Cold continuous antegrade blood cardioplegia: high versus low hematocrit

Rufus Baretti*, Asatoshi Mizuno, Gerald D. Buckberg, Helen H. Young, Roland Hetzer

Division of Cardiothoracic Surgery, UCLA School of Medicine, Los Angeles, CA, USA

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Abstract

Objective: Cold continuous antegrade blood cardioplegia (CCABCP) is used with different hematocrit values. We investigated the consequences of CCABCP with low hematocrit (LH: 20–25%) versus high hematocrit (HH: 40–45%). Methods: Anesthetized open chest pigs (25 kg) were placed on cardiopulmonary bypass (CPB). The hearts were arrested for 30 min by 6°C CCABCP with either LH or HH (n = 8, each): After an initial 3 min application of high potassium (20 mEq) BCP the hearts were arrested for subsequent 27 min by normokalemic 6°C cold blood delivered continuously antegradely. Thereafter the hearts underwent perfusion with warm systemic blood for an additional 30 min on CPB. Biochemical cardiac data (MVO₂ (ml min⁻¹ 100 g⁻¹), release of creatine kinase (CK; units min⁻¹ 100 g⁻¹)) and lactate (mg min⁻¹ 100 g⁻¹)) and the coronary vascular resistance index (CVRI (mmHg ml⁻¹ min g⁻¹)) were measured during CPB. Total tissue water content (%) and left and right ventricular stroke work indices (LV-and RV-SWI (g m kg⁻¹)) were assessed 30 min after discontinuation of CPB and compared to pre-CPB controls. Results: The hearts of the LH group had no biochemical or functional disturbance. The HH group showed marked CK leakage (0.6 ± 0.2* vs. 0.1 ± 0.1, *P < 0.05 for comparison of LH vs. HH with Student’s t-test for unpaired data), impaired initial oxygen consumption (4 ± 1* vs. 7 ± 1 after cardiac arrest, an increased CVRI (82 ± 12* vs. 50 ± 8), the formation of myocardial edema (81.0 ± 1.3* vs. 77.5 ± 1.2), and poor functional recovery (LVSWI 0.2 ± 0.1* vs. 1.0 ± 0.1; RVSWI 0.1 ± 0.1* vs. 0.5 ± 0.1). The absence of lactate production in both groups was in accord with the non-ischemic protocol. Conclusions: CCABCP with a low hematocrit of 20–25% is cardioprotective. In contrast, CCABCP with a high hematocrit of 40–45% jeopardizes the heart despite avoiding ischemic periods, and should be avoided. © 2001 Elsevier Science B.V. All rights reserved.

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1. Introduction

The continuous infusion of potassium based cardioplegia can be cumbersome in terms of systemic potassium overload. An impaired cardiac function due to general hyperkalemia is not seldom seen after the extended use of hyperkalemic blood cardioplegia (BCP) [1]. Hypothermia is generally known to support cardioplegic maintenance and can help to reduce the cardioplegic amount of potassium [2]. Many cardioplegic concepts recommend hypothermia in addition to cardioplegic agents. Recent studies show that following cold (6°C) blood-cardioplegic arrest, normal cold blood infusions without hyperkalemia can be used to maintain cardiac arrest [3,4]. Continuous coronary flow can be advantageous for cardiac metabolism when it does not impair visualization during the procedure [5].

Most extracorporal circuits are primed with a crystalloid solution to reduce transfusion and blood related problems [6]. A perioperative hematocrit of approximately 25% is acceptable, and may be useful with hypothermia due to its lower viscosity, shear rate and better microcirculation [7,8]. On the other hand, at periods of low pump flow rates, low hematocrit may cause neurologic dysfunction [9], which might be reversed by raising the hematocrit. Patients with cardiac insufficiency and critical circulation can be jeopardized by low hematocrit. Elevating the hematocrit to 35% can stabilize the hemodynamics of those patients [10]. The body’s oxygen demand increases during rewarming on cardiopulmonary bypass (CPB) [11]. For this period and the post-operative course a higher hematocrit would be desirable. Intra-operatively, the hematocrit can be raised by CPB ultrafiltration, drug-induced diuresis, or transfusion of packed red cells. The ‘ideal’ hematocrit during CPB is unknown [11,12].
The purpose of the present study was to test effects of different hematocrit values of cold (6°C) normokalemic coronary blood delivered continuously antegradely subsequent to cardiac arrest with cold hyperkalemic blood-cardioplegic solution. We tested the hypothesis that myocardial blood perfusion with low (20–25%) versus high (40–45%) hematocrit results in different outcomes of myocardial protection during cardiac arrest.

