Improved contractility with tepid modified full blood cardioplegia compared with cold crystalloid cardioplegia in a piglet model

Frank Münch†, Ariawan Purbojo†, Stephanie Kellermann, Carina Janssen, Robert Anton Cesnjevar and André Rüffer*

Abstract

OBJECTIVES: Experience regarding warm blood cardioplegia according to Calafiore results from its broad use in adult patients. In this experimental study, tepid (28°C) modified full blood cardioplegia (MBC) was adopted for paediatric use and compared with cold crystalloid cardioplegia (CCC).

METHODS: Twenty male piglets (mean weight: 11.1 ± 1.0 kg) were operated on cardiopulmonary bypass (CPB) in moderate hypothermia (28°C) and randomized to MBC (n = 8) or CCC (n = 12) for 60 min aortic cross-clamping. Blood levels of myocardial proteins [N-terminal pro-brain natriuretic peptide (NT-pro-BNP), myoglobin, creatine kinase type MB and troponin-I] were investigated at the beginning of the experiment and after CPB. Haemodynamic measurements included thermodilution and conductance-catheter technique inserted through the left ventricle-apex. Pressure–volume loop analysis was performed with dobutamine-stress test and inflow occlusion, enabling preload independent evaluation of myocardial performance. Changes of measured data post-CPB were calculated in relation to baseline-levels (%).

RESULTS: Baseline and operative data in both groups were similar. During the experiment, cardiac markers showed no significant variations between groups. Pressure–volume loop analysis during stress test revealed a significantly higher preload independent contractility (slope of end-systolic pressure–volume relation: Ees) with MBC compared with CCC (MBC: 123 ± 35% [confidence interval (CI95): 93–153%] vs CCC: 78 ± 34% [CI95: 54–102%]; P = 0.042), whereas cardiac output was not significantly different between groups (MBC: 122 ± 16% [95% confidence interval (CI95): 109–135] vs CCC: 105 ± 17% [CI95: 93–116]; P = 0.069).

CONCLUSION: This randomized animal study proves feasibility and safety of MBC for paediatric use. Haemodynamic evaluation and cardiac markers did not show inferiority to standard CCC. Moreover, MBC seems to be associated with superior contractility post bypass, which encourages us to use MBC in paediatric patients in the near future.

Keywords: Congenital • Blood cardioplegia • Cold crystalloid • Calafiore • Contractility

INTRODUCTION

The history of cardiac surgery is full of many approaches to optimize myocardial protection. Myocardial oxygen consumption (MVO2) in the normothermic (37°C) empty beating-heart on cardiopulmonary bypass (CPB) ranges between 2 and 7 ml/min/100 g and is reduced by cooling to 22°C to a range between 1 and 4 ml/min/100 g [1]. Induction of cardiac arrest by cardioplegic infusion reduces the MVO2 by 90% to 0–2 ml/min/100 g in the normothermic heart [1]. The combination of both hypothermia and cardioplegia has led to the widespread use of cold crystalloid cardioplegia (CCC) along with moderate hypothermia as the gold standard in paediatric cardiac surgery.

In the late 1970s Gerald Buckberg introduced cold (4°C) blood cardioplegia composed of blood enriched with Buckberg crystalloid solution in a 1:4 ratio [2]. Blood, unlike crystalloid solutions, carries oxygen, nutrients and energy to the cells and organs. It combines natural buffering capacity and ideal colloid-osmotic pressure with physiological rheology, which has a positive effect on the degree of oedema [3–5]. Additionally, high-energy phosphate, oxygen and anti-oedematous substrates are delivered to myocardial tissue, and free radicals and degradation products are washed out by repeated administration of blood cardioplegia every 20 min.

In order to reduce possible deleterious systemic side-effects of crystalloid solutions along with hypothermia [5], Calafiore et al. [4] have introduced their variant of full blood cardioplegia composed of blood mixed with potassium and magnesium, which has gained wide acceptance for normothermic use in adult cardiac surgery since the end of the 1990s. The lack of crystalloid solutions and no need for a heat exchanger reducing CPB priming would predispose full blood cardioplegia especially for use in children.
However until today, there is only limited experience regarding the use of Calafiore’s blood cardioplegia in the setting of congenital cardiac surgery.

