Venous Admixture in Human Septic Shock

Comparative Effects of Blood Volume Expansion, Dopamine Infusion and Isoproterenol Infusion on Mismatching of Ventilation and Pulmonary Blood Flow in Peritonitis

F. Jardin, M.D., M. C. Eveleigh, Ph.D., F. Gurdjian, M.D., F. Delille, M.D., and A. Margairaz, M.D.

SUMMARY A hemodynamic study with blood gas analysis was performed so we could observe changes induced by blood volume expansion, dopamine infusion and isoproterenol infusion in 20 adult patients suffering from peritonitis complicated with septic shock and acute respiratory failure. Blood volume expansion increased cardiac index (from 2.6 ± 1.2 l/min/m² to 3.4 ± 1.3 l/min/m²; p < 0.001), but also enhanced venous admixture (QS/QT) from 27 ± 14% to 36 ± 13%; p < 0.01. Dopamine infusion increased cardiac index (from 2.6 ± 0.9 l/min/m² to 3.4 ± 1 l/min/m²; p < 0.001), but also enhanced venous admixture (from 25 ± 11% to 31 ± 12%; p < 0.001). Isoproterenol infusion increased cardiac index (from 2.6 ± 0.9 l/min/m² to 3.6 ± 1.1 l/min/m²; p < 0.001), but also enhanced venous admixture (from 27 ± 12% to 33 ± 11%; p < 0.001). This worsening in mismatching of ventilation and blood flow is correlated with the enhancement in pulmonary blood flow obtained by these three therapeutic procedures.

MANAGEMENT OF PATIENTS with septic shock is very difficult when acute respiratory failure is also present, particularly in severe peritonitis, which may require several operations to eradicate intraperitoneal abscess. Such circumstances are common. Blood volume expansion (BVE), inotropic agents (dopamine infusion (DI) or isoproterenol infusion (II)) can improve circulatory status, but may also enhance respiratory failure. The purpose of our study was to assess and compare the effects of BVE, DI and II on blood gases in hypoxemic patients suffering from septic shock.

Materials and Method

We studied 20 adult patients 20–75 years old suffering from peritonitis complicated with septic shock. All patients had positive blood cultures. The shock syndrome was defined as hypotension (systolic arterial pressure <90 mm Hg) with inadequate organ perfusion manifested by physiological abnormalities, including pallor, cold skin, slow nail-bed capillary filling, oliguria (urinary output lower than 15 ml/hr), and decreased mental acuity. Mechanical assisted ventilation was used because all patients remained tachypneic, cyanotic and had a pronounced arterial hypoxemia despite oxygen therapy (6 l/min) by a nasal tube. Bilateral diffuse chest radiographic infiltrates were present in 10 patients, and interstitial patterns were present in 10 patients.

Patients were sedated with intravenous morphine and paralyzed with pancuronium bromide. Catheters were inserted for monitoring the following pressures: radial (or femoral) artery (AP), right atrial (RAP), pulmonary artery (PAP) and pulmonary capillary wedge (PCWP). Vascular pressures were measured with Statham P23dB transducers. Transducers were positioned on the midaxillary line, and atmospheric pressure was used as a zero reference point. Pulmonary vascular and systemic arterial resistances (PVR and SAR, respectively) were calculated from the cardiac index (CI) and the difference between mean PAP and PCWP for PVR, and between mean AP and RAP for SAR. Cardiac output was measured by thermodilution (right atrial injection of 10 ml iced water with temperature recording in the pulmonary artery). Rectal temperature was measured with an indwelling thermistor.

Physiological shunting in the lung (QS/QT), or venous admixture, was calculated with the arterial and mixed venous oxygen contents obtained by a coulometric method during 100% oxygen breathing.1*

Therapeutic interventions were made without randomization, but in the same order for each patient. The first hemodynamic evaluation was made (17 patients) before and after BVE (with “plasmagel” 7 ml/kg infused in 5 minutes); 30 minutes after this first hemodynamic evaluation, a second hemodynamic evaluation was made (20 patients) before and after a 10-minute DI (10 μg/kg/min); 30 minutes after

*QS/QT was calculated using the formula: \( QS/QT = \frac{C'_c - C_a}{C'_c - C_v} \)

where \( C_a \) = arterial oxygen content, \( C'_c \) = mixed venous oxygen content and \( C'_c \) = pulmonary capillary oxygen content. \( C'_c \) was calculated using the formula: \( C'_c = (Hb \times 1.34) + (Paco_2 \times 0.003) \) where \( Hb \) = hemoglobin concentration (g/ml of blood) and the formula: \( Pac_o_2 = PB - 47 - Paco_2 \), where \( PB \) = barometric pressure and Paco2 = arterial carbon dioxide tension.

