Hypothermic Low-Flow Cardiopulmonary Bypass Impairs Pulmonary and Right Ventricular Function More Than Circulatory Arrest

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Background. Hypothermic circulatory arrest (HCA) is used during surgical treatment of certain congenital heart defects. The possibility of ischemic neurologic injury associated with HCA has led some surgeons to use low-flow cardiopulmonary bypass (CPB) during the hypothermic interval (hypothermic low flow [HLF]). This study investigates the inflammatory response to HCA and HLF, and reports the consequences of this response on pulmonary and right ventricular function.

Methods. Piglets (3.1 to 6.6 kg) were cooled to 16° to 18°C using CPB, and randomized: HCA for 60 minutes (n = 7), or HLF (50 cc · kg⁻¹ · min⁻¹) for 60 minutes (n = 6). The piglets were rewarmed to 36°C and weaned from CPB. Serum tumor necrosis factor-alpha (TNF-α) concentration, percent lung water, and pulmonary and cardiac function were measured before and after CPB.

Results. Tumor necrosis factor-alpha was higher after HLF (2,990.5 ± 884.5 pg/mL), compared with HCA (347.6 ± 89.2 pg/mL; p = 0.03). The percent lung water was higher after HLF (84.8% ± 0.3%) than HCA (82.0% ± 0.4%; p < 0.001). The alveolar to arterial oxygen gradient was worse after HLF (457 ± 42 mm Hg) than HCA (285.8 ± 45 mm Hg; p = 0.02). Pulmonary vascular resistance was greater after HLF (36.08 ± 8.28 mm Hg · mL⁻¹ · m⁻² · min⁻¹) than HCA (14.55 ± 3.46 mm Hg · mL⁻¹ · m⁻² · min⁻¹; p = 0.049). The right ventricular pressure waveform peak derivative, corrected for systolic pulmonary artery pressure, was lower after HLF (14.1 ± 1.4 sec⁻¹), than HCA (23.8 ± 2.7 sec⁻¹; p = 0.01).

Conclusions. Hypothermic low flow extends exposure to CPB, and is associated with an increased inflammatory response compared with HCA. The greater inflammatory response after HLF may result in substantial nonneurologic morbidity in the postoperative period, demonstrated by pulmonary and right ventricular dysfunction. Interventions that attenuate the inflammatory response to CPB may prevent pulmonary and right ventricular dysfunction after HLF.


Hypothermic circulatory arrest (HCA) is used for the repair of certain complex congenital heart defects. Concerns for increased neurologic morbidity with prolonged periods of circulatory arrest have led some surgeons to use hypothermic low-flow cardiopulmonary bypass (HLF) as an alternative to HCA [1]. However, ongoing exposure to the cardiopulmonary bypass circuit during the hypothermic period occurs with HLF, but not with HCA.

Exposure to cardiopulmonary bypass (CPB) results in contact activation of the cellular and humoral inflammatory pathways, as well as tissue ischemia and reperfusion injury [2]. These events result in activation of the kinin-kallikrein, complement, and fibrinolytic cascades, which induce a systemic inflammatory response that is associated with reduced cardiac and pulmonary function after CPB [3–5]. Postulated mechanisms for this decrease in function include the induction of vasoactive substances as well as increased capillary permeability resulting in the accumulation of fluid in body tissues [5–7].

It is unknown whether the relative increase in CPB exposure during an intermediate length hypothermic interval in HLF compared with HCA is of clinical significance [8]. This study was designed to measure the fluid balance, pulmonary, and cardiac consequences of exposure to an intermediate interval of either HLA or HCA in an infant pig model.

