Changes of Microvascular Vasomotion and Oxygen Metabolism during Cooling and Rewarming Period of Cardiopulmonary Bypass

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Abstract: Microcirculation plays an important role in keeping a stable tissue metabolism during cardiopulmonary bypass (CPB). The relationship between microvascular vasomotion (MV) and total body’s oxygen metabolism with temperature alteration during CPB remains unclear. Is there a relationship, or is the autoregulation a consequence of CO₂ pressure and/or blood flow? The purpose of this study was to investigate the effect of temperature alteration on cutaneous MV and the total body’s oxygen metabolism during CPB.

Sixteen consecutive patients scheduled for elective cardiac valve replacement surgery were included in this study. The pump flow varied from 1.8–3.0 L/m²·min⁻¹ to maintain venous oxygen saturation above 65% and mean arterial blood pressure above 60 mmHg. At a nasopharyngeal temperature of 30°C, oxygen consumption (VO₂) and oxygen extraction (O₂ ext) were measured during the cooling and rewarming periods. MV and skin microcircular flow (SMF) were monitored dynamically at the middle of two sides of the eyebrow with a laser Doppler flowmeter simultaneously. VO₂ and O₂ ext at 30°C were significantly lower during the cooling period (VO₂, 49.9 ± 17.7 mL/m²·min⁻¹; O₂ ext, 19.3 ± 6.2%) than that during the rewarming period (VO₂, 133.3 ± 40.0 mL/m²·min⁻¹; O₂ ext, 35.2 ± 9.2%) (p < .05). SMF was significantly depressed during CPB (p < .05). SMF during the cooling period (50.2% ± 10.1%) was significantly less than that during the rewarming period (79.5% ± 12.3%) (p < .05). MV was significantly less active during CPB than that before CPB (5.8 ± 1.2 cyc/min) (p < .05), whereas there was no significant difference in MV between the cooling (3.7 ± 1.8 cyc/min) and the rewarming period (4.1 ± 1.5 cyc/min) and (p > .05). SMF and MV were depressed during hypothermic CPB, and there was some recovery during the rewarming period. Compared to baseline, SMF and MV were still significantly reduced during the warming period, indicating microvascular function was abnormal. Some measures should be taken for improvement of microvascular function during CPB.

Keywords: microvascular vasomotion, cardiopulmonary bypass, oxygen metabolism, temperature, perfusion.

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Cardiopulmonary bypass (CPB) involves several non-physiological conditions, such as hypothermia, nonpulsatile perfusion, and blood contacting with foreign materials, which lead to a series cascade of changes. These changes include reduction of erythrocyte deformability and various inflammatory reactions associated with dysfunction in major organs and in blood (1, 2). One of the most important things is to maintain tissue perfusion and avoid tissue ischemia during CPB. In addition to the hemodynamic effect, the status of microcirculation is important in regulating blood flow into the tissue. Microvascular vasomotion (MV) is a spontaneous contractile and relaxation that has no obvious relationship to cardiac or respiratory cycles. MV is key in maintaining sound function in hemodynamics. A normal functioning MV is responsible for the exchange of tissue fluid and formation of lymph (3). Microvascular disorder is also one of pathologic mechanisms of some diseases and symptoms. The relationship between MV and temperature alteration during CPB has not been elucidated. The purpose of this study was to investigate the effect of temperature alteration on cutaneous MV and total body’s oxygen metabolism during CPB.

MATERIALS AND METHODS

Patients

After Institution Review Board (IRB) approval and written informed consent were obtained, 16 consecutive patients (9 males and 7 females, aged from 34–50 years old, weighing from 51–74 kg) scheduled for elective car-
Heart valve replacement surgery were included in this study.

**Anesthesia Procedure**

Anesthesia management was standard for all patients. For premedication, 10 mg of diazepam and 0.2 mg/kg of morphine were given intramuscularly 2 h before operation. Induction of anesthesia was accomplished with 0.1 mg/kg of pancuronium bromide and 10 µg/kg of fentanyl. Anesthesia was maintained with continuous infusion of propofol (5 mg.kg⁻¹h⁻¹). Fentanyl infusion (10 µg/kg) and enflurane inhalation were used intermittently. Appropriate catheters were positioned in the right radial artery and internal jugular vein to allow pressure monitoring, fluid infusion, and agents to be administered. The patient’s temperature was monitored using both a nasopharyngeal and rectal temperature probe.

