Work in progress report - Cardiac general

Clinical testing of nicorandil supplemented normokalemic cardioplegic solution

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Abstract

Does nicorandil instead of supranormal potassium safely provide cardioplegia and cardioprotection in humans? Fifty patients eligible for coronary artery surgery were randomly divided into two groups; one group received standard St Thomas’ Hospital solution (STHS) and the other group got a crystalloid solution in which supranormal potassium was replaced with 0.2 mmol/l nicorandil. We measured time to arrest, rhythm abnormalities, pre- and postoperative troponin-T, CK-MB and myoglobin release as well as hemodynamic parameters. Time to arrest was significantly shorter in the STHS group (41.0 ± 16.8 s) than in the nicorandil group (120.9 ± 78.8 s, P < 0.001). Four patients in the nicorandil group needed additional STHS to achieve satisfactory cardiac arrest. Troponin-T was elevated in the nicorandil group at four (P = 0.042) and at eight (P = 0.044) hours after surgery, myoglobin levels were elevated at 0 h after surgery (P = 0.014). CK-MB levels were not group different. Hemodynamic performance was similar in both groups. Potassium should probably not be replaced by nicorandil alone in the cardioplegic solution. This study of low-risk patients with short (43.2 min) aortic cross-clamp times showed similar cardioprotection as revealed by hemodynamic performance whereas early release of troponin-T and myoglobin release in the nicorandil group raised some concern.

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1. Introduction

The cardioprotective role of nicorandil has been studied in various models of ischemia-reperfusion [1]. We have previously used nicorandil in a normokalemic, magnesium and procaine supplemented cardioplegic solution in pigs demonstrating improved myocardial energetics and contractility compared with standard hyperkalemic cardioplegia as well as comparable cardiac arrest [2,3]. Cardioplegia with potassium channel openers have been called ‘hyperpolarized’ arrest and is only described in experimental models. We have showed in an in vitro study that nicorandil in concentrations below 0.4 mM does not arrest isolated guinea pig papillary muscles at 37°C. Concentrations of nicorandil above 0.4 mM shortened the action potential duration at 37°C but not during hypothermia (27 or 22°C). Both low (0.1 mM) and high (1.0 mM) concentrations of nicorandil did protect the myocardium equally well against hypoxia and reperfusion damage during hypothermia (22°C) (own results, in press).

These results from our experimental studies led to this first clinical test of nicorandil, procaine and magnesium with normal potassium as intraoperative protection of the myocardium. To our knowledge nicorandil has not been clinically used in a cardioplegic solution with normal potassium concentration. Open heart surgery with clamped aorta is a situation with planned ischemia and hence a situation in which nicorandil might prove valuable.

The primary objective of this study was to evaluate the efficacy and safety of this low-potassium nicorandil, procaine and magnesium supplemented cardioplegic solution in clinical use.

2. Patients and methods

Fifty patients (10 women, 40 men) scheduled for coronary revascularization were randomly assigned to receive St Thomas’ Hospital Solution (STHS) or a solution consisting of nicorandil, procaine hydrochloride and magnesium as cardioplegia. Similar looking 20 ml vials were diluted in 1 l cold Ringer’s acetate. Only the hospital pharmacy knew which solution each patient received. Exclusion criteria were left ventricular ejection fraction less than 0.40, sulphonylurea medication, age over 75 years, pregnancy, and emergency or concomitant procedures. The regional Ethics Committee approved the study, as did the Norwegian Medicines Agency. All patients gave written consent prior to inclusion.