Material and Methods

Infant piglets (3 to 5 weeks old, weighing 3.1 to 6.6 kg) were studied with approval from the Oregon Health...
and Sciences Universities’ Institutional Animal Care and Use Committee. All animals received humane care in compliance with the “Guide for the Care and Use of Laboratory Animals” (NIH publication 85-23, revised 1985). The piglets were premedicated with intramuscular Telozole (8 mg/kg) and weighed to the nearest 10 grams. Body surface area was then calculated using the Mostellar formula: BSA = [(length in cm from crown of head to tail base) · (weight in kg) · 3,600]^{1/2}. A bolus of fentanyl citrate (100 µg/kg) was administered through ear vein access. A surgical tracheostomy was performed, and then anesthesia was maintained with inhaled isoflurane (1.0%) and an intravenous fentanyl citrate infusion (100 µg/H). Ventilation, used oxygen as a carrier gas, with an infant volume cycled ventilator (Harvard Apparatus, Boston, Massachusetts) to keep peak inspiratory pressures less than 25 mm Hg and a positive end expiratory pressure of 5 mm of Hg. The fraction of inspired oxygen (FiO_{2}) during ventilation was 100%. An arterial partial pressure of carbon dioxide (PaCO_{2}) of 35 to 45 mm Hg was obtained by adjusting minute ventilation or the rate of the sweep gas of the CPB circuit.

A catheter inserted into the femoral artery and advanced into the descending thoracic aorta was used for arterial blood pressure and blood gas monitoring. A femoral vein catheter, advanced into the right atrium, was used for right atrial pressure monitoring, as well as blood draws for serum TNF-α. The heart was exposed through a median sternotomy, and an ultrasonic flow probe (Transonic Systems, Ithaca, New York) was positioned around the main pulmonary artery to measure right ventricular output. A silicone elastomer catheter was inserted into the main pulmonary artery, distal to the ultrasonic flow probe, to measure pulmonary artery pressures. A silicone elastomer catheter was inserted through the left atrial appendage, for left atrial pressure measurement. A high-fidelity pressure transducer (Konigsberg Instruments, Pasadena, California) was placed in the right ventricular chamber through the right ventricular free wall. A fluid-filled silicone elastomer catheter was also placed in the right ventricle through the free wall to serve as a reference catheter for the Konigsberg transducer. Dynamic pulmonary compliance (C_{d,y}) was measured with the ventilator circuit disconnected from the tracheostomy. The functional residual capacity of the piglet’s lungs was achieved passively. A manual driven syringe was then connected in parallel to the tracheostomy and a mercury manometer. The syringe was used to deliver incremental inspiratory volumes of 20 cc (range, 20 cc to 100 cc), while simultaneous pressure measurements (converted from mm Hg to mm H2O) were obtained. The C_{d,y} was calculated as a mean value of the volume versus pressure measurements. Core body temperature was monitored with simultaneous rectal and nasopharyngeal temperature probes.

An enzyme-linked immunosorbent assay (ELISA) porcine cytokine kit (R&D Systems, Minneapolis, Minnesota) was used to assay the serum concentration of TNF-α at three time points. The sensitivity of the ELISA kit was 2.8 to 5.0 pg/mL, and the range for the standards was from 0 to 1,500 pg/mL. Serum samples with concentrations greater than 1,500 pg/mL were diluted in deionized water at 1 to 2, and 1 to 5 dilutions, to measure serum concentrations.

Cardiopulmonary Bypass

The extracorporeal circuit included a nonpulsatile Cobe Century roller pump (Cobe, Denver, Colorado), an infant Cobe Micro oxygenator and venous reservoir (Cobe), a 20-cc in-line arterial filter, and ⅛-inch arterial and ½-inch venous tubing. (Terumo Medical, Somerset, New Jersey). The circuit was primed with fresh, heparinized, whole blood obtained from donor adult pigs. The primed circuit also included 400 µg of fentanyl citrate and sodium bicarbonate to achieve a pH of 7.40. After instrumentation and baseline data acquisition the piglets received intravenous heparinization (500 U/kg), to maintain the kaolin activated clotting time greater than 480 seconds. A 10F arterial cannula and 22F venous cannula were inserted into the aortic root and right atrial appendage, respectively, through pursestring sutures. Normothermic CPB was established at a rate of 100 mL · kg^{-1} · min^{-1}. Mechanical ventilation was stopped. The animal was perfusion cooled to 18°C using pH-stat blood gas management. Hypothermic CPB (at 100 mL · kg^{-1} · min^{-1}) was maintained for 20 minutes, and then the animal was randomized into one of two groups: (1) in group HCA (n = 7), cardiopulmonary bypass was stopped, the animal was exanguinated into the cardiomy reservoir, and the heart was packed in ice. After 60 minutes of hypothermic circulatory arrest, CPB was resumed and rewarming was initiated. (2) For group HLF (n = 6), hypothermic cardiopulmonary bypass was maintained at 50 mL · kg^{-1} · min^{-1} and the heart was packed in ice. After 60 minutes of hypothermic low-flow CPB, flows were returned to normal and rewarming was initiated.

