Work in progress report - Experimental

Unclamping the inferior vena cava during retrograde cerebral perfusion increases the safe range of retrograde perfusion pressures and improves brain perfusion

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Abstract

We investigated the effect of different methods of management of the inferior vena cava (IVC) during retrograde cerebral perfusion (RCP) on the relationships between RCP pressure, regional cerebral blood flow, tissue oxygenation, and intracranial pressure (ICP). Fourteen pigs were subjected to hypothermic (15 °C) RCP at RCP pressures varying from 10 to 110 mmHg with clamping (closed group, \( n = 7 \)) or without clamping of the IVC (open group, \( n = 7 \)). Intracranial pressures increased more slowly in the open group than in the closed group and were significantly lower at any level of RCP pressure in the open group than in the closed group. In the closed group, RCP pressures of 20–30 mmHg resulted in an ICP of 25 mmHg. In contrast, in the open group, when RCP pressures were maintained below 70 mmHg, ICP never reached 25 mmHg. Brain tissue blood flow and CO\textsubscript{2} production were relatively higher in the open group than in the closed group. The maximum brain tissue blood flow was achieved at an RCP pressure of 40 mmHg in the open group. We conclude that the maximum safe RCP pressure differs according to the type of management of the IVC. Opening the IVC during RCP not only improves brain tissue perfusion, but also significantly increases the safety margin of RCP pressures. In the pig model, when the IVC is not clamped, the optimal RCP pressure appears to be 40 mmHg.

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1. Introduction

The clinical application of various retrograde cerebral perfusion (RCP) techniques has been reported, with inconsistent results. Several different techniques have been described, including (1) perfusion via the superior vena cava (SVC) with clamping of the inferior vena cava (IVC) and drainage from the aorta [1–3], (2) perfusion via the SVC and femoral artery with drainage from the aorta and IVC [4, 5], (3) perfusion via the SVC and IVC with drainage from the aorta (total body retrograde perfusion) [6, 7], and (4) perfusion by elevating the central venous pressure using the Trendelenburg position [8]. A few studies in dog models have shown the maximum safe RCP pressure to be 25 mmHg. In these studies, the IVC was clamped during RCP. No study has been reported on the maximum safe retrograde perfusion pressure that can be used during RCP without clamping of the IVC. Twenty-five millimeters of mercury has been presumed/accepted as the maximum safe perfusion pressure for RCP with either clamping or opening the IVC. The type of management of the IVC during RCP has not been considered to be a major factor when discussing the optimal/maximum RCP pressure. In many publications, the status of the IVC during RCP was not considered or described.

The type of IVC drainage used during RCP may play an important role in blood flow delivery or cerebral edema. Our most recent study in an animal model has demonstrated that, when the IVC is open, RCP at relatively high perfusion pressures (34–40 mmHg) significantly improves cerebral perfusion without any increase in brain edema [9].
It is not known whether the IVC should remain open or be clamped during RCP, whether the maximum safe RCP pressure differs according to the type of management of the IVC (open or clamped), or what the RCP pressure should be when the IVC is open during RCP. In this study, we investigated the effect of different types of management of the IVC during RCP on the relationships between RCP pressure, cerebral blood flow, tissue oxygenation, and intracranial pressure.

2. Material and methods

Fourteen young pigs less than 5 months of age were used after at least 12-days acclimatization in the animal facility at the Institute for Biodiagnostics. All pigs were fasted with access to water for 12 h prior to surgery. All animals received humane care in compliance with the guidelines of the Canadian Council on Animal Care.

2.1. Experimental groups and protocol

The surgical preparation has been described in our previous publications [9–11]. Fourteen pigs were randomly assigned to one of the following two groups. Group I (open group, n = 7) was subjected to RCP with drainage of the IVC. Group II (closed group, n = 7) was subjected to RCP with clamping of the IVC. All pigs received deep HCA at 15°C plus RCP at perfusion pressures from 10 to 110 mmHg in increments of 10 mmHg. The experimental protocol is shown in Table 1.

Table 1
Experimental protocol

<table>
<thead>
<tr>
<th>Action</th>
<th>CPB</th>
<th>RCP</th>
<th>Re-CPB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temperature (°C)</td>
<td>37</td>
<td>37 ⇒ 15</td>
<td>15</td>
</tr>
<tr>
<td>Pressure (mmHg)</td>
<td></td>
<td>10</td>
<td>20</td>
</tr>
<tr>
<td>Duration (min)</td>
<td>20</td>
<td>20</td>
<td>20</td>
</tr>
</tbody>
</table>

CPB, cardiopulmonary bypass; RCP, retrograde cerebral perfusion; Re-CPB, reperfusion with CPB.

