The Relationship Between Oxygen Delivery and Consumption during Fluid Resuscitation of Hypovolemic and Septic Shock

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The effects of increasing oxygen delivery (DO₂) on oxygen consumption (VO₂) in eight patients with septic shock and five patients with hypovolemic shock were studied during fluid resuscitation. In the septic shock group, DO₂ increased from 315 ± 29 to 424 ± 25 ml/min/m² (p < 0.01) and VO₂ increased from 134 ± 8 to 151 ± 7 ml/min/m² (p < 0.01). In the hypovolemic shock group, DO₂ increased from 239 ± 26 to 386 ± 48 ml/min/m² (p < 0.01) and VO₂ increased from 96 ± 9 to 135 ± 6 ml/min/m² (p < 0.01). There was no significant difference in either the increase in DO₂ or VO₂ between the septic shock and hypovolemic shock patients. We conclude that increasing DO₂ by fluid resuscitation increases VO₂ during both hypovolemic and septic shock.

Recovery from circulatory shock is dependent on the restoration of oxygen delivery and subsequent oxygen utilization for oxidative phosphorylation by the respiratory enzymes of the mitochondria. Decreases of oxygen consumption in patients with circulatory shock correlate with mortality. The decline in oxygen consumption in hypovolemic shock is a result of a decrease in oxygen delivery. The etiology of the decrease of oxygen consumption in septic shock is controversial. Some authors believe that arteriovenous shunting with a resultant deficiency in nutrient capillary flow occurs, whereas others implicate impaired cellular function with an inability of mitochondria to utilize delivered oxygen.

This prospective study was designed to evaluate how increases in oxygen delivery during volume loading affect oxygen utilization in patients with hypovolemic and septic shock.

Materials and Methods

A summary of the individual patient data is given in Table 1. Thirteen consecutive patients with circulatory shock in whom volume loading increased oxygen delivery were investigated. The patients ranged in age from 66 to 97 years (median = 81 years). Five (38 percent) of the patients were in hypovolemic shock. Eight (62 percent) of the patients had septic shock. Septis was verified by positive blood culture or identification of an infected site.

Patients were entered into the study if pretreatment determinations revealed: 1) a cardiac index (CI) less than 2.2 L/min/m² or a systolic intra-arterial pressure of less than 90 mm Hg, 2) an arterial lactate greater than 18 mg/dl, and 3) a pulmonary artery wedge pressure (PAWP) less than 15 mm Hg. Patients were excluded from the study if they were: 1) less than 18 years of age, 2) considered to be in a terminal state, or 3) failed to increase oxygen delivery (cardiac output × arterial oxygen content) in response to volume loading.

All patients underwent femoral artery (Longdwell, Becton-Dickinson) and pulmonary artery (Swan-Ganz, Edwards Laboratories) catheterization with continuous pulmonary artery pressure monitoring in order to guide a fluid challenge of 250 ml every 15 minutes until the PAWP reached 15 mm Hg. Hemodynamic and metabolic measurements were obtained at baseline and every 30 minutes during the fluid challenge. The point of maximum oxygen delivery during volume loading was chosen for comparison to baseline.

Data collected on each patient consisted of clinical, hemodynamic, metabolic and respiratory information. Primary hemodynamic data included heart rate (HR), mean intra-arterial pressure (MAP), mean central venous pressure (CVP), mean pulmonary artery wedge pressure (PAWP), thermodilution cardiac output (CO), and arterial lactate. All pressures were recorded with the patient in the supine position utilizing strain gauge transducers (7201, Bell and Howell) leveled to the mid-chest position, zeroed to atmosphere and calibrated to a known mercury standard. All pressures were recorded with a bedside microprocessor monitor (SOLO, Menken Medical, Inc). Thermodilution cardiac output was taken as the mean of triplicate measurements using 10 ml of 5 percent dextrose in water injected cooled to less than 1°C. Derived hemodynamic data included cardiac index (C), stroke volume index (SVI), left ventricular stroke work index (LVSWI), and systemic vascular resistance (SVR) calculated from the following formulae:

1) CI (L/min/m²) = CO / BSA
2) SVI (ml/m²) = HR × BSA
3) LVSWI (g-m/m²) = (SVI)(MAP-PAWP) × 0.0136
4) SVR (dynessec/cm²) = MAP / CO

Lactate samples were drawn from the arterial line into a sodium fluoride preservative tube that was immediately placed on ice, and measured within 20 minutes with an automated spectrophotometer (ABA-50, Abbott). The normal arterial lactate level in our laboratory is less than 7 mg/dl.