Considering the differences between immature and mature hearts with regard to the energetic requirements and electrolyte balance makes it potentially dangerous to just transfer the current method of Calafiore from adult heart surgery to neonates and infants [3, 6, 7]. Therefore, we modified Calafiore’s blood cardioplegia (MBC) by adopting the electrolyte composition for paediatric use.

The aim of this randomized experimental study was to prove efficacy and safety of MBC compared with CCC in a piglet model.

MATERIALS AND METHODS

Experimental set-up

The protocol was approved (no. 54-2532. 1-9/10) by regional state authorities (administration: Regierung Mittelfranken). In a prospective, experimental trial, 26 male piglets (German Landrace, age: 4–5 weeks, weight: 9–13 kg) were operated on CPB in moderate hypothermia (28°C) and randomized to either CCC (group CCC) or MBC (group MBC) for 60 min aortic cross-clamping. Haemodynamic measurements and comparison of cardiac proteins were performed before and after CPB. At the end of the experiment, piglets were sacrificed.

Anaesthesia and surgery

Prior to the experiments, all piglets were isolated for at least 3 days and underwent daily veterinary investigation. All piglets received premedication with intramuscular injection of Midazolam (0.2 mg/kg) and Ketamine (10 mg/kg). A peripheral venous catheter was placed and Atropine (0.02 mg/kg), Midazolam (0.2 mg/kg) and Ketamine (10 mg/kg) were injected intravenously. Piglets were placed on the back and received a rectal temperature sensor. They were intubated with an endotracheal tube (5–6 mm internal diameters) in lateral position and connected to a ventilator. Anaesthesia, analgesia and relaxation were done by inhalation of Isoflurane (initially 2–4%, thereafter 0.8–1.5%), administration of fentanyl (0.05–0.1 mg/kg) and Pancuronium (initial bolus 0.1 mg/kg, thereafter ~0.05 mg/kg) every 45 min.

Standard monitoring was established by using a 5 lead electrocardiogram. Arterial blood pressure was monitored by introducing a 3-Fr pulse-induced contour cardiac output catheter system (PICCO)-catheter (Pulsion Medical System, Munich, Germany) in the left carotid artery. Central venous pressure monitoring, catheter calibration, application of medication and collection of blood samples were performed by a central venous catheter via right jugular vein. A urinary bladder catheter was inserted via lower laparotomy. Following sternotomy, a pressure catheter was inserted into the left atrium via the left atrial appendage. Monitoring of perfusion to the alpha-stat blood gas was performed in the left carotid artery. Central venous pressure was monitored by introducing a 3-Fr pulse-induced contour cardiac output catheter system (PICCO)-catheter (Pulsion Medical System, Munich, Germany) in the left carotid artery. Central venous pressure (CVP), heart rate (HR), pulse pressure variation (PPV), stroke volume (SV), pulse contour curve (dPmax), stroke volume variation (SVV), global cardiac function index (CFI), global ejection fraction (GEF), global end-diastolic volume (GEDV), intrathoracic blood volume (ITBV) and extravascular lung water (EVLW).

Conductance catheter. The characteristic pressure–volume diagrams of cardiac work can be created from the periodic changes in left ventricular pressure and blood volume. The principle of conductance technology is based on the difference in conductivity between blood and the myocardial left ventricular wall. Statements about myocardial contractility and conclusions about the effectiveness of the different cardioplegic solutions can be drawn by this technique [11].

Analysis of pressure–volume loops was performed with the aid of a 4-Fr conductance catheter (C-cath) (CA-41063-PN; Leycom, Leiden, Netherlands) connected to a SigmaM® electronic signal conditioner-processor (Leycom, Leiden, Netherlands). The collected

Cardioplegia

CCC was applied with a single shot [8, 9] (30 ml/kg) at a rate of 60 ml/min with a temperature of 4°C of Bretschneider’s solution (Dr F. Köhler Chemie, Bensheim, Germany).

MBC consisted of tepid arterial blood (28°C) mixed with 2M potassium and 4M magnesium by a 50ml syringe pump (Perfusor fm, Braun, Melsungen, Germany) at an injection rate of 4 ml/kg BW/h, and was infused with a flow rate of 60 ml/min by a selective roller pump. This procedure was performed for 2 min and repeated after 20 and 40 min.

Electrolyte differences between ‘classic’ blood cardioplegia according to Calafiore and MBC in comparison with CCC and physiological intra- and extracellular medium are represented in Table 1.
data were analysed with the specific software (Conduct NT, version 3.18.1, Leycom, Leiden, Netherlands). A blinded re-analysis of all recorded measurements was performed by an expert unaware of randomization results.