2. Materials and methods

Sixteen Yorkshire–Duroc pigs (body weight 25 ± 2 kg, age 5–6 months) were premedicated with an intramuscular injection of ketamine (5 mg kg⁻¹) and anesthetized with an intravenous (i.v.) injection of sodium pentobarbiturate (30 mg kg⁻¹). Anesthesia was maintained by subsequent bolus injection of sodium pentobarbiturate. All animals used in these experiments received human care in compliance with the Principles of Laboratory Animal Care formulated by the Institute of Laboratory Animal Resources and the Guide for the Care and Use of Laboratory Animals prepared by the Institute of Laboratory Animal Resources and published by the National Institutes of Health (NIH Publication No. 86-23, revised 1985).

After tracheotomy and endotracheal intubation animals were put on a volume-controlled ventilator (900D, Siemens-Elema, Sweden). The femoral artery and vein were cannulated for arterial blood samples and volume infusion to raise preload during intubation of function curves. Arterial blood gases were measured every 20 min and physiologic values for PO₂, PCO₂, pH, and bicarbonate were maintained. A pressure-transducer tipped catheter (Millar Instruments, Inc., Houston, TX) was inserted into the aorta via the right carotid artery and a saline-filled catheter (Microwire Edwards Laboratory, Santa Ana, CA) and expressed as

\[
PFI_{syst} = \frac{PF_{syst}}{BW} \text{ (ml min}^{-1} \text{kg}^{-1})
\]

\[
PFI_{cor} = \frac{PF_{cor}}{HW} \text{ (ml min}^{-1} \text{g}^{-1})
\]

2.1.2. Myocardial performance

Myocardial function was assessed before starting CPB and 30 min after weaning from CPB by Frank–Starling curves. Atrial preload was raised by continuous infusion of blood from the CPB into the central venous line at 4 ml min⁻¹ kg⁻¹. Cardiac output was determined by thermodilution technique using a cardiac computer (Model 9520a, American Edwards Laboratory, Santa Ana, CA) and expressed as ml min⁻¹ kg⁻¹. Left and right ventricular stroke work indices (LV and RV SWI) were calculated by following equations:

\[
LV \text{ SWI} = (MAP - LAP) \times CO \times 0.0136 \times HR^{-1} \times BW^{-1} \text{ (g mkg}^{-1})
\]

\[
RV \text{ SWI} = (PAP - CVP) \times CO \times 0.0136 \times HR^{-1} \times BW^{-1} \text{ (g mkg}^{-1})
\]

2.1.3. Systemic and coronary vascular resistance index

The systemic and coronary vascular resistance indices (SVRI and CVRI) were determined every 5 min and calculated by following equations:

\[
SVRI = \frac{(MAP - CVP)}{PFI_{syst}} \text{ (mmHg ml}^{-1} \text{ min kg}^{-1})
\]
where MAP is mean aortic pressure (mmHg), CVP is central venous pressure (mmHg), PFI_{syst} is the systemic pump flow index (ml min^{-1} kg^{-1}), MAP is mean coronary artery pressure (mmHg) and PFI_{cor} is coronary pump flow index (ml min^{-1} g^{-1}).

2.1.4. Arterial blood gases, electrolyte-content and hematocrit

Arterial hemoglobin, hematocrit, blood gases, electrolyte content, pH and base excess were sampled every 15 min and analyzed in a blood gas analyzer (Blood Gas System 288, Ciba-Corning, Medfield, MA).

2.1.5. Biochemical data

Measurements of oxygen consumption, release of creatine kinase (CK), extraction and production of lactate were determined from arterial (A_{content}) and coronary sinus samples (V_{content}) withdrawn at a fixed rate over 2 min from the arterial and coronary sinus catheters. Based on these arteriovenous differences from the coronary blood flow delivered by the calibrated roller pump, biochemical data were calculated by the equation of Fick and expressed as consumption or release per minute per 100 g heart weight (HW) at a coronary perfusion flow corrected for 100 ml min^{-1}:

\[ \text{Myocardial consumption/release} = 100 \times (A_{content} - V_{content}) \times PFI_{cor}/HW \]

(ml O_2 min^{-1} 100 g^{-1}, (units CK min^{-1} 100 g^{-1}), (mg lactate min^{-1} 100 g^{-1}).

