Pulmonary Shunting during Venovenous Bypass

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SUMMARY

Using mongrel dogs, an experimental study was performed to investigate Qs/Qt during v-v bypass with or without oxygenation. During bypass, the systemic circulation was maintained under constant conditions, while bypass flow rate, Svo₂ and Pvco₂ varied independently.

The results were as follows:

1) In dogs undergoing v-v bypass without oxygenation, Qs/Qt and A-aDO₂ increased markedly in proportion to bypass flow in animals receiving blood infusion into the right ventricle, but a remarkable increase was not seen in animals receiving blood infusion into the right atrium. The pulmonary artery waveform appeared to influence Qs/Qt.

2) A significant positive correlation was found between Qs/Qt and Svo₂. A-aDO₂ showed no correlation to Svo₂.

3) The Qs/Qt showed no remarkable changes despite significant changes in Pvco₂ (from 22 to 96 mmHg).

4) With regard to Qs/Qt and Svo₂, it may be proper to perform v-v bypass at a flow rate of 30 ml/Kg/min with blood infusion into the right atrium.

Additional Indexing Words:

A-aDO₂  Cardiac output  Svo₂  Paco₂  Pvco₂  V-A bypass  Assisted circulation  Acute respiratory insufficiency

EMPLOYING the extracorporeal circulation technique, studies on venovenous (v-v) bypass began early in the 1960's and some investigators¹⁻³ proved this method to be of clinical value in hypoxic disorders of pulmonary
origin. In 1968, Hill et al\textsuperscript{4}) reported the first clinical application of v-v bypass in a female patient and later described other successful cases.\textsuperscript{5}) Kakvan et al\textsuperscript{6}) noted the following advantages of v-v bypass: a) inflow is into a vein against little resistance, thereby producing less turbulence and less blood damage than an arterial catheter and b) hemodynamic disturbances are negligible. Although many patients suffering from acute respiratory insufficiency have been treated by veno-arterial or v-v bypass with a membrane oxygenator,\textsuperscript{7}) this technique presents certain drawbacks,\textsuperscript{8}) especially when the pulmonary arterial Po\textsubscript{2} level is elevated.

In our previous report,\textsuperscript{9}) we studied physiological changes of the lung caused by v-v bypass, and in this report we investigated pulmonary shunting during v-v bypass. During ventilation with pure oxygen, there are two forms of physiologic shunt that reduce the oxygenation of the arterial blood in the normal pulmonary circulation. The first is the anatomical shunt of venous blood draining into the left heart from the bronchial, pleural or Thebesian veins which have no contact with alveoli. The second is the effective shunt caused by unoxygenated blood coming from nonventilated alveoli. Pulmonary shunting (Qs/Qt), similar to the alveolar-arterial oxygen difference (A-aDO\textsubscript{2}), is an important factor to estimate atelectasis and ventilation-perfusion imbalance, and is known to be affected by not only respiratory but also circulatory dynamics.

In this paper, bypass flow, mixed venous oxygen saturation (S\textsubscript{V}O\textsubscript{2}) and mixed venous CO\textsubscript{2} pressure (P\textsubscript{V}CO\textsubscript{2}) were altered independently of cardiac output and other factors. Definitions and symbols are used according to the description by Pappenheimer.\textsuperscript{10})

**Methods**

Twenty-nine mongrel dogs weighing 10–20 Kg were used. After intravenous administration of sodium thiopental 20–30 mg/Kg, the animals were placed in the supine position and intubated with an endotracheal tube with cuff. Two thin wall Teflon cannulae were inserted into the inferior vena cava and superior vena cava via the left femoral and left jugular vein, respectively, for venous drainage. A flexible cannula (Fr. 18) was introduced into the right atrium or the right ventricle via the right jugular vein for sending blood. A catheter was inserted into the ascending aorta via the right carotid artery for recording the arterial pressure and sampling blood. Another catheter kept in the main pulmonary artery via the right femoral vein was used for recording blood pressure and taking blood samples (Fig. 1). After intramuscular administration of 0.25 mg/Kg diaropherine, respiration of the animals was sup-
Fig. 1. Venovenous bypass circuit for ventricular infusion (a) and atrial infusion (b). F = blood filter; O = bubble oxygenator with heat exchanger; P = roller pump.

ported with a volume-limited respirator (F₁O₂; 1.0, tidal volume; 15 ml/Kg, frequency; 25 breaths/min). The intratracheal pressure was recorded with a U-shaped water manometer. Cardiac output was measured by the dye-dilution method with the aid of a densitometer (Water Instruments Inc), in which indocyanine green was injected through the catheter into the pulmonary artery and measured through a catheter in the ascending aorta.