After sternotomy and opening of the pericardium, C-cath was placed from the left ventricle-apex into the left ventricle and fixed with a purse-string-suture at the epicardium (Fig. 1).

C-cath calibration was performed by calculation of CO using thermodilution technique, and estimation of the parallel conductance discriminating between ventricle wall and blood by injecting 2 ml of 10% NaCl into the superior vena cava. Measurements were performed before and after CPB and included dobutamine stress test (10 µg/kg/min) and acute preload reduction by snaring the inferior vena cava with a tourniquet.

Measured preload-dependent variables included the end-diastolic volume (EDV), end-systolic volume (ESV), the stroke volume (SV), the ejection fraction (EF) and the relaxation parameter (tau). Preload-independent variables included slopes of end-systolic pressure-volume relationship (Ees) and end-diastolic pressure-volume relationship (Eed), characteristic for preload-independent contractility and compliance (Fig. 2A and B).

Cardiac proteins

NT-pro-BNP has been established as a marker for myocardial failure. Myoglobin is a non-specific marker for muscle damage. Creatine kinase type MB and troponin-I are specific cardiac proteins correlating with the degree of myocardial damage [12]. Measurement of these cardiac parameters was performed with an AQT 90 Auto analyser (Radiometer Medical, Copenhagen, Denmark).

Statistics

Exclusion criteria despite randomization were incidents regarding surgery or CPB interfering investigations, preoperatively elevated laboratory levels of markers indicating cardiac injury and the need for defibrillation before cardiac arrest.

RESULTS

Baseline characteristics

Six piglets had to be excluded due to preoperative elevated levels of NT-pro-BNP (MBC: \(n = 1\), CCC: \(n = 1\)), and intraoperative hazards (\(n = 4\)) interfering with cardiac analysis: cannula dislocation resulting in coronary malperfusion (MBC: \(n = 1\)), aortic dissection (CCC: \(n = 1\)), iatrogenous hypercalemia (MBC: \(n = 1\)) and air embolism resulting from overpressure in extracorporeal reservoir (MBC: \(n = 1\)).

Table 1: Electrolyte concentrations in serum and cardioplegia

<table>
<thead>
<tr>
<th>Ions</th>
<th>Human serum</th>
<th>Cardioplegia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Intracellular</td>
<td>Extracellular</td>
</tr>
<tr>
<td>Na⁺ (mmol/l)</td>
<td>12⁺</td>
<td>145⁺</td>
</tr>
<tr>
<td>K⁺ (mmol/l)</td>
<td>155⁺</td>
<td>4⁺</td>
</tr>
<tr>
<td>Mg²⁺ (mmol/l)</td>
<td>13⁺</td>
<td>1⁺</td>
</tr>
<tr>
<td>Ca²⁺ (mmol/l)</td>
<td>10⁻⁴⁺</td>
<td>2⁺</td>
</tr>
<tr>
<td>Cl⁻ (mmol/l)</td>
<td>4⁺</td>
<td>120⁺</td>
</tr>
<tr>
<td>Buffer (mmol/l)</td>
<td>4⁺</td>
<td>120⁺</td>
</tr>
<tr>
<td>Additives (mmol/l)</td>
<td>30⁺</td>
<td>Tryptophan 2</td>
</tr>
</tbody>
</table>

*Electrolyte concentrations represented with average human levels.
*bElectrolyte concentrations of blood cardioplegia resulting from patient’s blood (average serum concentrations: K = 4.5 mmol/l and Mg = 0.9 mmol/l) enriched with cardioprotective solution (K = 2M and Mg = 4M) injected over a syringe pump with a distinctive cardioplegia application flow (MBC: 60 ml/min and Calafiore-adult: 300 ml/min).

Na: sodium; K: potassium; Mg: magnesium; Ca: calcium; Cl: chloride; CCC: cold crystalloid cardioplegia; MBC: modified blood cardioplegia.

Figure 1: Conductance catheter position in the heart of the euthanized animal. Anterior left- and right ventricular wall has been removed. Transapical positioning of the conductance catheter in the left ventricle, with its tip in the left atrium through the mitral valve.