The blood oxygen content was determined with the blood gas analyzer (Blood Gas System 288, Ciba-Corning, Medfield, MA).

The CK content in plasma was spectrophotometrically and enzymatically determined [13] using a Sigma diagnostics kit (Sigma Chemical Co., St. Louis, MO). It had to be corrected for the hematocrit and the respective percentage of plasma of that blood sample. Separation of the plasma fraction from blood samples was performed by centrifugation at 1000 \times g at 4°C for 5 min.

Lactate content in blood was spectrophotometrically and enzymatically determined [14] using a Sigma diagnostics kit (Sigma). Briefly, lactate was determined from 1 ml blood extracted with 2 ml ice-cold 8% perchloric acid, stood on ice for 5 min, then centrifuged at 3000 \times g at 4°C for 10 min.

2.1.6. Myocardial total water content

At the end of the study, the left and right ventricular tissue water content was determined by weighing samples before and after drawing in an oven at 80°C for 24 h.

2.2. Experimental protocol

All pigs were placed on standard CPB (Fig. 1). The pump flow rate was adjusted to 70–90 ml min^{-1} kg^{-1} to maintain the aortic perfusion pressure at 50–60 mmHg. Eight pigs were perfused with low hematocrit blood (hct 20–25%, LH group), and eight other pigs with high hematocrit blood (hct 40–45%, HH group). After clamping the aorta, all hearts were arrested with cold (6°C) blood cardioplegia (BCP) containing potassium-chloride 20 mmol l^{-1} for 3 min and for subsequent 27 min with cold (6°C) normokalemic blood. BCP solution and subsequent cold blood were continuously delivered at a variable flow rate to adjust the perfusion pressure in the aortic root to 50–60 mmHg. The hearts were perfused for additional 30 min with warm (37°C) systemic blood on CPB. Thereafter they were weaned from CPB and kept in a beating working state for subsequent 30 min before myocardial performance was assessed and compared to the pre-CPB control function.

2.3. Statistical analyses

All data are given as mean ± standard deviation (SD). Comparable variance of the groups’ results was checked with the F-test; a Gaussian curve distribution of the results was validated by the method of David, Pearson and Stephens before parametric comparison. Differences between group LH and HH were analyzed with the Student’s t-test for unpaired data. For multiple comparison the Bonferroni correction was used. Statistical significance was accepted at a probability level (P) lower than 0.05. Statistical analyses were performed using the Statview software, second edition (SAS Institute Inc., Cary, NC) on an Apple G3 Powermacintosh computer (Apple Inc., Cupertino, CA).

**EXPERIMENTAL PROTOCOL**

<table>
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<td>COLD CONTINUOUS</td>
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Fig. 1. Experimental protocol. All pigs were placed on cardiopulmonary bypass (CPB) for 1 h. After clamping of the aorta, all hearts were arrested with cold hyperkalemic blood cardioplegia for 3 min (cold induction) and for a subsequent 27 min with cold normokalemic blood (cold continuous). Thereafter they were perfused for an additional 30 min with warm systemic blood on CPB in a beating empty state (warm continuous). Cardiac performance was assessed 30 min after discontinuation of CPB (working beating state).
3. Results

3.1. Myocardial state

Cardiac arrest always occurred within 50 s after starting the cardioplegic infusion and continuous cold normal blood was started for the last 27 min of cardioplegia. In six hearts of the LH group the myocardium remained arrested, but atrial fibrillation started at 25 min in two animals, and was not treated. In contrast, ventricular fibrillation occurred in four of eight hearts of the HH group at 8, 12, 17 and 23 min. These hearts required additional doses (for 2 min each) of hyperkalemic cardioplegia (KCl 20 mmol l$^{-1}$ BCP) to restore arrest.

Reversal of the perfusate to normal blood at 37°C caused recovery of sinus rhythm in all hearts of the LH group within 2 min of rewarming. One of them required a single 10-J defibrillation during the 30 min of normothermic perfusion. In contrast, five of eight hearts of the HH group fibrillated during the 30 min of normothermic perfusion. Defibrillation was needed between 1 and 4 times at 10–20 J. Three hearts of the HH group maintained sinus rhythm during this interval.