Extracorporeal circulation was done with a bubble oxygenator (Temp-trol) and roller pumps for about 3 hours at 37°C. The priming fluid was a mixture of freshly drawn heparinized autologous blood, lactated Ringer’s solution and low molecular weight dextran with a dilution rate of 25–30%. Hematocrit was maintained between 25–30% during bypass. The initial pH was adjusted to 7.35–7.45 and no further correction was done. Heparin was given to the animal initially at 3 mg/Kg and subsequently at a rate of 0.5 mg/Kg every 30 min of bypass. Diaropherine was also administered repeatedly during bypass.

When the fractional concentration of oxygen in the inspired gas is 1.0 and the Pao₂ is greater than 300 mmHg, the Sao₂ is consistently 100% and A-aDO₂ and Qs/Qt may be calculated according to the modified equation:

\[ \frac{Q_s}{Q_t} = \frac{0.0031(A-aDO_2)}{C(a-v)O_2 + 0.0031(A-aDO_2)} \]  \hspace{1cm} (1)

\[ A-aDO_2 = P_a - Pao_2 - Paco_2 - P_H_2O \]  \hspace{1cm} (2)
Table I. Allotment of Experimental Animals

<table>
<thead>
<tr>
<th>Group</th>
<th>number of animals</th>
<th>site of blood sending</th>
<th>site of blood drawing</th>
<th>blowing gas into oxygenator</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5</td>
<td>RV</td>
<td>IVC</td>
<td>no.</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>RA</td>
<td>SVC</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>5</td>
<td>RV</td>
<td>IVC</td>
<td>no.</td>
</tr>
<tr>
<td></td>
<td>only bypass flow altered</td>
<td>5</td>
<td>RA</td>
<td>SVC</td>
</tr>
<tr>
<td>3</td>
<td>only SVo2 altered</td>
<td>5</td>
<td>RV</td>
<td>IVC</td>
</tr>
<tr>
<td>4</td>
<td>only PVco2 altered</td>
<td>5</td>
<td>RV</td>
<td>IVC</td>
</tr>
</tbody>
</table>

RV = right ventricle; RA = right atrium; IVC = inferior vena cava; SVC = superior vena cava.

in which \( P_B \) is barometric pressure and \( P_{H_2O} \) is saturated water vapor pressure at 37°C. The oxygen content of arterial blood (\( CaO_2 \)) and mixed venous blood (\( CVO_2 \)) is calculated by the following formula:

\[
Co_2 = Hb(\,gr.) \times 1.34 \times \frac{Sat. \, (\%)}{100} + 0.0031 \times Po_2
\]  

(3)

The dogs were divided into the following 4 groups (Table I).

Group 1: Venovenous bypass without oxygenation was done for 3 hours at a flow rate of 30 ml/Kg/min to investigate the effects of bypass procedures upon \( Qs/Qt \). Animals in this group were further divided into 2 subgroups: a) venous blood in the bypass circuit was infused into the right ventricle (ventricular infusion group), and b) the blood was infused into the right atrium (atrial infusion group).

Group 2: Venovenous bypass without oxygenation was done for 3 hours and bypass flow was changed every 20 min while altering the venous gravity. Animals in this group were further divided into 2 subgroups: a) bypass flow was changed from 0 ml/Kg/min (before bypass) to 15, 30, and 50 ml/Kg/min during the first period of bypass and after 20 min cessation of perfusion the bypass was repeated as in the first period (the second period), and b) the bypass flow was progressively increased during the first period as in subgroup 2a but during the second period it was decreased in the reverse order from 50 ml/Kg/min to 30 and finally to 15 ml/Kg/min.

Group 3: Venovenous bypass was done at a flow rate of 30 ml/Kg/min and only \( SVO_2 \) was altered by changing components of the gas bubbled into the oxygenator.

Group 4: Venovenous bypass was done with oxygenation and only \( PVCO_2 \) was altered by changing the fractional concentration of \( CO_2 \) in the gas.
In Groups 3 and 4, the bypass was done by the circuit shown in Fig. 1a and \( S\text{\textsubscript{vo}} \) and \( P\text{\textsubscript{vo}} \) were altered at random to eliminate the influence of bypass time upon \( Q\text{\textsubscript{s}}/Q\text{\textsubscript{t}} \).