All haemodynamic measurements and evaluation of cardiac proteins were performed at baseline before surgery, and after CPB. Changes in measured variables by C-cath post-CPB were calculated in relation to baseline levels (%). The data are expressed as mean ± standard deviation (SD) with 95% confidence interval (CI95). Tests on significance have been carried out by the Student’s t-test or the non-parametric Mann–Whitney U-test, according to distribution. A P-value of <0.05 was considered statistically significant. Statistics were performed using the statistical software (SPSS, Version 21, Inc., Chicago, IL, USA).
Eight piglets from group MBC and 12 piglets from group CCC entered the analysis. There were no significant differences regarding weight, size, cardiac markers, haemodynamic variables, duration of CPB or perioperative administration of whole blood and levels of haemoglobin between groups. All included piglets survived the procedure until the end of the experiment except two from group CCC that could not be weaned from bypass. Those animals were not available for postoperative haemodynamic measurements.

Cardiac markers

There were no significant differences regarding cardiac proteins after coming off bypass: NT-pro-BNP (MBC: 12.3 ± 0.7 pg/ml, [CI95: 12.0–12.6] vs CCC: 13.9 ± 6.3 pg/ml, [CI95: 12.0–14.8]; P = 0.385), myoglobin (MBC: 397 ± 84 µg/l, [CI95: 339–456] vs CCC: 414 ± 173 µg/l, [CI95: 316–511]; P = 0.783), CK-MB (MBC: 26 ± 9.3 µg/l, [CI95: 19.6–32.4] vs CCC: 26.9 ± 9.8 µg/l, [CI95: 24.4–32.4]; P = 0.835) and troponin-I (MBC: 6.1 ± 2.4 µg/l, [CI95: 4.4–7.7] vs CCC: 5.5 ± 4.7 µg/l, [CI95: 2.9–8.2]; P = 0.739).

Haemodynamics

Thermodynamics. Haemodynamic evaluation by thermodynamics revealed higher pulse pressure variation (PPV) and stroke volume variation (SVV) with CCC compared with MBC (MBC: 8.3 ± 1.8% [CI95: 7.0–9.5] vs CCC: 10.8 ± 2.2% [CI95: 9.4–12.2]; P = 0.020) and MBC: 10.1 ± 2.6% [CI95: 8.3–12.0] vs CCC: 16.7 ± 6.7% [CI95: 12.5–12.9]; P = 0.015) (Table 2).

Conductance catheter. A significantly higher, volume-independent Ees in MBC in comparison with CCC (MBC: 123 ± 35% [CI95: 93–153] vs CCC: 78 ± 34% [CI95: 54–102]; P = 0.042) was shown during

### Table 2: Thermodynamics measurements after CPB

<table>
<thead>
<tr>
<th></th>
<th>MBC</th>
<th>CI95</th>
<th>P-value</th>
<th>CCC</th>
<th>CI95</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CO (l/min)</td>
<td>2.1 ± 0.4</td>
<td>1.8–2.4</td>
<td>0.45</td>
<td>2.2 ± 0.4</td>
<td>2.0–2.5</td>
<td>0.45</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>59 ± 17</td>
<td>47–70</td>
<td>0.23</td>
<td>68 ± 22</td>
<td>55–81</td>
<td>0.23</td>
</tr>
<tr>
<td>CVP (mmHg)</td>
<td>10 ± 1</td>
<td>9–12</td>
<td>0.60</td>
<td>10 ± 1</td>
<td>9–11</td>
<td>0.60</td>
</tr>
<tr>
<td>HR (1/min)</td>
<td>104 ± 13</td>
<td>85–113</td>
<td>0.40</td>
<td>108 ± 9</td>
<td>103–114</td>
<td>0.40</td>
</tr>
<tr>
<td>SV (ml)</td>
<td>8.3 ± 1.8</td>
<td>7.0–9.5</td>
<td>0.02</td>
<td>10.8 ± 2.2</td>
<td>9.4–12.2</td>
<td>0.02</td>
</tr>
<tr>
<td>dPmax (mmHg/s)</td>
<td>676 ± 207</td>
<td>533–820</td>
<td>0.06</td>
<td>671 ± 273</td>
<td>509–832</td>
<td>0.06</td>
</tr>
<tr>
<td>SVV (%)</td>
<td>10.1 ± 2.6</td>
<td>8.3–12.0</td>
<td>0.015</td>
<td>16.7 ± 6.7</td>
<td>12.5–20.9</td>
<td>0.015</td>
</tr>
<tr>
<td>CFI (min⁻¹)</td>
<td>11.7 ± 1.8</td>
<td>10.5–13.0</td>
<td>0.69</td>
<td>11.5 ± 0.8</td>
<td>10.9–12.0</td>
<td>0.69</td>
</tr>
<tr>
<td>GEF (%)</td>
<td>41 ± 11</td>
<td>33–49</td>
<td>0.57</td>
<td>44 ± 5</td>
<td>40–47</td>
<td>0.57</td>
</tr>
<tr>
<td>GEDV (ml)</td>
<td>178 ± 23</td>
<td>160–197</td>
<td>0.41</td>
<td>189 ± 26</td>
<td>174–204</td>
<td>0.41</td>
</tr>
<tr>
<td>ITBV (ml)</td>
<td>223 ± 33</td>
<td>200–246</td>
<td>0.40</td>
<td>236 ± 33</td>
<td>217–256</td>
<td>0.40</td>
</tr>
<tr>
<td>EVLV (ml)</td>
<td>166 ± 41</td>
<td>138–194</td>
<td>0.83</td>
<td>162 ± 33</td>
<td>141–183</td>
<td>0.83</td>
</tr>
</tbody>
</table>