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TABLE 1. Systemic Hemodynamic Data Before and After Blood Volume Expansion, Before and During Dopamine Infusion and Isoproterenol Infusion

<table>
<thead>
<tr>
<th></th>
<th>PCWP (mm Hg)</th>
<th>CI (l/min/m²)</th>
<th>HR (beats/min)</th>
<th>MAP (mm Hg)</th>
<th>SVR (mm Hg/l)</th>
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<tbody>
<tr>
<td><strong>Blood volume expansion (n = 17)</strong></td>
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<tr>
<td>Before</td>
<td>6.4 ± 3.5</td>
<td>2.6 ± 1.2</td>
<td>109 ± 18</td>
<td>67 ± 20</td>
<td>24.8 ± 10.2</td>
</tr>
<tr>
<td>After</td>
<td>9.1 ± 4.3 p &lt; 0.01</td>
<td>3.4 ± 1.3 p &lt; 0.001</td>
<td>108 ± 18 NS</td>
<td>72 ± 16 NS</td>
<td>20.4 ± 13.6 p &lt; 0.05</td>
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<tr>
<td><strong>Dopamine infusion (n = 20)</strong></td>
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<tr>
<td>Before</td>
<td>8.5 ± 5.5</td>
<td>2.6 ± 0.9</td>
<td>105 ± 16</td>
<td>56 ± 18</td>
<td>19.7 ± 7.6</td>
</tr>
<tr>
<td>After</td>
<td>8.9 ± 5.8 NS</td>
<td>3.4 ± 1 p &lt; 0.001</td>
<td>118 ± 24 p &lt; 0.001</td>
<td>67 ± 20 p &lt; 0.02</td>
<td>18.5 ± 7.2 NS</td>
</tr>
<tr>
<td><strong>Isoproterenol infusion (n = 15)</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Before</td>
<td>8.7 ± 3.9</td>
<td>2.6 ± 0.9</td>
<td>106 ± 19</td>
<td>61 ± 18</td>
<td>19.9 ± 9.6</td>
</tr>
<tr>
<td>After</td>
<td>5.7 ± 4 p &lt; 0.02</td>
<td>3.6 ± 1.1 p &lt; 0.001</td>
<td>132 ± 17 p &lt; 0.001</td>
<td>65 ± 10 NS</td>
<td>16 ± 9.5 p &lt; 0.001</td>
</tr>
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</table>

Abbreviations: PCWP = pulmonary capillary wedge pressure; CI = cardiac index; HR = heart rate; MAP = mean arterial pressure; SVR = systemic vascular resistance.

This second hemodynamic evaluation, a third hemodynamic evaluation was made (15 patients) before and after a 10-minute II. Unpaired t tests did not reveal difference between controls before any of the interventions. All these measurements were analyzed statistically by means of the t test for paired values; moreover, the increase in CI and the increase in venous admixture in each patient before and after BVE, before and during DI, and before and during II were correlated using an electronic calculator (Hewlett Packard HP 97).

Table 3 summarizes blood gas analysis: Pao₂ was reduced by BVE, DI and II, but not significantly; arteriovenous oxygen content difference was reduced by BVE, DI and II.

The increase in QS/QT, calculated in 17 patients before and immediately after BVE, in 20 patients before and during DI, and in 15 patients before and during II, is plotted against the increase in CI in figures 1, 2 and 3; the increase in CI and the increase in QS/QT are correlated (r = 0.70 for BVE, r = 0.87 for DI and r = 0.67 for II).

Table 2 summarizes pulmonary hemodynamic data: QS/QT was increased by BVE (33%), by DI (24%) and also by II (22%).