**RESULTS**

**Group 1.**

In animals undergoing ventricular infusion, the mean airway pressure, A-aDO\(_2\) and \( Q\text{\textsubscript{s}}/Q\text{\textsubscript{t}} \), increased by 1.7±0.26 cmH\(_2\)O, 31.3±6.35 mmHg and 3.83±0.12% respectively at the beginning of the bypass and presented no remarkable changes thereafter. Both \( P\text{\textsubscript{ao}} \) and arterial pH decreased mildly. In dogs undergoing atrial infusion, all parameters showed comparable tendencies to the corresponding values in the ventricular infusion subgroup. In each animal, \( P\text{\textsubscript{aco}} \) was maintained within the norm (34–44 mmHg) and cardiac output was steady (±6.7%).

**Group 2.**

In animals receiving ventricular infusion (Group 2a), \( P\text{\textsubscript{ao}} \) declined with increased increments of bypass flow and rose after discontinuing bypass. A-aDO\(_2\) and \( Q\text{\textsubscript{s}}/Q\text{\textsubscript{t}} \) increased parallel to bypass flow. The mean difference of \( P\text{\textsubscript{ao}} \) between stages 1 and 4 (64±10.4 mmHg) was significantly (\( p<0.02 \)) greater than that between stages 5 and 8 (39±15.9 mmHg). The mean differences of A-aDO\(_2\) and \( Q\text{\textsubscript{s}}/Q\text{\textsubscript{t}} \) between stages 1 and 4 (66±10.6 mmHg and 15.3±4.11%) were significantly (\( p<0.05 \)) greater than those between stages 5 and 8 (43±14.6 mmHg and 8.0±1.73%). In animals given atrial infusion (Group 2b), \( P\text{\textsubscript{ao}} \), A-aDO\(_2\), and \( Q\text{\textsubscript{s}}/Q\text{\textsubscript{t}} \) showed similar tendencies to Group 1a in the first period, but the mean differences of \( P\text{\textsubscript{ao}} \) (28±2.6 mmHg), A-aDO\(_2\) (30±6.0 mmHg), and \( Q\text{\textsubscript{s}}/Q\text{\textsubscript{t}} \) (5.5±1.81%) between stages 1 and 4 in Group 2b were significantly smaller than those between the same stages in animals of Group 2a (all \( p<0.01 \)). \( S\text{\textsubscript{vo}} \) was steady throughout this experimental procedure in all animals. Cardiac output also did not vary markedly in either subgroup (±6.1% in Group 2a, ±6.1% in Group 2b).

**Group 3.**

Gas bubbled into oxygenator was composed of \( O\text{\textsubscript{2}} \) (0–6 L/min) and \( CO\text{\textsubscript{2}} \) (0–60 ml/min) or \( N\text{\textsubscript{2}} \) (0–4 L/min) and \( CO\text{\textsubscript{2}} \) (0–40 ml/min). \( S\text{\textsubscript{vo}} \) changed to a range of 70 to 100%. Although a correlation between \( S\text{\textsubscript{vo}} \) and \( Q\text{\textsubscript{s}}/Q\text{\textsubscript{t}} \) was noted (Fig. 2), the relationship between \( S\text{\textsubscript{vo}} \) and A-aDO\(_2\) was indefinite (Fig. 3). \( P\text{\textsubscript{vo}} \) in this group remained in the normal range of 35–45 mmHg. Cardiac output did not vary markedly (±7.1%).

**Group 4.**

A mixture of \( O\text{\textsubscript{2}} \) (1 L/min) and \( CO\text{\textsubscript{2}} \) (0–1,000 ml/min) was blown into the
oxygenator and \( P_{\text{VCO}_2} \) changed to a range of 22 to 96 mmHg. The \( Q_s/Q_t \) approximated a straight line in spite of the alteration of \( P_{\text{VCO}_2} \) (Fig. 4). The \( P_{\text{aco}_2} \) changed to a range of 20–63 mmHg corresponding to the alteration in \( P_{\text{VCO}_2} \). Cardiac output did not fluctuate markedly (±5.7%).
DISCUSSION

In v-v bypass, unlike veno-arterial bypass, oxygenated blood flows into the pulmonary artery. The $Q_S/Q_T$, in conjunction with the $SvO_2$ and $PaO_2$, is an important indicator of the effectiveness of v-v bypass. In estimating $Q_S/Q_T$, it seems rational to select one of many factors affecting $Q_S/Q_T$ and to clarify its relationship to $Q_S/Q_T$. $Q_S/Q_T$ is known to be affected not only by respiratory parameters such as tidal volume, airway pressure, and CO\textsubscript{2} tension in the inspired gas, but also by circulatory parameters such as cardiac output. We tried to change only one of the following factors by v-v bypass: bypass flow, $SvO_2$, $PvCO_2$, and cardiac output.