Normothermic cardiopulmonary bypass (CPB; 37°C) was initiated and continued for 20 min to allow stabilization of body temperature and blood gases. During CPB, mean blood pressure was maintained at 60–70 mmHg. After obtaining baseline values for all variables, the pig was gradually cooled from 37 to 15°C with a temperature gradient of less than 10°C between the water bath and blood. Circulatory arrest was achieved when the esophageal temperature reached 15°C. Retrograde cerebral perfusion was performed at perfusion pressures from 10 to 110 mmHg in increments of 10 mmHg. The IVC and azygos vein were open to gravity drainage in the open group and clamped in the closed group during RCP. The RCP pressure measured in the internal jugular vein was carefully controlled at the level specified by the protocol. At the end of circulatory arrest, CPB was resumed and the pig was gradually rewarmed to 37°C with a temperature gradient of less than 10°C between the water bath and blood. Normothermic CPB was continued for an additional 20 min. The alpha-stat strategy of acid–base management was used during hypothermia.

2.2. Measurements

2.2.1. Cerebral cortical blood flow

Regional cerebral blood flow (rCBF) (ml 100 g⁻¹ min⁻¹) was continuously monitored using a BLF 21D (Advance Company Ltd., Tokyo, Japan) laser Doppler flowmeter fitted with a needle-type probe (Type Nspi:9051U). The probe was carefully advanced to touch the dura without visibly indenting the dura [9].

2.2.2. Cortical tissue oxygenation

Cerebral oxygenation was monitored using near-infrared (NIR) spectroscopy (Foss Analytical NIR Systems 6500 NIR spectrometer equipped with a randomized bifurcated fiber optic bundle). The probe was placed through a small hole in the skull bone. Spectra were acquired every 5 min [9].

2.2.3. Intracranial pressure

Intracranial pressure (mmHg) was continuously monitored and recorded using a catheter transducer (Millar Instruments Inc., Houston, TX) that was placed in the intracranial space under the dura.

2.2.4. Carbon dioxide production

Arterial and venous blood samples were obtained simultaneously at each stage of the protocol to monitor blood gases. The difference of CO₂ content between returned blood and perfused blood was also determined.

2.3. Statistical analysis

Mean cerebral blood flow, oxyhemoglobin, and deoxyhemoglobin obtained during initial normothermic CPB were used as baseline levels and set at 100%. Statistical analysis was performed using the Statistical Analysis
System. All data are presented as mean ± standard error of the mean (SEM). A repeated-measures ANOVA and Duncan’s multiple range test were used for comparison between different time points within a group, and Students’ \( t \)-test was used for comparison between the two groups. A \( P \) value less than 0.05 was considered significant.

3. Results

3.1. Intracranial pressure

Before CPB, ICP was 14.9 ± 0.1 mmHg in the open group and 15.4 ± 0.2 mmHg in the closed group. There was no difference in baseline intracranial pressure during normothermic CPB between two groups (17.9 ± 1.1 mmHg in the open group vs 20.1 ± 0.8 mmHg in the closed group, \( P > 0.05 \)). Intracranial pressure increased more slowly in the open group than in the closed group and was significantly lower at any level of retrograde perfusion pressure during RCP in the open group than in the closed group. In the open group, ICP never reached 25 mmHg in any of the pigs when RCP pressure was maintained below 70 mmHg. However, in the closed group, 3 of the 7 pigs had ICP of 25 mmHg when RCP pressure was 30 mmHg (Fig. 1).

3.2. Regional cerebral blood flow

As shown in Fig. 2A, at a RCP pressure of 10 mmHg, RCP provided a similar amount of blood flow to the brain in both groups (3.87 ± 0.80% of the baseline in the open group vs 3.67 ± 0.50% of the baseline in the closed group). In the open group, as RCP pressures increased from 10 to 40 mmHg, rCBF increased significantly, from 3.87 ± 0.8 to 7.07 ± 1.5% of baseline. Tissue blood flow reached a plateau when RCP pressure increased beyond 40 mmHg, and decreased slightly when RCP pressure was above 90 mmHg. In the closed group, as RCP pressure increased from 10 to 40 mmHg, the increase in rCBF was less (from 3.67 ± 0.5 to 4.58 ± 1.1% of the baseline) relative to the open group, and no further increase in rCBF was observed with increments in RCP pressure from 50 to 110 mmHg. rCBF appeared lower in the closed group than in the open group when RCP pressures were greater than 10 mmHg, although the difference was not statistically significant.

3.3. CO2 production (difference of CO2 content between returned blood and perfused blood)

The difference of CO2 content between returned blood and perfused blood was the same in both groups during RCP at 10 mmHg perfusion pressure. The difference of CO2 content appeared higher in the open group than in the closed group during RCP at perfusion pressures between 20 and 110 mmHg, which reached statistical significance at RCP pressures between 30 and 50 mmHg. The difference of CO2 content between returned and perfused blood is affected by cerebral blood flow. Since brain tissue blood flow was higher...
in the open group than in the closed group, it could be safely assumed that CO₂ production was higher in the open group than in the closed group. This would indicate that more oxygen was delivered to brain tissue during RCP without clamping of the IVC than with clamping of the IVC. Interestingly, in the open group, the increase in CO₂ production was linear for RCP pressures between 10 and 40 mmHg. Beyond 40 mmHg perfusion pressure, the change in CO₂ production reached a plateau (Fig. 2B). The change in CO₂ production was similar to that in rCBF (Fig. 2A).