Mechanical ventilation, using the pre-CPB settings, was resumed at the start of rewarming. All animals were rewarmed using cardiopulmonary bypass at 100 mL · kg^{-1} · min^{-1} to 36°C over a minimum of 30 minutes, using alpha-stat blood gas management. Arterial pressures were allowed to drift. The animals were weaned from CPB.

Data Collection

Blood for serum TNF-α was drawn at three time points: baseline before CPB, immediately before weaning from hypothermia, and immediately before weaning from CPB. Data from arterial blood gas, pulmonary and cardiac function were obtained at two time points: baseline before CPB, and at 5 to 10 minutes after weaning from CPB. Pressure and flow data were sampled and digitalized at 350 Hz over 10 to 15 seconds using Sonometrics software (Sonometrics, London, Ontario), while the animals were held at end expiration. The animals were euthanized and weighed to the nearest 10 g to determine end body weight. An autopsy was performed to look for the presence of any cardiac abnormalities.
Results

As a result of the experimental period of hypothermic CPB, the exposure time to CPB was higher in the HLF group as compared with the HCA group (Fig 1). Similarly, prolonged exposure to the CPB circuit was accompanied by increased serum TNF-α concentrations in the HLF group (Fig 2). At baseline, the animal weights for the HCA (4.69 ± 0.49 kg) and HLF (5.52 ± 0.22 kg) groups were similar. At the end of the experiment, the mean animal weight of the HCA (4.97 ± 0.54 kg) and HLF group (5.97 ± 0.25 kg) were not different. However, at the end of the experiment, the percent increase in weight in the HLF group (9.7% ± 1.5%) was higher than that of the HCA group (5.8% ± 2.9%; p = 0.01). Similarly after cardiopulmonary bypass, the percent of lung weight that was water was higher for the HLF group (84.8% ± 0.3%), than the HCA group (82.0% ± 0.4%; p < 0.001). Dynamic arterial oxygen gradient (mean of HCA estimated at 200 mm Hg, with an expected SD of 50 mm Hg) [9], and α = 0.05, and β = 0.80, the study required 6 animals in the control and 6 animals in the experimental groups to obtain significance with p less than 0.05. (Sigma Stat; SPSS, Chicago, Illinois) All data are expressed as mean ± SEM. Student’s paired t test was used to compare the means of data within groups between the baseline and post-CPB. Student’s unpaired t test was used to compare the means of data between the HCA and HLF groups at both baseline and post-CPB. A value of p less than 0.05 is considered significant.

Data Analysis

Before initiation of this study, a power calculation was performed: to observe a 50% increase in alveolar to arterial oxygen gradient (mean of HCA estimated at 200 mm Hg, with an expected SD of 50 mm Hg) [9], and α = 0.05, and β = 0.80, the study required 6 animals in the control and 6 animals in the experimental groups to obtain significance with p less than 0.05. (Sigma Stat; SPSS, Chicago, Illinois) All data are expressed as mean ± SEM. Student’s paired t test was used to compare the means of data within groups between the baseline and post-CPB. Student’s unpaired t test was used to compare the means of data between the HCA and HLF groups at both baseline and post-CPB. A value of p less than 0.05 is considered significant.

Peripheral lung specimens, weighing 1 to 2 g were taken from the anterior right middle lobe of each animal. To calculate the lung water content, the lung tissue was weighed fresh, and then desiccated in a warming oven at 60°C for 72 hours, before being reweighed dry.

Measured data included arterial pH, arterial partial pressure of oxygen (PaO₂), PaCO₂, hematocrit, Cdyn, arterial blood pressure, heart rate, left atrial pressure (LAP), right atrial pressure (RAP), right ventricular pressure (RVP), pulmonary artery pressure (PAP), pulmonary artery flow, and the derivative of the right ventricular pressure wave form (RV DP/dt). Calculated data include the following:

