td>1</td>
<td>0</td>
<td>2.5 (bolus only)</td>
</tr>
<tr>
<td>Nicorandil (mmol)</td>
<td>0</td>
<td>0</td>
<td>0.1</td>
</tr>
<tr>
<td>Solvent</td>
<td>Ringer’s Acetate</td>
<td>Blood</td>
<td>Blood</td>
</tr>
<tr>
<td>Temperature</td>
<td>4°C</td>
<td>10°C</td>
<td>10°C</td>
</tr>
</tbody>
</table>

Table 1
Additives of cardioplegic solutions

\[ G_{\text{t}} = \frac{1}{\alpha} \times \frac{F}{L^2} \times (G_{\text{t}} - G_{\rho}) \]

Where \( \alpha \) is the slope factor relating conductance volume to
an independent volume estimation, \( L \) is the interelectrode
distance, \( \rho \) is blood resistivity, \( G_{\text{t}} \) is the sum of segmental
conductances and \( G_{\rho} \) is parallel conductance. The slope
factor \( \alpha \) was calculated by comparing cardiac output from
the pulmonary artery transit-time flow probe with cardiac
output from the conductance catheter. The pressure-volume
one way analysis of variance were performed. Tukey or Dunnett t post hoc tests were used to analyse pairwise group differences. The analyses were performed using the statistical software package SPSS (SPSS10.0®, SPSS Inc., IL).

3. Results

Eight animals were excluded; two before cardioplegia due to major bleeding episodes and three during bypass due to technical errors such as ex vivo coagulation and air embolisms. Any excluded animal was followed by an animal allocated the same group. Five animals, three in the crystalloid group and two in the hyperkalemic blood cardioplegia group, needed an extra 20 min of CPB support after cross-clamp release before they could be weaned from CPB. Three animals were excluded after cross-clamp release because they could not be weaned from CPB after the second attempt, all in the crystalloid group.

Four animals in the nicorandil group and one animal in the crystalloid group regained sinus rhythm spontaneously during reperfusion, all other animals had to be electroconverted.

Tables 2–4 give haemodynamic and mechanical parameters. Heart rate, systemic vascular resistance (SVR) and MBF increased after cardioplegic arrest but there were no significant group differences. Heart rate was higher at baseline in the nicorandil group compared with crystalloid mean arterial pressure (MAP) was significantly higher at baseline in the nicorandil group compared with hyperkalemic blood (P < 0.006) and crystalloid (P < 0.005), the two post-ischemic measurements combined in the calculation. Passive end-diastolic function expressed as the stiffness constant β, was unchanged in the nicorandil group, moderately increased in the hyperkalemic blood group and significantly increased in the crystalloid group. The late diastolic function was thus preserved in the nicorandil group. The time constant of LV pressure decay (τ) and peak negative dP/dt declined in all groups with no group differences indicating prolonged early relaxation or, impaired active diastolic function.

3.1. Left ventricular mechanical function

Contractility of the left ventricle is expressed as the slope of PRSW, Mw (Fig. 1), derived from the left ventricular stroke work-end diastolic volume relation during VCO. The nicorandil group had significantly better preserved Mw compared to both hyperkalemic blood (P = 0.001) and crystalloid (P = 0.005), the two post-ischemic measurements combined in the calculation. Passive end-diastolic function increased as the stiffness constant β, was unchanged in the nicorandil group, moderately increased in the hyperkalemic blood group and significantly increased in the crystalloid group. The late diastolic function was thus preserved in the nicorandil group. The time constant of LV pressure decay (τ) and peak negative dP/dt declined in all groups with no group differences indicating prolonged early relaxation or, impaired active diastolic function.

3.2. Myocardial energetics: MVO2-PVA relationship

The MVO2-PVA relationships at baseline and 2 h after cross-clamp release are shown in Table 5. The y-axis of the MVO2-PVA relationship (Unloaded MVO2) represents oxygen consumption for non-contractile purposes consisting of basal metabolism and Ca2+ handling in excitation-contraction coupling (E-C-coupling). There were no changes in Unloaded MVO2 between groups or over time. The slope of the MVO2-PVA relationship represents efficiency, that is, an increased slope represents a decrease in efficiency. The slope was significantly increased in the crystalloid group compared with both the cold hyperkalemic blood group and the nicorandil group. The slope of the hyperkalemic blood group was significantly steeper than the slope in the nicorandil group, which was unchanged from

Table 2

Mean ± standard deviation of haemodynamic variables at baseline and 60 and 120 min after cross-clamp release in 21 pigs, n = 7 in each group