Values are expressed with 95% confidence interval (CI95).

CPB: cardiopulmonary bypass; CCC: cold crystalloid cardioplegia; MBC: modified full blood cardioplegia; CO: cardiac output; MAP: mean arterial pressure; CVP: central venous pressure; HR: heart rate; PPV: pulse pressure variation; SV: stroke volume; dPmax: maximum gradient of the increase in arterial pressure determined by the pulse contour curve; SVV: stroke volume variations; CFI: cardiac function index; GEF: global ejection fraction; GEDV: global end-diastolic volume; ITBV: intrathoracic blood volume; EVLV: extravascular lung water.
dobutamine stress test. CO was not significantly different between groups \([\text{MBC}: 122 \pm 16\% \text{ (CI95: 109–135)} \text{ vs } \text{CCC: 105 \pm 17\% \text{ (CI95: 93–116)}}; P = 0.069]\) (Table 3 Fig. 3A and B).

**DISCUSSION**

Calaﬁore’s cardioplegia consists of full blood enriched with potassium and magnesium according to a universal formula and is widely used for adult patients. This simple and efﬁcient method for myocardial protection has gained acceptance for normothermic adult cardiac surgery since the late 1990s. The advantages of blood in comparison with crystalloid solutions \([3, 13]\) as well as the possibility to adopt moderate hypothermia \((28^\circ\text{C})\) for both systemic and cardioplegic infusion have driven us to modify Calaﬁore’s blood cardioplegia for paediatric hearts. The difference regarding electrolyte composition of MBC consists in further enrichment with 20% more potassium and 25% more magnesium as opposed to the adult formula. We conducted a prospective randomized study where the feasibility of MBC was proved in a piglet model. CCC representing standard cardioplegia of our CPB-routine for repair of congenital cardiac defects served as control.

**Conductance catheter**

Children undergoing palliative or corrective congenital cardiac surgery using CPB and cardiac arrest often have to cope with cyanosis, volume overload or borderline left ventricular size and hypertrophy. It is reasonable that especially those patients would beneﬁt from any improvement in myocardial protection regarding preservation of left ventricular contractility.

None of the preload-dependent parameters revealed any significant difference between analysed groups, except a statistical trend towards a higher postoperative CO with MBC \((P = 0.069)\). However, by using temporary cava vein occlusion and dobut-