- Percent weight gain / body weight = (post-CPB weight - pre-CPB weight) · 100 / pre-CPB weight
- Percent lung water = (post-CPB lung weight - post-desiccation lung weight) · 100 / post-CPB lung weight
- Alveolar to arterial oxygen gradient (A-a gradient [in mm Hg]) = [FiO₂ · (Patmosphere – 47 mm Hg)] – (PaO₂ – PaCO₂)
- Cardiac index (CI [in cc · kg⁻¹ · min⁻¹]) = pulmonary artery flow per minute / pre-CPB weight
- Pulmonary vascular resistance index (PVRI [in mm Hg · mL⁻¹ · m⁻2 · min⁻¹]) = [(mean PAP – LAP) / pulmonary artery flow / body surface area]
- Peak derivative of the right ventricular wave form corrected for the peak systolic pulmonary artery pressure (RV DP/dt · PAPs⁻¹) = [maximum RV DP/dt] / systolic PAP

Data Analysis

Before initiation of this study, a power calculation was performed: to observe a 50% increase in alveolar to arterial oxygen gradient (mean of HCA estimated at 200 mm Hg, with an expected SD of 50 mm Hg) [9], and α = 0.05, and β = 0.80, the study required 6 animals in the control and 6 animals in the experimental groups to obtain significance with p less than 0.05. (Sigma Stat; SPSS, Chicago, Illinois) All data are expressed as mean ± SEM. Student’s paired t test was used to compare the means of data within groups between the baseline and post-CPB. Student’s unpaired t test was used to compare the means of data between the HCA and HLF groups at both baseline and post-CPB. A value of p less than 0.05 is considered significant.
pulmonary compliance was similar at baseline for the HCA (4.26 ± 0.62 cc/cm H2O) and HLF (4.60 ± 0.82 cc/cm H2O) groups. After weaning from cardiopulmonary bypass, the dynamic pulmonary compliance decreased within both the HCA (3.04 ± 0.37 cc/cm H2O, p = 0.016) and HLF groups (2.5 ± 0.12 cc/cm H2O, p = 0.001), but was not different between groups. The arterial blood gas values for the HCA and HLF groups before and after cardiopulmonary bypass are listed in Table 1.

The decrease in PaO2 from baseline to post-CPB led to substantial decreases in the A-a gradient in both the HLF and HCA groups, but this effect was much more pronounced in the HLF group. The measured hemodynamic values are listed in Table 2. After weaning from CPB the pulmonary artery pressures were higher in both the HLF and HCA groups when compared with baseline; however, the post-CPB pulmonary artery pressures were higher in the HLF, compared with the HCA group. The elevation in pulmonary artery pressures after CPB led to an increase in the post-CPB pulmonary vascular resistance in both the HLF and HCA groups, which was markedly elevated for the HLF group. In the HLF group, but not the HCA group, the increased pulmonary vascular resistance was accompanied by reduced right ventricular contractility, as measured by the derivative of the right ventricular pressure wave form corrected for peak systolic pulmonary artery pressure.

Table 1. Arterial Blood Gas Measurements in All Animals, Before and After Cardiopulmonary Bypass

<table>
<thead>
<tr>
<th>Value</th>
<th>Group</th>
<th>Baseline</th>
<th>End Experiment</th>
</tr>
</thead>
<tbody>
<tr>
<td>PH (mm Hg)</td>
<td>HCA</td>
<td>7.41 (± 0.04)</td>
<td>7.41 (± 0.05)</td>
</tr>
<tr>
<td></td>
<td>HLF</td>
<td>7.45 (± 0.02)</td>
<td>7.36 (± 0.04)</td>
</tr>
<tr>
<td>PaCO2 (mm Hg)</td>
<td>HCA</td>
<td>33.4 (± 3.7)</td>
<td>33.4 (± 3.7)</td>
</tr>
<tr>
<td></td>
<td>HLF</td>
<td>33.4 (± 3.7)</td>
<td>33.4 (± 3.7)</td>
</tr>
<tr>
<td>PaO2 (mm Hg)</td>
<td>HCA</td>
<td>314 (± 43)a</td>
<td>162 (± 41)ab</td>
</tr>
<tr>
<td></td>
<td>HLF</td>
<td>501 (± 30)</td>
<td>162 (± 41)ab</td>
</tr>
<tr>
<td>A-a gradient (mm Hg)</td>
<td>HCA</td>
<td>285.8 (± 45.0)</td>
<td>285.8 (± 45.0)</td>
</tr>
<tr>
<td></td>
<td>HLF</td>
<td>457.4 (± 42.0)</td>
<td>457.4 (± 42.0)</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>HCA</td>
<td>31.1 (± 1.6)</td>
<td>31.1 (± 1.6)</td>
</tr>
<tr>
<td></td>
<td>HLF</td>
<td>32.8 (± 1.6)</td>
<td>32.8 (± 1.6)</td>
</tr>
</tbody>
</table>

*a p < 0.05, paired t test within group, end experiment versus baseline.