Anesthesia was induced with intravenous fentanyl, midazolam and thiopentone. Pancurinoum was used for muscle relaxation. For analgesia and anesthesia maintenance, fentanyl and propofol were used in combination with isoflurane in a mixture of oxygen and air. Heparin was given at a dose of 3 mg/kg to achieve a target activated clotting time...
(ACT) of 480 s or more before commencing cardiopulmonary bypass (CPB). Circuits were heparin coated and primed with 1800 ml Ringers acetate. The oxygenator was Quadrox Bioline with an extra softbag reservoir (Jostra, Hirrlingen, Germany). The ascending aorta was cannulated and a two-stage venous cannula was put through the right atrium. An initial bolus of 750 ml cold 4 °C antegrade crystalloid cardioplegia was delivered into the aortic arch followed by 200 ml every 20th minute. Systemic moderate hypothermia (32–34 °C) was applied. If the heart did not stop within 4 min after 750 ml of infused cardioplegic solution the resulting 250 ml cardioplegia was given and surgeons were allowed to convert to STHS. Epinephrine was infused if systolic blood pressure, despite adequate preload, was less than 60 mmHg during CPB. After cardiopulmonary bypass, 1.5 mg of protamin was administrated for each mg of heparin.

Ejection fraction was assessed preoperatively with ventriculography. Cardiac function; cardiac index (CI), stroke volume (SV), and systemic vascular resistance (SVR) was measured pre- and postoperatively with the BioZ impedance cardiogram (ICG) monitor (CardioDynamics, San Diego, CA). The maximum rate of change of impedance, the overall thoracic impedance and a volume constant of the chest (determined by age, weight, height and body surface), were used to calculate the stroke volume of the left ventricle [4]. These indexes were recorded at rest preoperatively and postoperatively for at least 12 h continuously in the intensive care unit. A 12-lead electrocardiogram (EKG) was recorded prior to surgery and daily until the 5th day after surgery.

### 2.1. Laboratory analysis

Blood samples (CK-MB, troponin-T, myoglobin and electrolytes) were obtained before and immediately (0 h) after surgery. They were followed by blood samples at 4, 8, 12, 18, 24, 36, 48 and at 72 h after surgery and at the 5th day after surgery. All blood samples were analyzed consecutively together with daily routine tests.

### 2.2. Statistics

Differences and time-dependent changes were analyzed with repeated measures analysis of variance (RANOVA) and Student’s t-test when appropriate. Mann-Whitney U-test for non-Gaussian distributed data were used. Values of P < 0.05 were considered statistically significant. Data are given as mean ± S.D. unless stated otherwise.

### 3. Results

#### 3.1. Preoperative

There were no statistical differences in gender, age, EuroSCORE, CSS class or ejection fraction preoperatively (Table 1). There were no statistically significant differences in hemodynamic measurements preoperatively except for the cardiac index (CI) that was significantly (P = 0.001) lower in the nicorandil group than in the STHS group preoperatively (Fig. 3).

#### 3.2. Perioperative results

The time required to achieve cardioplegic arrest was significantly shorter in the STHS group (41.0 ± 16.8 s) than in the nicorandil group (120.9 ± 78.8 s, P < 0.001) (Fig. 1). Four patients in the nicorandil group were converted to STHS within the first 5 min after cross clamping of the aorta due to unsatisfactory arrest as judged by the surgeon.

Aortic cross-clamp time and time on cardiopulmonary bypass was similar in both groups. There were no group differences in epinephrine administration. Ten patients had