3.2. Ventricular function

Weaning from CPB was always possible (Figs. 2 and 3). The right ventricular stroke work index of the LH group was normal, and the left ventricular stroke work index of the LH group was comparable to control value when preload reached 15 mmHg. These observations were different for the HH group, where four of the eight hearts needed to be replaced on CPB for 10 additional minutes due to hemodynamic decompensation. They needed two or three efforts of weaning from CPB support before a satisfactory beating working state for 30 min was achieved to evaluate cardiac function. Right and left ventricles of the HH group were severely impaired; their stroke work indices reached approximately 30% of control value ($P = 0.004$ for LVSWI at LAP at 11 mmHg and $P = 0.008$ for RVSWI at CVP 11 mmHg). During the whole protocol nor inotropic agents neither vasoactive substances were used.

3.3. Coronary vascular resistance

The coronary perfusion flow varied between 80 and 140 ml min$^{-1}$. Coronary vascular resistance remained stable at hematocrit of 20–25% during the 30 min cold BCP/blood infusion (Fig. 4). CVRI fell 20% upon rewarming, and returned to the stable level throughout the remaining infusion interval of normal 37°C blood delivery.

Coronary perfusion with hematocrit of 40–45% at 50–60 mmHg raised (significantly for single comparisons but not significant in the Bonferroni-correction) CVRI 30–50% during the period of cold arrest. CVRI also fell approximately 20% upon rewarming, followed thereafter by a moderate rise so that resistance rose again to approximately 50% during the last 15–30 min on CPB.
3.4. Systemic vascular resistance

The systemic vascular resistance increased (not significant in the Bonferroni-correction) throughout the duration of CPB by 25%. The SVRI of the HH group paralleled the LH group but exceeded it by 30%.

3.5. Myocardial oxygen consumption

All hearts consumed a similar amount of oxygen in the initial beating empty state on CPB (Fig. 5). The oxygen consumption fell at cold cardiac arrest. Rewarming caused augmented oxygen consumption. Hearts of the LH group consumed significantly \( P \leq 0.04 \) more oxygen than those of the HH group at the initial period of rewarming.

3.6. Creatine kinase release

A small myocardial CK release was similar in all hearts before aortic clamping (Fig. 6). Immediately after the beginning of warm blood perfusion CK rose significantly \( P = 0.03 \) more in the HH group than in the LH group.

3.7. Lactate metabolism

The absence of lactate production in both groups was in accord with the non-ischemic protocol except for a slight production of the HH group at the beginning of CPB before aortic clamping (Fig. 7).

3.8. Myocardial water content

The ventricular water content of the LH group was slightly increased for the left ventricle and moderately increased for the right ventricle at the end of the study (Fig. 8). Hearts of the HH group developed marked ventricular edema \( P = 0.005 \) for LV and \( P = 0.003 \) for RV, each versus controls.

At the end of warm blood perfusion hearts of the LH group nearly returned to the small basic release in contrast to an increasing release of the HH group \( P = 0.008 \).
4. Discussion

The present investigation confirms the safety of cold blood cardioplegia and subsequent cold continuous blood with hematocrit of 20–25% for cardiac arrest [4]. Our findings also show a disadvantage of this protocol if hematocrit is raised to 40%. These data include a rise of coronary and systemic vascular resistance, impaired oxygen utilization when warm blood is restored, creatine kinase release, edema formation, and reduced left and right ventricular function despite continuous perfusion through the period of aortic clamping.