3.4. Tissue oxyhemoglobin and deoxyhemoglobin

Oxyhemoglobin and deoxyhemoglobin were expressed as the ratio of oxyhemoglobin or deoxyhemoglobin/total hemoglobin. The increase in the deoxyhemoglobin level was significant when RCP pressure increased from 10 to 40 mmHg in both groups. There were no statistical differences between the two groups in the changes in oxyhemoglobin and deoxyhemoglobin throughout the experimental protocol (Fig. 3). There was no difference in brain oxygen extraction between the two groups.

4. Discussion

Our present study clearly demonstrates that clamping the IVC does not augment blood flow to brain tissue. rCBF appears to be higher during RCP with an open IVC than with a clamped IVC. The increase in rCBF caused by increasing RCP pressures from 10 to 40 mmHg is more dramatic with an open IVC than when it is clamped. The brain also produces more CO₂ during RCP in pigs with an open IVC, probably indicating a greater supply of oxygen to the brain. Our results suggest that clamping the IVC does not improve brain tissue perfusion.

Our study has demonstrated that the relationship between intracranial pressure and RCP pressure (internal jugular venous pressure) differs depending on whether or not the IVC is clamped during RCP. When the IVC is clamped during RCP, the cerebral perfusion pressure (RCP pressure–intracranial pressure) remains low and it is possible to compress intracranial vessels as a result of high intracranial pressures, which is detrimental to the brain perfusion. This may explain why, with increasing RCP pressure, brain tissue blood flow does not increase as significantly with a clamped IVC as with an open IVC. When the IVC is open during RCP, the intracranial pressure does not increase significantly with increasing RCP pressure. This may be because an open IVC functions as a safety valve to allow extra blood flow to shunt from the brain and prevents any significant increase in intracranial pressure, reducing the risk of brain edema, while maintaining good cerebral perfusion pressure and improving brain perfusion. Therefore, leaving the IVC open during RCP provides great benefits, not only by avoiding higher intracranial pressures that may cause brain edema and injury, but also by improving brain tissue perfusion by safely increasing RCP pressure (beyond 25 mmHg).

The maximum or optimal perfusion pressure for RCP has been presumed to be 25 mmHg, regardless of the status of the IVC, although there is little clinical or experimental evidence to support this concept. To our knowledge, there has been no report on the relationship between RCP pressure, brain tissue perfusion, intracranial pressure, and brain edema when the IVC is not clamped. A few groups have investigated the relationship between perfusion pressure and flow/metabolism/tissue edema [12,13] in a canine model where the IVC is clamped during RCP. Our study has clearly demonstrated that the maximum or optimal RCP pressure appears to vary depending on the type of management of the IVC during RCP. The optimum perfusion pressure for RCP appears to be around 40 mmHg when the IVC is not clamped, at which pressure intracranial pressure is below 17.5 mmHg while maximum brain tissue flow is achieved. Theoretically, intracranial pressures beyond 25 mmHg pose a risk for brain edema and injury, although some reports suggest that any cerebrospinal fluid pressure that exceeds 17.5 mmHg may be associated with brain edema [12,14]. Our previous study demonstrates that with an open IVC during 120 min of RCP, increasing

![Fig. 3. Changes in brain tissue oxyhemoglobin (A) and deoxyhemoglobin (B) determined by near-infrared spectroscopy during retrograde cerebral perfusion (RCP) performed without clamping the inferior vena cava (open group) and with the inferior vena cava clamped (closed group). The levels obtained during initial normothermic cardiopulmonary bypass (CPB) were used as baselines (100%). Re-CPB, reperfusion with cardiopulmonary bypass. There were no differences between the two groups.](image-url)
retrograde perfusion pressure from 25 to 34–40 mmHg significantly increases brain tissue blood flow and does not cause brain tissue edema [9].

Because of possible anatomical and size differences between humans and animals, and because we used an acute pig model, our data cannot be completely translated into clinical situations. However, animal models provide controlled experimental conditions and allow measurements that are often not feasible in humans.

In conclusion, to our knowledge, this is the first detailed report on the relationship between RCP pressure, brain tissue blood flow, brain tissue oxygenation, and intracranial pressures during RCP in an experimental model with an open IVC. The maximum safe retrograde perfusion pressure during RCP differs depending on the type of management used for the IVC. In a porcine model, the maximum safe RCP pressure appears to be 20–30 mmHg when the IVC is clamped. When the IVC is open during RCP, the optimal RCP pressure appears to be 40 mmHg. From this study, we believe that the IVC is better not clamped during RCP, not only to improve brain perfusion, but also to reduce the risk of RCP-induced high intracranial pressure and brain injury.

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References