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### Table 1

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>STHS n = 25</th>
<th>Nicorandil n = 25</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preoperative</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (year) median (range)</td>
<td>64 (48–75)</td>
<td>65 (44–74)</td>
</tr>
<tr>
<td>Female/Male</td>
<td>5/20</td>
<td>5/20</td>
</tr>
<tr>
<td>EuroSCORE</td>
<td>2.4 ± 1.6</td>
<td>2.8 ± 2.1</td>
</tr>
<tr>
<td>EF (%)</td>
<td>69 ± 8.8</td>
<td>64 ± 10.7</td>
</tr>
<tr>
<td>CSS class I/II/III/IV, mean ± S.D.</td>
<td>6/13/6/0, 2.0 ± 0.8</td>
<td>4/9/12/0, 2.3 ± 0.7</td>
</tr>
<tr>
<td>Recent MI &lt;30 days</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Cardiac index</td>
<td>3.1 ± 0.5</td>
<td>2.5 ± 0.5 P = 0.001</td>
</tr>
<tr>
<td>Operative</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time to arrest (s)</td>
<td>41.0 ± 16.8</td>
<td>120.9 ± 78.8, n = 21 P &lt; 0.001</td>
</tr>
<tr>
<td>Cross-clamp time (min)</td>
<td>43.4 ± 15.1</td>
<td>43.0 ± 14.1</td>
</tr>
<tr>
<td>Time on bypass (min)</td>
<td>70.0 ± 21.0</td>
<td>73.1 ± 18.7</td>
</tr>
<tr>
<td>Spontaneous rhythm</td>
<td>22</td>
<td>18</td>
</tr>
<tr>
<td>DC shocks (direct current)</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>Ventricular fibrillation</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>Postoperative</td>
<td></td>
<td></td>
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<tr>
<td>Nitrogen infusion</td>
<td>13</td>
<td>12</td>
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<tr>
<td>Reoperated 1 day due to bleeding</td>
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<td>3</td>
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<tr>
<td>Atrial fibrillation &lt;6 days</td>
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<td>3</td>
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<tr>
<td>Perioperative myocardial infarction</td>
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<td>1</td>
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<tr>
<td>Pressor (Abbodop)</td>
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<td>1</td>
</tr>
<tr>
<td>Cardiac index (/min m²)(pooled data)</td>
<td>2.6 ± 0.18</td>
<td>2.3 ± 0.17</td>
</tr>
<tr>
<td>IABP</td>
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<td>0</td>
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</table>
ventricular fibrillation after cross-clamp release, three in the STHS group. Seven were DC-converted (direct current) in the nicorandil group and two in the STHS group. One in the STHS group was converted to sinus rhythm using intravenous potassium (Table 1).

There was one perioperative myocardial infarction in the nicorandil group defined as CK-MB 50 IU the first and second postoperative day combined with ST elevations. CK-MB had a peak level of 77 in this patient and all ST elevations were reversible. No new Q waves or bundle branch blocks were observed.

### 3.3. Postoperative course

There were no between group differences in the levels of CK-MB or potassium (Fig. 2). There was a between group difference in troponin-T and myoglobin levels, and contrast analysis revealed that the difference was for troponin-T at 4 and at 8 h after surgery with a $P=0.042$ and $P=0.044$, respectively, and for myoglobin at 0 h after surgery, $P=0.014$.

There was no statistically significant difference after surgery in cardiac index (CI) (Fig. 3), and there were no differences in heart rate (HR), systemic vascular resistance (SVR), or stroke volume (SV) before or after surgery (Fig. 3).

One patient in the nicorandil group died on day 40 after surgery at her local hospital after refusing dialysis; the same patient was reoperated due to surgical bleeding and received inotropic support during the first postoperative day in the ICU. She had preoperatively a renal failure and EuroSCORE 10.

### 4. Discussion

Nicorandil instead of potassium provided adequate cardiac arrest in 21 of 25 patients, although with a slower onset. Troponin-T release was higher in the nicorandil group at 4 and at 8 h after surgery suggesting a lesser myocardial protection in the nicorandil group.
Four patients in the nicorandil group were converted to STHS (modified St Thomas’ Hospital solution) and achieved cardiac arrest after an average time of 207.5 ± 54 s. According to the protocol, surgeons were allowed to convert to standard cardioplegia after 4 min if no satisfactory cardiac arrest was achieved. The conversion to STHS was somewhat surgeon-dependent. One patient in the nicorandil group with ventricular hypertrophy achieved cardiac standstill 360 s after commencing cardioplegic infusion and in this patient the cardioplegia was not switched. Four minutes (240 s) passed in only one of the patients before it was decided to switch cardioplegia. The slower onset of cardiac arrest was in most cases noted by the surgeon who then would suspect the experimental solution.