*b p < 0.05, unpaired t test between groups, HLF versus HCA.

A-a gradient = alveolar to arterial oxygen gradient; CPB = cardiopulmonary bypass; HCA = group hypothermic circulatory arrest; HLF = group hypothermic low flow; PaCO2 = arterial partial pressure of carbon dioxide; PaO2 = arterial partial pressure of oxygen.

Table 2. Hemodynamic Values for All Animals, Before and After Cardiopulmonary Bypass

<table>
<thead>
<tr>
<th>Value</th>
<th>HCA</th>
<th>Baseline</th>
<th>Post-CPB</th>
<th>HLF</th>
<th>Baseline</th>
<th>Post-CPB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right atrial pressure (mm Hg)</td>
<td></td>
<td>7.7 (± 1.4)</td>
<td>9.3 (± 2.9)</td>
<td></td>
<td>4.7 (± 0.7)</td>
<td>12.4 (± 1.8)*</td>
</tr>
<tr>
<td>Right ventricular pressure (mm Hg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td></td>
<td>18.1 (± 1.6)</td>
<td>25.5 (± 2.5)*</td>
<td></td>
<td>19.3 (± 2.4)</td>
<td>30.9 (± 1.8)*</td>
</tr>
<tr>
<td>Diastolic</td>
<td></td>
<td>4.5 (± 0.8)</td>
<td>7.4 (± 2.1)</td>
<td></td>
<td>3.6 (± 0.9)</td>
<td>8.0 (± 2.0)</td>
</tr>
<tr>
<td>Mean</td>
<td></td>
<td>9.7 (± 1.0)</td>
<td>10.8 (± 1.2)*</td>
<td></td>
<td>15.9 (± 2.2)</td>
<td>20.6 (± 1.5)*</td>
</tr>
<tr>
<td>Pulmonary artery pressure (mm Hg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td></td>
<td>16.2 (± 2.0)</td>
<td>23.6 (± 2.3)*</td>
<td></td>
<td>14.2 (± 1.1)</td>
<td>33.3 (± 3.2)*</td>
</tr>
<tr>
<td>Diastolic</td>
<td></td>
<td>7.8 (± 1.1)</td>
<td>13.6 (± 2.1)*</td>
<td></td>
<td>8.4 (± 1.2)</td>
<td>24.5 (± 2.6)*</td>
</tr>
<tr>
<td>Mean</td>
<td></td>
<td>10.8 (± 1.0)</td>
<td>19.6 (± 2.2)*</td>
<td></td>
<td>11.3 (± 1.2)</td>
<td>28.0 (± 2.8)*</td>
</tr>
<tr>
<td>Left atrial pressure (mm Hg)</td>
<td></td>
<td>8.9 (± 0.8)</td>
<td>7.9 (± 1.1)</td>
<td></td>
<td>5.1 (± 0.9)</td>
<td>5.1 (± 1.0)</td>
</tr>
<tr>
<td>Aortic pressure (mm Hg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td></td>
<td>57.7 (± 3.3)</td>
<td>52.9 (± 5.4)</td>
<td></td>
<td>56.5 (± 2.6)</td>
<td>41.5 (± 5.5)</td>
</tr>
<tr>
<td>Diastolic</td>
<td></td>
<td>37.3 (± 1.4)</td>
<td>31.1 (± 4.1)</td>
<td></td>
<td>34.9 (± 1.3)</td>
<td>23.9 (± 2.7)*</td>
</tr>
<tr>
<td>Mean</td>
<td></td>
<td>46.2 (± 1.9)</td>
<td>40.0 (± 4.5)</td>
<td></td>
<td>44.0 (± 1.8)</td>
<td>30.4 (± 4.1)*</td>
</tr>
<tr>
<td>Cardiac index (cc · min⁻¹ · kg⁻¹)</td>
<td></td>
<td>1.40 (± 0.01)</td>
<td>1.26 (± 0.19)</td>
<td></td>
<td>1.79 (± 0.16)b</td>
<td>0.73 (± 0.12)ab</td>
</tr>
<tr>
<td>Pulmonary vascular resistance index (mm Hg · ml⁻¹ · m⁻² · min⁻¹)</td>
<td></td>
<td>1.6 (± 0.2)</td>
<td>14.9 (± 3.5)a</td>
<td></td>
<td>3.5 (± 0.8)</td>
<td>36.1 (± 8.3)ab</td>
</tr>
<tr>
<td>[RV DP/dt] · sPAP⁻¹ (in seconds⁻¹)</td>
<td></td>
<td>20.6 (± 0.19)</td>
<td>23.8 (± 2.7)</td>
<td></td>
<td>28.4 (± 4.7)</td>
<td>14.1 (± 1.4)ab</td>
</tr>
</tbody>
</table>