Primary respiratory data included the partial pressure of oxygen in arterial blood (PaO₂), the partial pressure of oxygen in mixed venous blood (PVo₂), arterial hemoglobin (Hb), percentage of oxygen saturation of arterial blood, and percentage of oxygen saturation of...
mixed venous blood. Derived respiratory data included arterial oxygen content (\(\text{CaO}_2\)), venous oxygen content (\(\text{CVO}_2\)), arterial-venous oxygen content difference (A-VdO\(_2\)) and oxygen extraction ratio, calculated from the following formulas:

1. \(\text{CO}_2 (\text{vol}\%) = 1.34 (\text{Hb}) \times (\text{sat} ) + 0.003 (\text{Po}_2)\)
2. \(\text{A-VdO}_2 (\text{vol}\%) = \frac{\text{CaO}_2 - \text{CVO}_2 \times \text{O}_{2}}{100}\)
3. oxygen extraction ratio (%) = \(\frac{\text{A-VdO}_2}{\text{CaO}_2}\)

Blood gases were measured by an automated blood gas laboratory (ABL 2, Radiometer) which was calibrated hourly. Hemoglobin concentration and oxyhemoglobin saturation were measured directly using a hemoximeter (OSM-2, Radiometer).

Derived metabolic data included oxygen delivery index (\(\text{DO}_2\)) and oxygen consumption index (\(\text{VO}_2\)) calculated as follows:

1. \(\text{DO}_2 (\text{ml/min/m}^2) = CI \times \text{CaO}_2 \times 10\)
2. \(\text{VO}_2 (\text{ml/min/m}^2) = CI \times (\text{A-VdO}_2) \times 10\)

Statistical analysis was accomplished utilizing the Student's \(t\) test for independent and dependent samples (two tailed). Differences were considered significant at the 0.05 level. All data are reported as mean ± standard error of the mean (SEM).

**RESULTS**

The time to peak \(\text{DO}_2\) during fluid challenge was 78 ± 18 min in the hypovolemic patients and 66 ± 11 min in the septic group (NS). Comparison of baseline values to values obtained at peak \(\text{DO}_2\) revealed significant increases in PAWP, CI, SVI, LVSWI and MAP in both the septic and hypovolemic group of patients. The A-VdO\(_2\) and the oxygen extraction ratio decreased in both groups, but not significantly. Fluid resuscitation resulted in a significant increase in \(\text{DO}_2\) in both groups. In the hypovolemic shock group \(\text{DO}_2\) increased from 239 ± 25 to 386 ± 48 ml/min/m\(^2\) (\(p < 0.01\)). In the septic shock group, \(\text{DO}_2\) increased from 315 ± 29 to 424 ± 24 ml/min/m\(^2\) (\(p < 0.01\)). The increase in \(\text{DO}_2\) was associated with a significant increase in \(\text{VO}_2\) in both patient groups, rising from 96 ± 9 to 135 ± 6 ml/min/m\(^2\) (\(p < 0.04\)) in the hypovolemic shock patients and from 134 ± 8 to 151 ± 7 ml/min/m\(^2\) (\(p < 0.01\)) in the septic shock patients. The individual changes in \(\text{DO}_2\) and \(\text{VO}_2\) are shown in Figures 1 and 2.

There were no significant differences in the increases of PAWP, CI, SVI, LVSWI, MAP and \(\text{DO}_2\) with fluid challenge between the hypovolemic and septic...
Oxygen consumption is an overall index of total body metabolism. The optimal oxygen consumption is determined by the metabolic needs of the tissues. Wilson et al. documented in critically ill patients that decreases in oxygen consumption were associated with increases in mortality. Duff et al. noted that in patients with septic shock oxygen consumption was inversely related to arterial lactate level. Indeed, the development of anaerobic metabolism and consequent lactic acidosis serves as a metabolic marker of shock and a prognostic indicator in critically ill patients. The severity of circulatory shock in our patients is documented by the profound lactic acidosis.