In the patients who were converted to hyperkalemic cardioplegia (STHS) different reasons for the switches were given; one lost arterial pressure measurement during cardioplegia delivery, cardiac arrest was achieved after a total of 115 s. Another had rich collaterals and needed rigorous venting throughout the operation and cardiac arrest was achieved after 283 s. The last two patients had no apparent reason for the delayed standstill but after switching to hyperkalemic cardioplegia cardiac arrest was achieved after 240 and 192 s, respectively, from the onset of the first infusion.

Low concentrations of nicorandil activate mitochondrial K<sub>ATP</sub> channels only and higher concentrations activate both sarcolemmal and mitochondrial K<sub>ATP</sub> channels [5]. Activation of sarcolemmal channels is necessary to affect membrane potential but not to initiate cardioprotection. When performing open heart surgery, the heart is usually cooled and hypothermia has pronounced effects on most processes in the body. Action potential shortening by bimakalim, a K<sub>ATP</sub> channel opener, is diminished during cooling [6]. Similarly with nicorandil, but nicorandil maintains its cardioprotective properties also after hypothermia (own results, in press).

Concomitant treatment with sulfonphonylurea was an exclusion factor since these medications inhibit the opening of potassium channels. Glibenclamide blocks both the sarcolemmal and the mitochondrial K<sub>ATP</sub> channels and represents a theoretical limitation of the use of nicorandil.

We did not expect any group differences in postplegic performance due to the low-risk patient population (ejection fraction ≥0.4) and short aortic cross-clamp time (43.2 min). However, the higher troponin-T release in the nicorandil group at 4 (P = 0.042) and at 8 h (P = 0.044) after surgery suggests a somewhat larger myocardial injury in the nicorandil group (Fig. 2). CK-MB levels were equal suggesting that the group difference in myocardial damage was not large (Fig. 2). The myoglobin levels in the nicorandil group were elevated at one point from preoperative levels to 0 h after surgery (P = 0.014), otherwise the levels increased similarly in the two groups after surgery (Fig. 2). In the nicorandil group, four patients had suffered a myocardial infarction within 30 days before surgery, and one in the STHS group. These patients had an initial emergency admittance due to unstable angina pectoris and were included in the study during the in-house waiting period for surgery. They were all stable before surgery. These patients contributed to the elevated troponin-T and when removing these from analysis there were no significant group differences in cardiac marker release.

The cardiac index (CI) was preoperatively significantly (P = 0.001) lower in the nicorandil group than in the STHS group (Table 1). The lower CI in the nicorandil group preoperatively suggests that the groups were not equal before surgery.

All patients received isoflurane during anesthesia off the heart-lung machine. This anesthetic gas has been reported to induce pharmacologic preconditioning [7,8] and this effect is blocked by 5HD indicating that this protection requires activation of mitochondrial K<sub>ATP</sub> channels [9]. Opioid-based anesthesia [10] and cardiopulmonary bypass per se [11] can also induce preconditioning. Pharmacologic preconditioning may hence already have been induced in all the patients and thus override any additional protection due to nicorandil.

In the present composition nicorandil does probably not add any cardioplegic effect, due both to its low concentration and hypothermia. However, this formulation arrested the heart satisfactorily in 21 out of 25 hearts. The factors contributing the most to cardiac arrest were probably hypothermia, procaine and magnesium, respectively.

5. Conclusion

The study has shown that cardiac arrest was achieved without high potassium concentration, although with slower onset. In this series of low-risk patients having an EF 40% and with short (43.2 min) aortic cross-clamp times, similar cardioprotection when replacing supranormal potassium...
with nicorandil in the cardioplegic solution was achieved as judged from hemodynamic performance. Increased early release of troponin-T and myoglobin in the nicorandil group raises some concern. However, analysis showed that the groups were different prior to inclusion and exclusion of patients with recent myocardial infarction resulting in no between group differences in release of cardiac markers.

Acknowledgments

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References