### Table 3: Pressure-volume loop analysis after CPB under dobutamine stress test

<table>
<thead>
<tr>
<th></th>
<th>MBC</th>
<th>CCC</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± SD</td>
<td>CI95</td>
<td>Mean ± SD</td>
</tr>
<tr>
<td>HR (1/min)</td>
<td>83 ± 10</td>
<td>75–91</td>
<td>85 ± 11</td>
</tr>
<tr>
<td>CO (l/min)</td>
<td>122 ± 16</td>
<td>109–135</td>
<td>105 ± 17</td>
</tr>
<tr>
<td>EF (%)</td>
<td>108 ± 26</td>
<td>87–128</td>
<td>91 ± 11</td>
</tr>
<tr>
<td>EDV (ml)</td>
<td>149 ± 56</td>
<td>104–194</td>
<td>142 ± 32</td>
</tr>
<tr>
<td>ESV (ml)</td>
<td>228 ± 283</td>
<td>2–455</td>
<td>159 ± 58</td>
</tr>
<tr>
<td>ESP (mmHg)</td>
<td>125 ± 33</td>
<td>99–152</td>
<td>130 ± 20</td>
</tr>
<tr>
<td>MDP (mmHg)</td>
<td>174 ± 155</td>
<td>50–298</td>
<td>228 ± 279</td>
</tr>
<tr>
<td>EDP (mmHg)</td>
<td>99 ± 49</td>
<td>60–138</td>
<td>138 ± 60</td>
</tr>
<tr>
<td>Tau (msec)</td>
<td>98 ± 20</td>
<td>82–114</td>
<td>97 ± 16</td>
</tr>
<tr>
<td>Ees (Slope)</td>
<td>123 ± 35</td>
<td>93–153</td>
<td>78 ± 34</td>
</tr>
<tr>
<td>Eed (Slope)</td>
<td>110 ± 70</td>
<td>49–172</td>
<td>119 ± 46</td>
</tr>
</tbody>
</table>

Values are expressed in relation to baseline levels (%) with 95% confidence interval (CI95).

CPB: cardiopulmonary bypass; CCC: cold crystalloid cardioplegia; MBC: modified full blood cardioplegia; CO: cardiac output; HR: heart rate; EF: ejection fraction; EDV: end-diastolic volume; ESV: end-systolic volume; ESP: end-systolic pressure; MDP: mean pressure; EDP: end-diastolic pressure, Ees: slope of end-systolic pressure–volume relationship; Eed: slope of end-diastolic pressure–volume relationship.

![Figure 3: AB boxplot Ees (A) and CO (B) during inflow occlusion (pre- vs post-CPB). Cold crystalloid cardioplegia (CCC), modified full blood cardioplegia (MBC), slope of end-systolic pressure–volume relationship (Ees), cardiac output (CO).](https://digital-library.oxfordjournals.org/doi/abs/10.1093/ejcts/ezy181)
mine stress test, we were able to determine significantly improved preload-independent contractility in the MBC group as opposed to the CCC group.

The Ees-slope is a highly sensitive measurement of myocardial contractility generated independently of the respective preload [14]. Changes of Ees have been already used in studies investigating pharmacological preconditioning in the context of CPB with 60 min hypothermic cardioplegic arrest in a canine animal model. Contractile dysfunction investigated by relative changes of Ees was significantly reduced using pharmacological preconditioning [15]. Intraoperative studies of infants with congenital heart defects could prove that the postoperative, or post-CPB, volume-independent contractility was 40% reduced compared with the starting values [11]. From the same study group, an improvement in the volume-independent contractility through the use of modified ultrafiltration was demonstrated [16].

Thermodilution

In the presented study, significantly higher PPV and SVV were found with CCC after CPB by thermodilution measurement. Both SVV and PVV are markers for a defined respiratory-dependent SV, as well as pulse pressure. A variation of >10% for SVV and PVV indicate a more respiratory-dependent SV, which is usually interpreted as hypovolemia. However, no significant differences regarding preload-dependent parameters, such as GEDV and CVP, could be established between groups. Moreover, there was no difference in preload-dependent CO as well as GEF between groups. To better understand the difference in SVV and PVV between groups, we adopted the Frank-Starling model to our experimental results representing both MBC and CCC with comparable preload-dependent SV (similar EF and CO: same angle to x-axis), as opposed to another fictive group with reduced cardiac performance (lower EF and CO: sharper angle to x-axis) (Fig. 4). According to our model, we suggest that CCC reaches its plateau later than MBC and appears to be still 'under-filled' (SVV and PVV > 10%), implementing a higher need of volume load. Diseased dilated hearts usually need a higher preload in order to generate an adequate SV but these hearts are consistent with lower preload-dependent myocardial performance. As explained above, we could demonstrate a significantly better preload-independent contractility with the conductance technology for MBC substantiated by a significantly higher Ees. We therefore suggest that higher SVV could be indicative for decreased left ventricular dysfunction not expressed by standard preload-dependent measurements.

Amark et al. [17] demonstrated a higher CO using blood cardioplegia on atrioventricular canal patients in comparison with CCC. Furthermore, the coronary vein blood in the CCC group had significantly higher lactate levels post-CPB.