Concern over blood related problems has led to the use of crystalloid prime in the cardiopulmonary bypass circuit to lower hematocrit to 20% and measures to restore hematocrit before sternal closure [8,15]. Continuous coronary perfusion with oxygenated blood (hematocrit 20–25%) and a flow rate of 100 ml min\(^{-1}\) delivers approximately 10 ml O\(_2\) min\(^{-1}\). This covers the oxygen requirement of arrested hypothermic hearts, which is only 0.3 ml min\(^{-1}\) 100 g\(^{-1}\) [16]. Lactate was not produced in accord with the non-ischemic protocol. The abrupt onset of oxygen utilization of the hearts perfused with low hematocrit blood after restoration of warm blood shows a working metabolism of the myocytes when electro-mechanical activity started. In contrast, hearts perfused with high hematocrit blood utilized less oxygen at that time possibly as a result of an impaired metabolism of non-protected myocytes. This is surprising, as a positive correlation between myocardial oxygen consumption and the hematocrit value [17] or oxygen delivery [18] is known. This correlation may be due to Gregg’s phenomenon, i.e. cardiac oxygen consumption and contractile strength are changed by coronary perfusion [19], or the Anrep effect, i.e. the inotropic response to change in afterload. Some of the hearts perfused with high hematocrit blood developed electro-mechanical activity already during the cold continuous perfusion. We suspect continuous coronary perfusion with high hematocrit cold blood causing regional maldistribution of perfusion as subendocardial hypoperfusion with recurrent electro-mechanical activity, with subsequent adverse biochemical and functional results.

Coronary perfusion with high hematocrit blood resulted in a marked rise of the coronary resistance. The vascular resistance is dependent on the pressure, flow rate, viscosity [6] and hematocrit [7] of the perfused fluid. The low hematocrit blood perfusion resulted in a nearly constant resistance index, except for temporary changes due to myocardial rewarming (temperature induced vasodilation and autoregulation) and subsequent start of beating (increased vascular resistance at a contraction phase). In contrast, high hematocrit blood perfusion resulted in a continuously increasing resistance index, being finally 70% higher than that of low hematocrit blood perfused hearts. The detrimental biochemical and functional effects of perfusion with cold blood with hematocrit 40–45% were not initially apparent, as the increased coronary vascular resistance could also be caused by raised oxygen delivery, increased shear stress or subsequent coronary vasoconstriction. Subsequent observations, however, show that the myocardium was inadequately protected as creatine kinase rose, edema formed, and left and right ventricular function was impaired, when findings were compared to control and hematocrit 20% studies. Clearly, the triple combination of hypothermia, high hematocrit and artificial perfusion is dangerous as one or two of these conditions alone is not detrimental: hypothermia is a classic and widespread method for myocardial protection [2,20], high (45%) hematocrit blood is a physiologic perfusate with sufficient oxygen transport capacity and works as a hyperosmolaric medium, and artificial coronary perfusion with adequate flow and pressure range is safely performed everywhere. The combination of hypothermia and high hematocrit increases the viscosity of blood. This increased viscosity can result in regional hypoperfusion and subsequent ischemia related consequences such as the release of creatine kinase and the generation of arrhythmias. High hematocrit blood cannot be accused of the formation of myocardial edema unless the perfusion is traumatic and damages the vascular barrier. In the present study, during aortic clamping coronary perfusion was applied to the aortic root in a limited flow and pressure range. Its safety is known for intermittent application of cardioplegic and cardioprotective perfusates [21]. The artificial character of the iatrogenically adjusted flow and pressure condition may have hindered coronary autoregulation of the vascular tone, although flow and pressure were continuously determined and its safe value was respected. A subsequent non-physiologic dyscorrelation of flow and pressure forces on the coronaries plus a hypoperfusion during CPB on adults suffering from coronary artery disease [8,15,22] and children and neonates with congenital heart disease [23]. Several successfully treated cases are reported in which more extreme hemodilutions down to 19% [8], 15% [17] and 10.5% [23] were applied, although hemodilution down to 15% is reported elsewhere to result in an impaired gas exchange function [24].

We conclude that continuous perfusion of cold blood cardioplegia followed by blood at 6°C is safe if hematocrit is kept between 20 and 25%. This accords with the positive clinical experience of low hematocrit (down to 20%) perfusion during CPB on adults suffering from coronary artery disease [8,15,22] and children and neonates with congenital heart disease [23]. Several successfully treated cases are reported in which more extreme hemodilutions down to 19% [8], 15% [17] and 10.5% [23] were applied, although hemodilution down to 15% is reported elsewhere to result in an impaired gas exchange function [24].

Conversely, continuous infusion techniques of cold blood cardioplegia followed by cold blood in a system with a low prime perfusion (i.e. high hematocrit) should be applied carefully in order not to jeopardize the heart: cold blood with a normal to high-range hematocrit (45%) should not be used in this strategy whereby coronary perfusion with
blood and blood cardioplegia is maintained throughout the operation.

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References