Table 2. Pulmonary Hemodynamic Data Before and After Blood Volume Expansion, Before and During Dopamine Infusion and Isoproterenol Infusion

<table>
<thead>
<tr>
<th></th>
<th>MPAP (mm Hg)</th>
<th>PCWP (mm Hg)</th>
<th>PVR (mm Hg/l)</th>
<th>QS/QT (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Blood volume expansion (n = 17)</strong></td>
<td></td>
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<tr>
<td>Before</td>
<td>20.2 ± 5.4</td>
<td>6.4 ± 3.5</td>
<td>5.9 ± 3.4</td>
<td>27 ± 14</td>
</tr>
<tr>
<td>After</td>
<td>23.3 ± 7.1 p &lt; 0.001</td>
<td>9.1 ± 4.3 p &lt; 0.001</td>
<td>3.9 ± 1.8 p &lt; 0.05</td>
<td>36 ± 13 p &lt; 0.01</td>
</tr>
<tr>
<td><strong>Dopamine infusion (n = 20)</strong></td>
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<td></td>
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<tr>
<td>Before</td>
<td>21.3 ± 6.7</td>
<td>8.5 ± 5.5</td>
<td>5.2 ± 2.1</td>
<td>25 ± 11</td>
</tr>
<tr>
<td>After</td>
<td>23.4 ± 5.7 p &lt; 0.001</td>
<td>8.9 ± 5.8 NS</td>
<td>4.4 ± 2.1 p &lt; 0.05</td>
<td>31 ± 12 p &lt; 0.001</td>
</tr>
<tr>
<td><strong>Isoproterenol infusion (n = 15)</strong></td>
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<tr>
<td>Before</td>
<td>24.5 ± 6.1</td>
<td>8.7 ± 3.9</td>
<td>7.3 ± 3.6</td>
<td>27 ± 12</td>
</tr>
<tr>
<td>After</td>
<td>26.7 ± 6.7 p &lt; 0.001</td>
<td>5.7 ± 4 p &lt; 0.02</td>
<td>6.6 ± 3.1 p &lt; 0.05</td>
<td>33 ± 11 p &lt; 0.001</td>
</tr>
</tbody>
</table>

Abbreviations: MPAP = mean pulmonary arterial pressure; PCWP = pulmonary capillary wedge pressure; PVR = pulmonary vascular resistance; QS/QT = venous admixture.

Table 3 summarizes blood gas analysis: Pao₂ was reduced by BVE, DI and II, but not significantly; arteriovenous oxygen content difference was reduced by BVE, DI and II.

The increase in QS/QT, calculated in 17 patients before and immediately after BVE, in 20 patients before and during DI, and in 15 patients before and during II, is plotted against the increase in CI in figures 1, 2 and 3; the increase in CI and the increase in QS/QT are correlated (r = 0.70 for BVE, r = 0.87 for DI and r = 0.67 for II).

Discussion

Arterial hypoxemia frequently occurs with septic shock; QS/QT is increased in sepsis. This mismatching of ventilation and blood flow results from three disorders: an abnormal pattern of gas distribution with closure of alveoli or airways or both, an abnormal pattern of blood flow distribution in the lung with closure of capillaries by interstitial edema or microembolization, and an increase in pulmonary extravascular water with interstitial or alveolar edema, caused by altered capillary permeability, the role of overt infection in altering capillary...
TABLE 3. Blood Gas Analysis Before and After Blood Volume Expansion, Before and During Dopamine Infusion and Isoproterenol Infusion

<table>
<thead>
<tr>
<th></th>
<th>PaO₂ (torr)</th>
<th>PvO₂ (torr)</th>
<th>PaCO₂ (torr)</th>
<th>av DO₂ (vol %)</th>
<th>QS/QT (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Blood volume expansion (n = 17)</strong></td>
<td></td>
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<tr>
<td>Before</td>
<td>207 ± 156</td>
<td>35.2 ± 8.5</td>
<td>33 ± 9</td>
<td>6.1 ± 2.4</td>
<td>27 ± 14</td>
</tr>
<tr>
<td>After</td>
<td>198 ± 142</td>
<td>38.9 ± 8.3 p &lt;0.05</td>
<td>34 ± 9 NS</td>
<td>5.8 ± 1.2 p &lt;0.001</td>
<td>36 ± 13 p &lt;0.01</td>
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<tr>
<td><strong>Dopamine infusion (n = 20)</strong></td>
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<tr>
<td>Before</td>
<td>200 ± 132</td>
<td>34.8 ± 6.3</td>
<td>30 ± 6</td>
<td>5.4 ± 1.5</td>
<td>25 ± 11</td>
</tr>
<tr>
<td>After</td>
<td>189 ± 132</td>
<td>39.2 ± 7.5 p &lt;0.001</td>
<td>31 ± 5 NS</td>
<td>4.3 ± 1.3 p &lt;0.001</td>
<td>31 ± 12 p &lt;0.001</td>
</tr>
<tr>
<td><strong>Isoproterenol infusion (n = 15)</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Before</td>
<td>184 ± 146</td>
<td>34.3 ± 6.6</td>
<td>31 ± 7</td>
<td>5.8 ± 1.9</td>
<td>27 ± 12</td>
</tr>
<tr>
<td>After</td>
<td>163 ± 135</td>
<td>39.9 ± 6.7 p &lt;0.001</td>
<td>32 ± 6 NS</td>
<td>4.5 ± 1.6 p &lt;0.001</td>
<td>33 ± 11 p &lt;0.001</td>
</tr>
</tbody>
</table>