Oxygen consumption decreases in hypovolemic shock as a result of a decrease in oxygen delivery. Interventions which increase oxygen delivery would be expected to increase oxygen consumption. Mohr et al. noted that patients in shock who increased their cardiac index and oxygen consumption after fluid challenge usually had shock due to hypovolemia. Siegel and associates noted that in patients with hypovolemic shock small increments in cardiac output were associated with large increments in oxygen consumption. The effects of fluid resuscitation in our five patients with hypovolemic shock are consistent with the findings of these previous studies. During fluid challenge, increases in cardiac output and oxygen delivery resulted in significant increases in oxygen consumption. The oxygen consumption in septic shock patients is adequate to meet their metabolic demands. The pathophysiology of inadequate oxygen consumption and subsequent development of a lactic acidosis in septic shock is still unclear. At present, the most widely accepted theories to account for this oxygen debt are either the redistribution of blood flow, with consequent decrease in nutrient capillary flow, or the development of a cellular metabolic blockade at the mitochondrial level such that delivered oxygen cannot be utilized.

Hypovolemia commonly occurs in septic shock. The hypovolemia may be secondary to pre-existing illness, decreased fluid intake, increased insensible loss, or peritonitis with sequestration of fluid within the peritoneal cavity. In addition, some septic shock patients may have an inappropriate polyuria due to the development of a hyperdynamic renal circulation. Increases in capillary permeability with interstitial fluid accumulation and cellular edema has also been postulated as a cause of the intravascular volume

### Table 2—Difference between Hypovolemic and Septic Shock

<table>
<thead>
<tr>
<th>Hypovolemic Shock (HS)</th>
<th>Septic Shock (SS)</th>
<th>HS vs SS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline</strong></td>
<td><strong>Peak DO&lt;sub&gt;2&lt;/sub&gt;</strong></td>
<td><strong>ΔBaseline</strong></td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>89.6 ± 8.6</td>
<td>85.6 ± 7.1</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>50.2 ± 5.1</td>
<td>67.0 ± 5.4</td>
</tr>
<tr>
<td>PAWP (mm Hg)</td>
<td>7.1 ± 7</td>
<td>10.6 ± 1.3</td>
</tr>
<tr>
<td>CI L/min/m&lt;sup&gt;2&lt;/sup&gt;</td>
<td>1.56 ± 0.12</td>
<td>2.54 ± 0.26</td>
</tr>
<tr>
<td>SVR (dynes<em>sec</em>cm&lt;sup&gt;5&lt;/sup&gt;)</td>
<td>1368 ± 136</td>
<td>1167 ± 172</td>
</tr>
<tr>
<td>Hb (g/dl)</td>
<td>12.3 ± 0.6</td>
<td>11.7 ± 0.7</td>
</tr>
<tr>
<td>PaO&lt;sub&gt;2&lt;/sub&gt; (mm Hg)</td>
<td>93.2 ± 19.0</td>
<td>98.8 ± 19.0</td>
</tr>
<tr>
<td>PaCO&lt;sub&gt;2&lt;/sub&gt; (mm Hg)</td>
<td>34.9 ± 2.0</td>
<td>33.2 ± 3.1</td>
</tr>
<tr>
<td>PrVO&lt;sub&gt;2&lt;/sub&gt; (mm Hg)</td>
<td>31.2 ± 3.3</td>
<td>34.8 ± 1.8</td>
</tr>
<tr>
<td>A-VDO&lt;sub&gt;2&lt;/sub&gt; (Vol%)</td>
<td>6.4 ± 9</td>
<td>5.5 ± 0.5</td>
</tr>
<tr>
<td>DO&lt;sub&gt;2&lt;/sub&gt; (ml/min/m&lt;sup&gt;2&lt;/sup&gt;)</td>
<td>238.5 ± 26.2</td>
<td>286.46 ± 26.2</td>
</tr>
<tr>
<td>VO&lt;sub&gt;2&lt;/sub&gt; (ml/min/m&lt;sup&gt;2&lt;/sup&gt;)</td>
<td>95.7 ± 9.1</td>
<td>134.8 ± 5.8</td>
</tr>
<tr>
<td>O&lt;sub&gt;2&lt;/sub&gt;Ext (%)</td>
<td>42% ± 6.7</td>
<td>37% ± 5.0</td>
</tr>
<tr>
<td>Lactate (mg/dl)</td>
<td>66.4 ± 17.3</td>
<td>52.0 ± 11.1</td>
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</table>
depletion. Nishijima et al have documented low plasma volumes in patients with septic shock. Furthermore, they found a close relationship between cardiac output and plasma volume in septic shock patients. Loeb and associates documented decreases in right atrial pressure despite normal blood volume in patients with septic shock, possibly related to peripheral venous pooling of blood. Thus, the initial cardiac index in patients with septic shock may be a function of the venous return and therefore the preload presented to the heart.