Cardiac proteins

No significant differences with regard to established blood tests for cardiac markers, such as CK-MB, troponin-I, NT-pro-BNP and myoglobin were found. Various advantages of using blood cardioplegia with regard to cardiac markers, heart rhythm and outcome have been well shown in the literature [4, 12, 18, 19]. Guru et al. [19] performed a meta-analysis of 34 randomized clinical trials, which was mainly composed of coronary artery bypass surgery, and compared blood cardioplegia with CCC. Blood cardioplegia was associated with a better CO and lower levels of CK-MB, but with the same incidence of myocardial infarction and mortality in both groups. In addition, Jacob et al. [18] encompassed a further 18 randomized trials and could prove a significant advantage in blood cardioplegia with an improved clinical outcome and a lower rise in cardiac enzyme levels.

Possibly longer aortic cross-clamping or longer postoperative observation would have given stronger evidence for the cardio-protective potential of MBC. However, the goal was to prove that MBC is at least as safe as CCC for 60 min of cross-clamping, which is quite common for most standard paediatric repairs. Further longer observation periods post-bypass were not approved by state authorities.

Temperature

In this experiment, identical temperature (28°C) for both systemic and cardioplegic perfusion with MBC was chosen, which gives us the opportunity in the future to abandon the heat exchanger from the cardioplegic circuit, which leads to an effective reduction of CPB priming. Less haemodilution expected by using full blood cardioplegia and reduction in priming decrease the probability of electrolyte imbalances and transfusion requirements.

Moderate hypothermia is commonly used during congenital heart surgery and enables an adequate systemic oxygenation even under low-flow conditions. In the absence of circulatory arrest, mild hypothermia appears to be an advantage for neuroprotection only but not myocardial protection [5]. If further reduction of myocardial temperature occurs, excessive leftward shifting of the oxyhaemoglobin curve inhibits cellular oxygen uptake, which counteracts the positive effect of blood cardioplegia as an energy deliverer. The disadvantages of deep hypothermia include weakening of the cell’s energy-dependent membrane potential equalizing pump mechanism more than the physical diffusion processes, leading to a passive influx of fluid and thereby to turgidity within the cell, impairment of clotting function, higher transfusion requirements and longer time needed in intensive
care [20, 21]. Additionally, the relationship between myocardial raised wall tension and reduced MVO₂ through hypothermia is considered to be ideal at 28°C [1]. Accordingly, Hayashida et al. [22] determined the optimal cardioplegia temperature and concluded that tepid antegrade blood cardioplegia (29°C) is associated with a reduction in metabolic myocardial damage and delivers the best myocardial protection. Several studies have emphasized an advantage of warm, or rather tepid cardioplegia temperatures in comparison with cold cardioplegia, with regard to less myocardial damage, a quicker recovery of left ventricular function and improved clinical outcomes [12, 23–25]. Only a few centres are able to report on their experience with normothermic blood cardioplegia in the context of congenital cardiac surgery. Durandy from the Jacques-Cartier hospital in Paris assessed patients undergoing congenital cardiac surgery with normothermic blood cardioplegia compared with CCC in a retrospective study, and found a reduced intensive care period and a smaller increase in troponin-I levels in the normothermic blood cardioplegia group [24].

Financial considerations

Based on the underlying pricing of cardioplegic solutions, CCC was 20 times more expensive than MBC. The cost for a single shot of (300 ml) CCC used during our experiment for a 10 kg piglet was 61€, whereas for a triple application of MBC during 60 min cross-clamping €3 was calculated. Saving costs, of course, should not stay in focus with regard to infant and neonatal perfusion. However, in times of increased economic pressure cost reduction could be recognized as a pleasant side-effect of an improvement in technical issues. By changing their cardioplegia regimen from CCC to Calafiore’s blood cardioplegia, the adult heart surgery unit in our hospital has reduced their costs for cardioplegic solutions by approximately €90.000 per year.

Technical issues

Administration of CCC is simple by cooled solution taken from the icebox. Single-dose application is recommended by the manufacturer and has been proven to establish sufficient myocardial protection for cross-clamp periods up to 180 min. [8, 9] MBC on the other hand is technically more demanding and has to be repeated every 20 min. Frequent infusion of some crystalloid cardioplegic solutions, for example, St. Thomas, has been recommended in order to remove toxic metabolites and to enable energy production via anaerobic pathway. However, by comparing repeated administration of St. Thomas solution to CCC-single shot in a retrospective trial including 118 infants, more spontaneous defibrillations, lower levels of creatin kinase, and a lower mortality was consistent with the use of CCC [9].