**Cardiopulmonary Bypass**

CPB was performed with a nonpulsatile roller pump (Stockert Shilley II, Stockert, Munich, Germany), a membrane oxygenator (Bentleye, Baxter, Irvine, CA), and a 40-µm arterial line filter (AF-1040 Gold, Benteley, Baxter, Irvine, CA). A balanced prime (1000 mL of Ringer’s lactate solution, 1000 mL of modified gelatin substitute, 20 mg heparin) was used. After systemic heparinization (400 IU/kg, ACT >450 sec), CPB with moderate systemic hypothermia (26°C – 28°C nasopharyngeal temperature) was initiated as follows. The ascending aorta was cannulated with an angled 8.0-mm cannula and separated superior and inferior vena cava with 32F ∼ 36F cannula. On-line monitoring of oxygen saturation for both arterial and venous blood was made with Baxter Sat 100 (Baxter, Irvine, CA). The pump flow varied from 1.8–3.0 L/m²/min⁻¹ to keep venous oxygen saturation above 65% and mean arterial pressure above 60 mmHg. The temperature alteration was about 0.3°C/min during the cooling and rewarming periods. The difference between water temperature and nasopharyngeal temperature was adjusted to less than 10°C. Our previous study has showed that the blood temperature is 0.5°C ∼ 1°C above or than nasopharyngeal temperature. During hypothermic CPB, alpha-stat management of acid-base balance was adopted. The target hematocrit was 24%. Myocardial protection was achieved with cold blood cardioplegia (4:1) and topical ice on the myocardium during cross clamping. During the procedure of measuring, no vasoactive infusions and anesthetic agents were administered to avoid their influence on venous saturation and arterial pressure. The pump flow was maintained 2.4 L/m²/min⁻¹ to avoid the impact of blood flow.

**Sampling and Statistical Analysis**

The skin microvascular flow (SMF) and MV were dynamically observed at the middle of the two sides of eye-brow with a laser Doppler flowmeter (Periflux PF2B, Permed, Stockholm, Sweden). The measurements were made at room temperature (22°C ∼ 24°C) and peak readings were used for analysis after stable blood flow had been noted over the area for at least 5 min. The time constant was 0.2 sec. The depth of the assessed area was 1 mm, and only probes of similar size and characteristics were used. Continuous recording curves were obtained 30 min before CPB (baseline) and at nasopharyngeal temperature of 30°C during the cooling and rewarming periods. The signals were transformed to digital form and stored in one computer. Spectrum analysis was made for the data with the special software. All readings of SMF data were presented as percentage of baseline. Some researchers have described the apparatus and methods of obtaining the readings (4,5).

Arterial and venous blood samples were drawn and measured simultaneously for blood gas and oxygen saturation. Blood lactate was assessed by automatic bioanalysis instrument (Nova Biomedical, Stav Profile M, USA) at baseline, cooling, and rewarming periods. Oxygen consumption (VO₂) was calculated using Fick’s principle. The following physiologic variables were determined.

- **Systemic oxygen delivery (mL/min⁻¹/m²):** \( \text{DO}_2 = \text{pump flow.CaO}_2 \)
- **Systemic O₂ consumption (mL/min⁻¹/m²):** \( \text{VO}_2 = \text{pump flow.(CaO}_2 - \text{CvO}_2) \)
- **Arteriovenous O₂ content difference (mL/dL):** \( \text{AVDO}_2 = \text{CaO}_2 - \text{CvO}_2 \)
- **Arterial or venous content (mL/dL):** \( \text{CxO}_2 = 1.34(\text{Hgb})(\text{SxO}_2) + 0.003(\text{PxO}_2) \)
- **O₂ Extraction ratio:** \( \text{O}_2\text{ext} = \text{VO}_2 / \text{DO}_2 / 100\% \)

All data are expressed as the mean and standard deviation. A paired t-test and a chi-square test made comparisons between different points. All statistical analysis was performed with SPSS 7.0 software (SPSS Inc, Chicago, IL). A p value less than .05 was considered significant.

**RESULTS**

There was no significant difference in rectal temperature between the cooling and rewarming periods when nasopharyngeal temperature was about 30°C (32.6 ± 1.8°C vs. 31.6 ± 1.6°C, \( p > .05 \)). \( \text{O}_2\text{ext} \) and \( \text{VO}_2 \) were significantly lower during the cooling period than that during the rewarming period (19.3 ± 6.2% vs. 35.2 ± 9.2%, and 49.9 ± 17.7 mL/m²/min⁻¹ vs. 133.3 ± 40.0 mL/m²/min⁻¹ \( p < .05 \); Table 1).

Compared with baseline, SMF was depressed significantly during CPB (\( p < .05 \)). It was especially less during the cooling period than during the rewarming period (50.2 ± 10.1% vs. 79.5 ± 12.3%, \( p < .01 \), Figure 1). MV decreased significantly during CPB compared with baseline (\( p < .05 \)). However, there was no significant difference between the
cooling and rewarming periods (3.7 ± 1.8 cyc/min vs. 4.1 ± 1.5 cyc/min, p > .05, Figure 2).