<table>
<thead>
<tr>
<th>Index</th>
<th>Group</th>
<th>Baseline</th>
<th>After cross-clamp release</th>
<th>P-valueb</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>60 min</td>
<td>120 min</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>Crystalloid</td>
<td>78 ± 7</td>
<td>69 ± 23</td>
<td>70 ± 24</td>
</tr>
<tr>
<td></td>
<td>Nicorandil</td>
<td>97 ± 19</td>
<td>80 ± 18</td>
<td>71 ± 14</td>
</tr>
<tr>
<td>CO (l/min)</td>
<td>Crystalloid</td>
<td>106 ± 16</td>
<td>98 ± 18</td>
<td>86 ± 11</td>
</tr>
<tr>
<td></td>
<td>Nicorandil</td>
<td>106 ± 16</td>
<td>98 ± 18</td>
<td>86 ± 11</td>
</tr>
<tr>
<td>CVP (mmHg)</td>
<td>Crystalloid</td>
<td>3.5 ± 0.9</td>
<td>3.8 ± 1.3</td>
<td>3.7 ± 1.2</td>
</tr>
<tr>
<td></td>
<td>Nicorandil</td>
<td>3.7 ± 0.9</td>
<td>4.1 ± 1.0</td>
<td>3.6 ± 1.0</td>
</tr>
<tr>
<td>SVR (dynes/s cm5)</td>
<td>Crystalloid</td>
<td>2.7 ± 2.4</td>
<td>5.9 ± 2.6</td>
<td>5.7 ± 3.1</td>
</tr>
<tr>
<td></td>
<td>Nicorandil</td>
<td>3.7 ± 2.4</td>
<td>6.1 ± 3.0</td>
<td>6.7 ± 3.3</td>
</tr>
<tr>
<td>MBF (ml/min)</td>
<td>Crystalloid</td>
<td>133 ± 36</td>
<td>216 ± 70</td>
<td>224 ± 88</td>
</tr>
<tr>
<td></td>
<td>Nicorandil</td>
<td>150 ± 37</td>
<td>301 ± 90</td>
<td>250 ± 77</td>
</tr>
</tbody>
</table>

a HR, heart rate; MAP, mean arterial pressure; CO, cardiac output; CVP, central venous pressure; SVR systemic vascular resistance; MBF, myocardial blood flow.
b Response variable as difference between baseline and later measurements in analysis of variance for repeated measures model.
baseline, indicating preserved efficiency in the nicorandil group only (Fig. 2).

### 3.3. Myocardial water content

Myocardial water content increased in all groups from 77.8% (SD 2.9) at baseline to 78.2% (SD 2.8) at the end of the experiment. There were no differences between groups ($P = 0.924$).

### 3.4. Myocardial blood flow

All groups had an increase in MBF after cardioplegia as shown in Table 2. The MBF in the hyperkalemic blood group and in the nicorandil group increased more than in the crystalloid group 1 h after cross-clamp release. After reperfusion for another hour there were no significant differences in MBF between groups.

<table>
<thead>
<tr>
<th>Table 4</th>
<th>Mean ± SD of indices describing left diastolic function at baseline and at 60 and 120 min after cross-clamp release in 21 pigs, $n = 7$ in each group$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Index</td>
<td>Groups</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Beta</td>
<td>Crystalloid</td>
</tr>
<tr>
<td></td>
<td>Blood</td>
</tr>
<tr>
<td></td>
<td>Nicorandil</td>
</tr>
<tr>
<td>Tau (ms)</td>
<td>Crystalloid</td>
</tr>
<tr>
<td></td>
<td>Blood</td>
</tr>
<tr>
<td></td>
<td>Nicorandil</td>
</tr>
<tr>
<td>$dP/dt_{max}$ (mmHg/s)</td>
<td>Crystalloid</td>
</tr>
<tr>
<td></td>
<td>Blood</td>
</tr>
<tr>
<td></td>
<td>Nicorandil</td>
</tr>
</tbody>
</table>

$^a$ $dP/dt_{max}$ is the first derivative of pressure decay with respect to time; Tau is the time constant of relaxation; Beta refers to a variable in the exponential equation to describe the end-diastolic pressure-volume relation.

$^b$ Response variable as difference between baseline and later measurements in analysis of variance for repeated measures model.

$^c$ $P = 0.023$ between the nicorandil and crystalloid group (RANOVA with post hoc Tukey’s test).

### 4. Discussion

Using nicorandil-based cardioplegia, left ventricular contractility and energetics were unchanged after 60 min of ischemia while these functional indices deteriorated substantially after crystalloid and hyperkalemic blood cardioplegic arrest. The nicorandil group performed best overall in terms of LV performance and energy transfer. The hyperkalemic blood group performed better than the crystalloid group in terms of diastolic function and slope of the MVO$_2$-PVA relationship. Both the hyperkalemic blood and crystalloid groups had reduced contractility to almost half of baseline values after reperfusion.

The major findings in this study are preserved mechanoenenergetics and contractility after cardioplegia with the ATP-sensitive potassium channel opener (KATP channel) nicorandil. KATP Channels are present in both sarcolemma and in mitochondrias and the cardioprotective effects have mostly been attributed to mitoKATP [20]. Hypothermia, activation of KATP channels with nicorandil and procaine in...
the bolus dose was sufficient to promptly induce and maintain a stable cardiac arrest.