Abbreviations: PaO₂ = arterial oxygen tension; PvO₂ = mixed venous oxygen tension; PaCO₂ = arterial carbon dioxide tension; av DO₂ = arteriovenous oxygen difference; QS/QT = intrapulmonary shunting.

permeability is well-known. Respiratory insufficiency may contribute significantly to the mortality of patients who have suffered major sepsis.

Septic shock is associated with two hemodynamic responses: a low-output state (hypokinetic state) and a normal or high-output state (hyperkinetic state). During the low-output state, as the mixed venous blood becomes progressively stripped of oxygen, the effect of any given degree of venous admixture upon the arterial oxygen tension becomes magnified; thus, the hypokinetic state can enhance hypoxemia. The hyperkinetic state can reduce time courses in pulmonary capillaries and thus produce diffusion impairment on oxygen.

BVE, DI and II all increase cardiac output. During BVE, this response results essentially from preload increase; BVE also decreases afterload. During DI, increase in cardiac output is due to a potent inotropic effect; in our patients, cardiac output was also enhanced by accelerating heart rate; failure of this inotropic drug to reduce PCWP suggests an additional increase in venous return. During II, increase in cardiac output can be attributed to inotropic and chronotropic action; moreover, isoproterenol reduces afterload. Our findings emphasize the linear relationship between increase in cardiac output and increase in QS/QT during BVE, DI and II.

In our patients, QS/QT was measured during 100% oxygen breathing; it is known that patients with adult respiratory distress syndrome may increase their

![Figure 1](http://circ.ahajournals.org/)

**Figure 1.** The increase in pulmonary blood flow (or cardiac index, Δ IC) plotted against the increase in venous admixture (Δ QS/QT) during blood volume expansion.
shunt when given 100% oxygen to breathe. Removal of gas from poorly ventilated lung units by pulmonary capillary blood flow can collapse these units. This process may be hastened when pulmonary blood flow is increased; but our patients presented evidence of major mismatching of ventilation and pulmonary blood flow before breathing 100% oxygen, and their respiratory distress syndrome required in all cases mechanical assisted ventilation. A large physiologic shunt was not surprising in these patients.

Similar relations between cardiac output and QS/QT have been previously documented by Yamamura et al. in dogs under general anesthesia and by Hedley-White et al. in patients with
respiratory failure; these latter findings suggested that with increasing pulmonary blood flow the critical opening pressure of capillaries in unventilated portions of the lung is suddenly exceeded, and that increases in the rate of flow of blood past thickened alveolar membranes mean that insufficient time is available for full saturation of hemoglobin despite 100% oxygen breathing. The relationship we observed between the increase in cardiac output and the increase in QS/QT during BVE, DI, and II suggests a similar recruitment mechanism. It is likely that a marked redistribution of pulmonary blood flow, due to acute enhancement of pulmonary blood flow in nonhomogeneous lung, plays a major role. Theoretically, increases in PCWP might be expected to result in increased transudation of fluid, and thus worsen ventilation-perfusion imbalance. The differing effects of BVE, DI, and II on PCWP should, therefore, affect the relationship between change in cardiac output and change in QS/QT. In fact, there is very little difference between the three slopes and the increase in venous admixture is quite similar for any of the therapeutic procedures (BVE, DI or II). This increase seems to be primarily related to a rise in pulmonary blood flow. The similar effect of quite similar therapeutic procedures on blood gas exchange have been previously documented in patients with mitral valve disease.25

The hemodynamic effect of these three therapeutic procedures (BVE, DI and II) during septic shock improves systemic oxygen transport, and thereby improves tissue PO2. The latter would, theoretically, be expected to result in raised mixed venous oxygen content and PAo2. In fact, in our patients PAo2 decreased slightly because the increase in mixed venous oxygen content was offset by the increase in QS/QT.

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