*a p < 0.05, paired t test within group, end experiment versus baseline.

*b p < 0.05, unpaired t test between groups, HLF versus HCA.

CPB = cardiopulmonary bypass; HCA = hypothermic circulatory arrest group; HLF = hypothermic low flow group; [RV DP/dt] · sPAP⁻¹ = peak derivative of the right ventricular pressure waveform corrected for the peak systolic pulmonary artery pressure.

Comment

Currently, many centers use some method of continuous perfusion during the surgical treatment of congenital heart defects. These methods may avoid neurologic morbidity associated with prolonged episodes of circulatory arrest [1, 10]. However, use of continuous perfusion strategies will extend the patient’s exposure to CPB [8, 11].
It is widely accepted that exposure to CPB activates the immune system resulting in a systemic inflammatory response [6]. This response can manifest clinically as capillary leak syndrome, positive fluid balance, total body weight gain, and pulmonary edema [7]. Prolonged HLF bypass has been associated with reduced pulmonary function and increased body weight and fluid balance, when compared with HCA [9, 11]. Controversy exists regarding the clinical significance of the prolonged exposure to hypothermic cardiopulmonary bypass that occurs with continuous perfusion strategies [8]. For example, several reports demonstrate less weight gain in patients undergoing HCA opposed to HLF [1, 8, 10]. However, others have suggested that the increased weight gain after HLF is not associated with loss of hemodynamic function, duration of mechanical ventilation, or length of stay in the intensive care unit or hospital, when compared with HCA [8]. The results of these studies do not necessarily reflect the natural history of cardiac or pulmonary function after exposure to HCA or HLF [8]. This study was performed to examine the cardiac, pulmonary, and systemic effects of HCA versus HLF in an infant piglet model.

In this animal model, HLF resulted in nearly twice the exposure time to CPB when compared with HCA. In addition, HLF resulted in a substantial elevation in serum TNF-α, during the hypothermic period, which increased further after rewarming. This is contrasted to the HCA group, where only modest increases in serum TNF-α occurred after the hypothermic circulatory arrest period. Although this study documents an increase in serum TNF-α, it does not presume that this mediator is the progenitor or common pathway for systemic inflammatory response syndrome (SIRS) related organ dysfunction. Rather, the increase in serum TNF-α is likely an indicator that up-regulation of the inflammatory system is occurring. A recent report by Tassani and colleagues [11] compared the systemic inflammatory response resulting from exposure to either HCA or HLF in 23 infants. In this study, the infants exposed to HLF had higher levels of proinflammatory mediators, including anaphylatoxin C3a and interleukin-8, in the perioperative period. One explanation for these findings may be that the continued exposure to CPB seen with HLF results in ongoing and cumulative activation of the immune system. It has been demonstrated that the degree of inflammatory response can be correlated to the length of exposure to CPB [12]. Further, profound hypothermia during CPB appears to influence leukocyte activation and TNF-α concentration [13, 14]. The combination of these two conditions, hypothermia and cardiopulmonary bypass, may result in an exaggerated inflammatory response.