Study limitations

Results from animal studies are not fully comparable with humans. Sample size was small and marginal for statistical evaluation. A longer aortic cross-clamping period would have been perhaps more conclusive. Because of animal protection requirements, we were not permitted to use neonatal piglets and to extend postoperative survival period. It should be discussed whether sampling of blood tests directly after CPB was too early for a diagnostically conclusive comparison of both groups. The model does not allow us to draw conclusions for cyanotic patients. This experiment reflects more two different ‘philosophies’ to obtain cardioplegia than a comparison of two solutions. Our results cannot be extrapolated to all kinds of crystalloid cardioplegic solutions. The influence of repeated administration of CCC during cardiac ischaemia has not been determined in this study. In this experiment, the heart was not surgically opened during cardiac ischaemia, thus the risk of air embolism during repeated administration of MBC was eliminated. In addition, total cardioplegia application duration was 1 min longer with MBC during aortic cross-clamping.

CONCLUSION

This experimental study displays the feasibility and safety by using MBC in a piglet model. Prospective randomization revealed an improved preload-independent contractility after 1 h of aortic cross-clamping with MBC compared with CCC. A positive side-effect of MBC is the possible reduction of CPB priming by using identical temperature for both systemic and cardioplegic perfusion, whereby further positive effects with respect to the systemic inflammatory reaction can be assumed. In addition, effective cost savings are expected after clinical implementation of MBC.

ACKNOWLEDGEMENTS

We thank Jan Schreuder, for his thorough evaluation of conductance files.

Funding

The study was supported by the research and education fond of the Friedrich–Alexander University Erlangen-Nürnberg (ELAN-fonds, no. 54550001).

Conflict of interest: none declared.

References

The major components of myocardial protection using cardioplegic solutions are as follows: (i) rapid induction of cardiac arrest associated with its maintenance during global ischaemia to decrease useless energy consumption, (ii) cooling the heart to decrease energy demand for restoring myocardial cell integrity such as sodium–potassium pump, (iii) addition of oxygen and substrate for production of high-energy phosphates during ischaemia, (iv) removal of acidic toxic metabolites such as lactate associated with correction of myocardial acidosis and (v) prevention of reperfusion injury caused by calcium paradox and oxygen radical species.

Various types of CCC solutions have been developed, and they can be divided into two types according to their electrolyte components: one is an intracellular-type solution represented by St Thomas Hospital Bretschneider solution and the other is an extracellular-type solution represented by cold crystalloid cardioplegia (CCC) and blood cardioplegia (BC). Although the main concept is quite similar in both types of cardioplegic solutions, namely maintenance of integrity of the heart during global ischaemia in cardiac surgery, the optimal application method of cardioplegic solution is quite different between the two types of cardioplegic solutions because of their different characteristics.

The major components of myocardial protection during cardiac surgery had been well established through the late 1980s to 1990s. There are two main types of cardioprotective solutions: cold crystalloid cardioplegia (CCC) and blood cardioplegia (BC). Although the main concept is quite similar in both types of cardioplegic solutions, namely maintenance of integrity of the heart during global ischaemia in cardiac surgery, the optimal application method of cardioplegic solution is quite different between the two types of cardioplegic solutions because of their different characteristics.

The major components of myocardial protection using cardioplegic solutions are as follows: (i) rapid induction of cardiac arrest associated with its maintenance during global ischaemia to decrease useless energy consumption, (ii) cooling the heart to decrease energy demand for restoring myocardial cell integrity such as sodium–potassium pump, (iii) addition of oxygen and substrate for production of high-energy phosphates during ischaemia, (iv) removal of acidic toxic metabolites such as lactate associated with correction of myocardial acidosis and (v) prevention of reperfusion injury caused by calcium paradox and oxygen radical species.

Various types of CCC solutions have been developed, and they can be divided into two types according to their electrolyte components: one is an intracellular-type solution represented by Bretschneider’s solution and the other is an extracellular-type solution represented by St Thomas Hospital’s solution. Regardless of its electrolyte components, the most important factor of CCC is deep hypothermia, because CCC has a very little oxygen-carrying capacity by dissolved oxygen. An optimal temperature of CCC is considered ~4°C with systemic hypothermia associated with/without topical cooling to maintain myocardial temperature ~10–15°C. Intermittent infusion of CCC is considered very useful not only to maintain hypothermia but also to supply substrate for...