Bendixen et al\textsuperscript{11} emphasized the importance of intermittent hyperinflation during anesthesia in order to prevent atelectasis and a resulting elevation of $Q_S/Q_T$. In our experiment, ventilation was done with pure oxygen using a volume-limited respirator in a frequency of 25 breaths/min with a tidal volume of 15 ml/Kg, and $Paco_2$ was maintained in a range of 33 to 46 mmHg before bypass. Intermittent hyperinflation was done just before each measurement.

Influences of anesthesia and 3 hours' perfusion upon $PaO_2$, $A-aDO_2$ and $Q_S/Q_T$ were studied in animals of Group 1. The elevation in $Q_S/Q_T$, observed just after initiating bypass, was attributed to hemodilution and a reduction in $PaO_2$, which may have been in part caused by microemboli\textsuperscript{12} in the lung following massive infusion of autologous blood in the bypass circuit. The abrupt elevation in airway pressure seen immediately after commencing bypass may also be attributed to this procedure. The mild progressive de-
Fig. 5. Waveforms in the main pulmonary artery in Group 2a (ventricular infusion) at various bypass flow rates. The tall wave at the middle of the record indicates the inspiration of the animal.

crease in \( P_{aO_2} \) and mild increases in A-aDO\(_2\) and Qs/Qt were apparently due to a limited tidal volume of 15 ml/Kg, ventilation with pure oxygen\(^{13,14}\) and the already mentioned bypass procedure.\(^{15,16}\) These progressive changes, however, were small and negligible.

It was interesting that the Qs/Qt rose more markedly in dogs undergoing ventricular infusion (Group 2a) than those receiving atrial infusion (Group 2b) as bypass flow was increased. To clarify this phenomenon, we investigated the pressure curve in the main pulmonary artery and noted that as bypass flow was increased, the waveform showed reductions in amplitude and slope in Group 2a (Fig. 5), but not in Group 2b. We assume that these changes in pulmonary waveform somehow influenced internal shuttle ventilation in alveoli and the pulmonary capillary circulation, resulting in a rise in Qs/Qt.\(^{17,18}\) Although this suggests an advantage of atrial infusion in v-v bypass, in animals with a constant bypass flow of 30 ml/Kg/min, as shown in Group 1, the blood infusion site had no influence upon Qs/Qt.

Many investigators\(^{19,20}\) reported correlations between Qs/Qt and \( S_{VO_2} \) and between Qs/Qt and cardiac output. In most of these reports, elevation of \( S_{VO_2} \) was induced by an increase in cardiac output under definite oxygen
consumption. In dogs, Smith et al.\textsuperscript{21} performed v-v perfusion while successfully altering $S\text{VO}_2$ independently of cardiac output. They observed that a decrease in $S\text{VO}_2$ from 70 to 50\% caused a decrease in $Q_s/Qt$ from 10.1 to 7.9\%, and supposed that the decrease in $S\text{VO}_2$ elicited pulmonary vasoconstriction and a reduction in blood flow in non-ventilated alveoli, and vice versa. In our experiment, animals of Group 2 likewise revealed a correlation between $S\text{VO}_2$ and $Q_s/Qt$ independently of cardiac output. Although some reports\textsuperscript{22} claimed a correlation between $Q_s/Qt$ and A-aDO$_2$ during pure oxygen inhalation, relationships between $S\text{VO}_2$ and A-aDO$_2$ or $Q_s/Qt$ and A-aDO$_2$ were not evident in the present study.

According to formula (3), when $S\text{VO}_2$ fluctuates in the range of 70 to 100\%, CVO$_2$ changes markedly but CaO$_2$ only minimally even when Pao$_2$ increases. The reason for this is that SaO$_2$ is consistently 100\% and Pao$_2$ is also very high during pure oxygen inhalation. According to formula (1) for calculating $Q_s/Qt$, an increase in $S\text{VO}_2$ produces a diminution of C(a-v)O$_2$ and the denominator of formula (1) sufficient enough to avoid a decrease in A-aDO$_2$, and to bring about an increase in $Q_s/Qt$.