In this experiment, significant deteriorations in several clinical variables accompanied the increased TNF-α expression in the HLF group. Exposure to either HLF or HCA resulted in increased body weight, although this change was greater in the HLF group. Further, the lung water weight was also greater in the HLF group than the HCA group. These findings corroborate other human studies and animal-based experiments that demonstrate that a net fluid shift into the interstitium occurs after exposure to CPB [8, 11, 15]. This net movement of water into body tissue may result from two mechanisms. First, proinflammatory mediators result in capillary leak, and the extravasation of protein rich fluid into the interstitium [7]. Other evidence indicates that hypothermic CPB results in a shift of fluid and small solutes, from the vascular to the interstitial space, to a greater degree than normothermic CPB [16]. The movement of small solutes into the interstitium may occur through a mechanism which is independent from inflammatory mediated capillary leak. Tissue water accumulation may be greater after HLF compared with HCA because of the combination of hypothermia and ongoing exposure to cardiopulmonary bypass. The increase in tissue water content may explain, in part, the relative increase in organ dysfunction seen after exposure to HLF.

An alternative explanation for the organ dysfunction seen after HLF could be a direct effect of the inflammatory mediators on the heart and lungs. Cardiopulmonary bypass has been shown to increase the production of vasoactive substances that result in pulmonary vasconstriction, reduced pulmonary microvascular reactivity, and reduced pulmonary compliance independent of lung water content [17, 18]. Additionally, both activated complement proteins and inflammatory interleukins have been implicated in impaired left ventricular function, reduced myocardial contractility, and cardiac myocyte injury [19, 20]. In our study, HLF was associated with worse pulmonary function, pulmonary vascular resistance, and cardiac output when compared with HCA. It is unclear if the decline in right ventricular contractility resulted from a direct inhibition of myocyte contractility, or rather an increase in right ventricular strain resulting from elevated pulmonary vascular resistance. Regardless, it appears that HLF can have greater clinical consequences, than HCA. This may have important clinical implications for procedures in which postoperative ventilation and cardiac output management (e.g., Norwood procedures for hypoplastic left heart syndrome). The impairment to pulmonary and ventricular function after HLF could adversely affect outcome.

It is important to note that the only difference in the experimental protocol between the two groups was the one hour period when one group was exposed to HCA and the other to HLF. If CPB or hypothermia were the major responsible factors, we would have expected to see similar values for each group, as they were both exposed to profound cooling and a period of rewarming on CPB. It may be possible that the combination of HLF and hypothermia are more injurious than the period of normal flow CPB used for cooling and rewarming. It may also be possible that there is a critical CPB exposure period that is exceeded in the HLF group and not in the HCA group. Answers to these questions will require further investigation.

An additional group undergoing hypothermic cardiopulmonary bypass at 100 cc · kg⁻¹ · min⁻¹ during the 1-hour period might have further differentiated the effects of hypothermia from low-flow cardiopulmonary
bypass. Secondly, although an assay of the proinflammatory cytokine TNF-α is reported, other mediators, including down regulators of the immune system such as interleukin-10, were not obtained. It is possible that increases in serum TNF-α were accompanied by increases in the serum concentrations of anti-inflammatory cytokines, which would tend to maintain capillary integrity and preserve organ function, especially in the HCA group. That would be an interesting explanation, if it occurred, to explain the better outcomes for the HCA animals. Thirdly, no microscopic or molecular investigation of pulmonary or right ventricular injury was obtained that could identify the mechanism underlying the organ dysfunction measured in this study. Finally, the time course after exposure to cardiopulmonary bypass is limited. It is possible that at further time points after weaning from cardiopulmonary bypass, the serum concentrations of TNF-α in the HCA and HLF groups could be comparable. In addition, at these extended time points, the differences in pulmonary and cardiac function between the two groups could be minimal. Regardless, the results of this study indicate that an exaggerated activation of the immune system with a relative decrease in cardiac and pulmonary function may be present after exposure to HLF, compared with HCA.

These consequences may be prevented by interventions that attenuate the inflammatory response to either cardiopulmonary bypass or hypothermia. First, pharmacologic agents that down-regulate the inflammatory response to cardiopulmonary bypass, such as methylprednisolone or aprotinin, might also prevent organ dysfunction after HLF [21, 22]. Secondly, pharmacologic agents that directly block the activity of inflammatory mediators, such as complement receptor antagonists, may also help prevent organ dysfunction [19, 23]. Biocompatible CPB components, such as heparin-bonded circuits, could be another method to reduce the systemic inflammatory response after HLF and HCA [24]. Finally, ultrafiltration techniques may remove excess cytokines and limit the deleterious effects of these proinflammatory mediators [25, 26].