According to Suga, the slope of the total MVO₂-PVA relationship describes efficiency in all processes converting oxygen to mechanical work: (1) oxygen-to-ATP conversion; and (2) ATP consumption in myofibrillar contraction [19]. The unaltered slope of the MVO₂-PVA relationship after cardioplegia in the nicorandil group shows preserved efficiency in oxygen to mechanical work transfer in this group. In the other groups there was a substantial elevation of the slope of the MVO₂-PVA relationship and hence a reduced efficiency on one or two of the above-mentioned steps after cardioplegia.

The mechanisms of mitochondrial protection is still debated and several hypotheses are proposed, including uncoupling, increased reactive oxygen species production and depolarisation leading to reduced mitochondrial calcium uptake [13,21]. One hypothesis is that opening of the mitoK_{ATP} maintains the architecture of the mitochondrial inter-membrane space challenged by ischemia, thereby preserving outer membrane permeability, the function of mitochondrial creatine kinase and subsequently preserve cellular ATP levels [22]. Protection of mitochondrias by nicorandil cardioplegia could explain the observed beneficial effect opening of mitoK_{ATP} had on myocardial energetics in this study.

Initially we wanted a longer period of cardiac arrest but 60 min of global ischemia was the absolute maximum for the hearts of the crystalloid group to be able to complete the protocol. The fact that three animals in the crystalloid group could not be weaned from CPB demonstrated this. Crystalloid cardioplegia usually offers adequate cardioprotection when patients are at low risk and the ischemic times are kept below 90 min [23]. On the other hand, there is a substantial risk of at least a temporary reduction in contractility also in patients after cardiac surgery using potassium cardioplegia [24]. Potassium-induced cardiac arrest facilitates intracellular movement of calcium ions and the exportation of this calcium load during reperfusion may contribute to the reduced efficiency in the postischemic heart [25].

Elevated tissue water and increased myocardial oxygen demand during reperfusion have previously been described as probable drawbacks when using another K_{ATP} channel opener, pinacidil, in blood cardioplegia [26]. In our study, neither oedema nor increased oxygen demand represented a problem with nicorandil in cold blood. The water content increased similarly in all groups as revealed by the microgravity method. Myocardial blood flow increased more after hyperkalemic blood and nicorandil cardioplegia but the unchanged slope of the MVO₂-PVA relationship in the nicorandil group denotes preserved efficiency. Whether or not the impaired hyperemia in the crystalloid group

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**Table 5**

Changes in left ventricular energetics 120 min after cross-clamp release in 21 pigs, mean ± SD, n = 7 in each group

<table>
<thead>
<tr>
<th>Index</th>
<th>Groups</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Crystalloid</td>
<td>Hyperkalemic blood</td>
</tr>
<tr>
<td>MVO₂ (J × beat⁻¹ × 100 g⁻¹)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>1.34 ± 0.21</td>
<td>1.52 ± 0.45</td>
</tr>
<tr>
<td>After 120 min</td>
<td>1.17 ± 0.32</td>
<td>1.13 ± 0.39</td>
</tr>
<tr>
<td>PVA (J × beat⁻¹ × 100 g⁻¹)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>0.47 ± 0.13</td>
<td>0.62 ± 0.19</td>
</tr>
<tr>
<td>After 120 min</td>
<td>0.21 ± 0.09</td>
<td>0.23 ± 0.10</td>
</tr>
<tr>
<td>y-intercept</td>
<td>0.70 ± 0.19</td>
<td>0.69 ± 0.29</td>
</tr>
<tr>
<td>After 120 min</td>
<td>0.61 ± 0.27</td>
<td>0.76 ± 0.40</td>
</tr>
<tr>
<td>Slope</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>1.38 ± 0.27</td>
<td>1.43 ± 0.26</td>
</tr>
<tr>
<td>After 120 min</td>
<td>2.88 ± 0.56</td>
<td>2.12 ± 0.49</td>
</tr>
</tbody>
</table>

* Post hoc Tukey’s test: crystalloid versus nicorandil P < 0.001; crystalloid versus blood P = 0.018; and blood versus nicorandil P = 0.016.
represents a detrimental effect on vascular endothelium is not answered by our study. Previous authors have suggested that the $K_{ATP}$ channel opener pinacidil has to be given continuously as cardioplegia in blood to achieve systolic recovery [27]. Our study demonstrates that we may use nicorandil intermittently and still preserve systolic function.

Nicorandil is approved for human use and it has been used as an antianginal agent in nearly two decades. Nicorandil is a drug with both nitrate-like and $K_{ATP}$ channel activating properties [11]. The half-life is about 1 h and the drug is excreted in the kidneys. Possible systemic effects are increased heart rate and dilatation of the vascular bed. Heart rate was increased and systemic vascular resistance was lowered but we found no differences between groups. This indicates minimal systemic influence of nicorandil, probably due to the low doses necessary and the administration of the drug directly to the heart.

Nicorandil given intermittently in cold blood as sole cardioplegic agent was feasible in the intact animal, providing reliable and rapid mechanical arrest. This regimen preserved mechanoenergetics and systolic and diastolic functions markedly better than the two most common methods of cardioprotection used today. The results of this study strongly warrant further investigations of this alternative to hyperkalemic cardioplegia both experimentally and clinically.

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