Several authors have stressed the beneficial effects of volume expansion in patients with either hypodynamic or hyperdynamic septic shock. Survival has been reported to be improved in patients who can increase their stroke volume or cardiac output in response to fluid challenge. Nevertheless, few data are available on the effect of volume expansion on oxygen consumption in patients with septic shock. Mohr and associates demonstrated that fluid challenge in patients in septic shock failed to increase oxygen consumption despite hemodynamic improvement. However, the baseline oxygen consumption prior to fluid challenge was 200 ml/min/m². The elevated level of oxygen consumption in these patients may be indicative of adequate oxygen delivery prior to volume loading, and thus, oxygen consumption would not be expected to increase further. The effects of fluid resuscitation on oxygen consumption in our patients with septic shock do not support the findings of Mohr's study. We found that increases in cardiac output and oxygen delivery in response to volume loading significantly increased total body oxygen consumption. This suggests that the increase in oxygen consumption reflected increased nutrient capillary blood flow. The most probable explanation for the differing response to volume loading in our septic shock patients versus those in Mohr's series is that the initial oxygen consumption in our patients was only 134 ml/min/m², indicative of a more profound state of shock at the time of volume loading. Alternatively, our patients may be representative of an early state of septic shock where oxygen delivery may be rate limiting to oxygen consumption, whereas Mohr's patients may have been studied during a later phase in which intracellular metabolic block to oxygen utilization was evidenced.

The increase of oxygen consumption with fluid resuscitation in patients with both hypovolemic shock and septic shock suggests that a deficit in nutrient capillary flow existed in both groups. In hypovolemic shock, the deficit may result entirely from a decrease in oxygen delivery and would be expected to result in mixed venous desaturation, as was true of the patients in our study. In septic shock the deficit may result from a redistribution of blood flow, as oxygen delivery can be normal or increased. An inefficient distribution of the cardiac output is consistent with the relatively normal mixed venous oxygen in our septic shock patients. Since mixed venous oxygen represents the weighted means of the venous effluents of the body's tissues, a high or normal value could be maintained even in the face of areas with inadequate tissue oxygenation if other areas receive excessive flow. Tissue oxygen in areas of decreased nutrient flow would be expected to be decreased. Hiller et al measured tissue oxygen in dogs injected with E coli endotoxin and found that mixed venous oxygen remained in the normal range while tissue oxygen was decreased. Similar results were obtained by Fry et al in a rat model of septic shock. After inducing peritonitis by cecal perforation, hepatic tissue oxygenation decreased even though arterial oxygen and blood pressure were initially maintained. In addition, these authors found that there was no primary injury to hepatic mitochondria, but rather mitochondrial oxygen utilization efficiency increased. On the other hand, Wright et al found that in dogs with sepsis increased cardiac output was accompanied by increased capillary blood flow but decreased oxygen extraction. Finley et al documented similar results in that increases in cardiac output were not associated with decreases in capillary blood flow in septic patients, as would be expected if anatomic shunts existed. Since both studies evaluated capillary blood flow during the hyperdynamic septic state but not in septic shock, they do not exclude a decreased capillary blood flow as the mechanism leading to increased anaerobic metabolism during septic shock.

Our findings that at comparable increases of cardiac index and oxygen delivery there was no significant difference in the increase in oxygen consumption between hypovolemic shock and septic shock patients are consistent with the experimental findings of unaltered mitochondrial utilization of oxygen in septic shock. They do not support the hypothesis that the patient in septic shock cannot consume oxygen due to mitochondrial blockade. To the contrary, we conclude that increasing oxygen delivery during fluid resuscitation increases tissue oxygen consumption in patients with both hypovolemic and septic shock.

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