In summary, this study demonstrates that HLF extends the exposure to CPB during hypothermic conditions, compared with HCA. Similarly, HLF results in increased serum TNF-α and decreased pulmonary and right ventricular function when contrasted to HCA. The use of HLF in congenital heart surgery may result in significant nonneurologic morbidity in the postoperative period when compared with HCA. Interventions that attenuate the inflammatory response may preserve right ventricular and pulmonary function after exposure to hypothermic cardiopulmonary bypass.

We thank Michael Gravett, MD, for his assistance in completing the serum TNF-α assays.

References


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DISCUSSION

DR J. WILLIAM GAYNOR (Philadelphia, PA): Doctor Gaynor, Dr Murray, I would like to congratulate Dr Schultz and his colleagues on an excellent and important study. There is no topic in congenital heart surgery that arouses greater controversy than the ongoing debate concerning the use of deep hypothermic circulatory arrest as well as hypothermic low-flow cardiopulmonary bypass. As noted by Dr Schultz, the risk of central nervous system (CNS) injury in the early postoperative period. A recent report from the Boston Circulatory Arrest Trial demonstrated that longer duration of intensive care unit stay after surgery is associated with an increased incidence of cerebral white matter injury, characterized by periventricular leukomalacia, in neonates undergoing cardiac surgery. Interestingly, longer bypass times were a risk factor for an increased incidence of injury, however, the use of deep hypothermic circulatory arrest was not. The strongest predictors were hypoxia and hypotension in the early postoperative period. A recent report from the Boston Circulatory Arrest Trial demonstrated that longer duration of intensive care unit stay after surgery is associated with an increased risk of neurodevelopmental problems at 8 years of age. Thus, a bypass strategy which increases the risk of organ dysfunction and increases postoperative morbidity may increase the risk of central nervous system (CNS) injury in the early postoperative period. Use of bypass, as noted by Dr Schultz, elicits an intense inflammatory response, which may result in organ dysfunction of the heart, the brain, the lungs, and other organs.

In the current study, the authors have demonstrated that the intensity of this inflammatory response is exacerbated by the use of continuous low-flow bypass as compared with deep hypothermic circulatory arrest. They have demonstrated that continuous low-flow bypass is associated with an increased incidence of cardiac and pulmonary dysfunction. In addition, there is an increase in total body water. These findings are consistent with those of previous studies. In addition to producing cardiac and pulmonary dysfunction, elevated levels of inflammatory cytokines, such as TNF-α, may result in CNS injury. In addition, organ dysfunction induced by the inflammatory response may lead to hypoxia and hypotension in the postoperative period, further exacerbating the CNS injury.

This study demonstrates that we have much to learn about the mechanisms of brain and other organ injury during cardiopulmonary bypass, and that the decision is not a simple choice between the use or nonuse of deep hypothermic circulatory arrest.

I have two questions for the authors. Do they have any data concerning the effect of this enhanced inflammatory response on brain injury in their model? How have the findings of this study changed their use of continuous bypass and circulatory arrest in their clinical population and how do they choose the optimal bypass strategy for a particular patient? I would like to thank the Society for the privilege of discussing this paper.

DR SCHULTZ: Thank you for your comments, Dr Gaynor. Regarding the first question, unfortunately, this study did not entail systematic evaluation of possible neurologic injury related to elevated cytokine levels.

Regarding the second question, there has been a modification in the method of brain protection during hypothermia at Oregon Health and Sciences University, specifically, a combination between circulatory arrest and low-flow perfusion is used where an intermittent period of approximately 1 to 2 minutes of low-flow perfusion for every 15 minutes of circulatory arrest are utilized during the hypothermic period.

The rationale behind this is, one, we do want to provide some regional perfusion to the brain intermittently; and, two, we do want to minimize the overall exposure to the cardiopulmonary bypass circuit during the hypothermic period. We do have a later study that will be presented later today that will go into further detail about the cerebral metabolic requirements and demands under such a circumstance and compare it to both circulatory arrest as well as hypothermic low-flow cardiopulmonary bypass.