There were no significant differences in the concentrations of lactate acid at the baseline (2.0 ± 0.3 mmol/L), during the cooling period (2.1 ± 0.4 mmol/L), and the rewarming period (2.3 ± 0.3 mmol/L)(p > .05, Figure 3).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Cooling</th>
<th>Rewarming</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nasopharyngeal (°C)</td>
<td>30.1 ± 0.4</td>
<td>30.2 ± 0.2</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Rectal (°C)</td>
<td>32.6 ± 1.8</td>
<td>31.6 ± 1.6</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>68.1 ± 7.3</td>
<td>62.8 ± 5.6</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>pH</td>
<td>7.36 ± 0.12</td>
<td>7.37 ± 0.01</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>PaO₂ (mmHg)</td>
<td>210 ± 38</td>
<td>232 ± 40</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>PaCO₂ (mmHg)</td>
<td>38.1 ± 5.4</td>
<td>40.1 ± 2.1</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>VO₂ (ml.m⁻².min⁻¹)</td>
<td>40.9 ± 17.7</td>
<td>133.3 ± 40.0</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>O₂sat (%)</td>
<td>19.3 ± 6.2</td>
<td>35.3 ± 9.3</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Hct (%)</td>
<td>27.2 ± 1.2</td>
<td>28.4 ± 1.0</td>
<td>&gt;0.05</td>
</tr>
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</table>

DISCUSSION

Peripheral microcircular perfusion is key in maintaining organ function. MV is a spontaneous, rhythmic contractile and relaxation in capillaries microvessels (3). Blood-flow measurement of microcirculation is a quantitative indicator of tissue perfusion. Laser Doppler flowmeter (LDF), giving an integral instantaneous flux value through a measured microcircular blood flow of tissue, was used for the measurement on skin. It has been postulated that LDF can reflect microvascular perfusion and movement to some degree (6, 7). It can overcome the side effects of optic microcircular observation during CPB, such as unstable vision and half quantitative recording (8). Clinical observations with LDF are easily made at the middle point of two sides of eyebrow.

The microcircular automatic movement is an important force to push blood to tissue. When the heart is arrested during CPB, a blood pump supports the blood circulation. The blood is circulated in a nonpulsatile waveform. However, in this study, the results showed MV was still present. It suggested that MV is independent of the heart. The depression of MV during CPB might result from an inflammatory reaction, nonpulsatile perfusion, anesthesia drugs, and muscle-relaxant drugs. Wagerle et al. (9) speculated that loss of endothelium-dependent regulatory factors in the cerebral microcirculation during hypothermic CPB might enhance vasoconstriction, and impaired cerebrovascular function might be a basis for associated neurologic injury during or after hypothermic CPB.

The obvious purpose of using hypothermia is to provide a degree of organ (and organism) protection and prolong a safe margin during CPB. Hypothermia exerts its protective effect by multiple mechanisms. The most important mechanism is a reduction in metabolic rate and oxygen consumption. Hypothermia also helps to preserve high-energy phosphate stores and reduces excitatory neurotransmitter release, which is especially important to central nervous system protection. However, this concept has been modified recently, and warm heart surgery has been used in many hospitals. Some researchers have showed that hypothermia also has some side effects on enzyme function, membrane stability, calcium sequestration, glucose utilization, tissue oxygen uptake, pH, and osmotic homeostasis (10). For example, despite the same temperature and pump flow during CPB, it is often found that venous oxygen saturation during the cooling period is much higher than that during the rewarming period according to our practices. Regional perfusion varies between organs, contributing to the “mixed” venous saturation being lower with the rewarming, although measured temperatures may not change immediately. It is well known that hypothermia causes a decrease in blood flow to all organs of the body. However, some areas experience greater declines than others. Skeletal muscle and the ex-
tremities have the greatest reduction in flow, followed by the kidneys, splanchnic bed, heart, and brain. The kidneys show the largest proportional decrease in blood flow of all the organs.

However, oxygen consumption has the opposite tendency. It is possible that during the cooling period some bypassing or stealing in microcirculation occurs in these tissues and organs. These phenomena may be caused by depression of MV during the cooling period and restoration during the rewarming period. Pathi et al. (2) found that during hypothermic nonpulsatile CPB glomerulus was reduced in size because of capillary narrowing. This was consistent with diversion of blood through bypass channels. With restoration of normothermia, suboptimal perfusion of the superficial cortex perhaps results in potential damage to these nephrons during the rewarming period because of increased metabolic demands. It is important to increase pump blood flow and fraction of oxygen before active rewarming. Some metabolic production, such as lactate, may be washed out, which is beneficial to the perfusion of tissue. During the rewarming period, the rate of rewarming is regulated less than 0.3°C/min to compensate for oxygen debt that accumulates in the cooling period. The venous oxygen saturation above 65% is considered good management of perfusion flow during CPB (11). Temporary oxygen debt may not be very serious because blood flow perfusion is maintained in some vital organs, such as brain and kidney (12). Although it also cannot represent the real situation of tissue completely, online monitoring of oxygen saturation still may provide some useful information for management during CPB. It has been reported that an Sj-vo₂ less than 50% during the rewarming period is correlated with cognitive dysfunction in humans (13). Therefore, in this study, venous oxygen saturation above 65% was maintained in all of the patients. The measurement of lactate acid showed this kind of management could avoid lactate accumulation.

In conclusion, cutaneous microcirculatory function is depressed, and decreased oxygen consumption of total body is partly related to reduced metabolism with hypothermia. During the rewarming period, microcirculatory function was partly restored because SMF and MV were still below baseline during the rewarming period. Some measurements, such as regulation of blood flow and rate of rewarming, should be made to compensate for increased oxygen consumption. It is important and indispensable to monitor venous oxygen saturation during CPB.

REFERENCES