It is a well known fact that carbon dioxide has both direct depressant effects on the myocardium as well as indirect stimulant effects mediated by catecholamine production. In patients undergoing cardiopulmonary bypass surgery, Hewitt et al.\textsuperscript{23} observed that a rise of Paco$_2$ from 31.4 to 48.8 mmHg brought about significant increases in cardiac output and Pao$_2$, and stated that cardiac output was higher when Paco$_2$ was normal to slightly elevated than when low. Cullen et al.\textsuperscript{24} also observed in an awake man that when exogenous CO$_2$ was administered during controlled or spontaneous respiration cardiac output increased significantly and they stressed the influence of the anesthetic agents and drugs upon the circulatory response to CO$_2$.

In an anesthetized man, Michenfelder et al.\textsuperscript{25} observed that when cardiac output was steady ($\pm 10\%$) and the initial shunt was large (>0.10), an increase in Paco$_2$ was associated with a reduction in $Q_s/Qt$ and a resultant rise in Pao$_2$. Prys-Roberts et al.\textsuperscript{26} recognized a reciprocal relationship between A-aDO$_2$ and Paco$_2$ although significant alterations of $Q_s/Qt$ were not detected even when changes in Paco$_2$ occurred. Marshall et al.\textsuperscript{27} also observed in anesthetized men that $Q_s/Qt$ remained constant during hypo-, eu-, and hypercapnia.

All of the foregoing investigators, however, produced an increase in Paco$_2$ by adding CO$_2$ to the inspired gas, while we induced it by bubbling CO$_2$ into the oxygenator during v-v bypass. In Group 4, although Pcco$_2$ fluctuated in range from 22 to 96 mmHg and Paco$_2$ altered from 22 to 63 mmHg, $Q_s/Qt$ and A-aDO$_2$ were almost constant. Despite remarkable changes in
PaCO₂, the cardiac output remained steady (±5.6%) and Pao₂ decreased mildly in association with an elevation of PVco₂. We attribute this reduction in Pao₂ partially to a drop in Pao₂ caused by increased CO₂ tension in alveoli, and partially to the lack of a remarkable increase in cardiac output. It is obscure why cardiac output did not increase in spite of a significant rise in Paco₂.

In evaluating the clinical performance of v-v bypass, the following three points are important: 1) negligible hemodynamic disturbances, 2) sufficient oxygen supply, and 3) no irreversible damage to normal lung tissue and beneficial influences upon damaged lung tissue. Concerning point (1), at a perfusion flow of 30 ml/Kg/min, both subgroups undergoing blood infusion into the right ventricle (2a) and atrium (2b) demonstrated stable hemodynamics including ECG, while some animals receiving ventricular infusions (2a) at a perfusion flow of 50 ml/Kg/min showed depression of ST segment and inverted T wave in ECG. Although re-drainage of oxygenated blood is a potential source of risk, blood infusion into the right atrium is preferable to infusion into the right ventricle, especially in clinical cases with a flow rate exceeding 30 ml/Kg/min. Concerning point (2), in Group 3 with a bypass flow of 30 ml/Kg/min, Svo₂ was changed from 70 to 100%. A flow rate of 30 ml/Kg/min may be sufficient to meet oxygen requirements in animals. In our clinical experience with assisted circulation, including both v-v and v-A bypass with peripheral cannulation, it was very difficult to maintain the bypass flow at 30 ml/Kg/min throughout the perfusion. A thin-wall venous cannulae should be developed for clinical use. Concerning point (3), the results of Groups 1 and 2 showed that an irreversible increase in Qs/Qt was caused by changes in bypass flow especially in the group undergoing ventricular infusion, suggesting that the right atrium is the most reasonable site for blood infusion. Increased Qs/Qt was also observed in Group 3 accompanied by a rise in Svo₂, but this was reversible and might be a physiological response intended to protect normal tissues from oxygen intoxication.

It is not yet quite clear if increases in Svo₂ also elevate Qs/Qt in damaged lung tissue, but we suppose that increased oxygen content in the pulmonary artery may be beneficial in improving hypoxia in damaged lung tissue.

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