Norepinephrine or Dopamine for the Treatment of Hyperdynamic Septic Shock?

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Study objective: To compare the ability of dopamine and norepinephrine to reverse hemodynamic and metabolic abnormalities of human hyperdynamic septic shock.

Design: Prospective, double-blind, randomized trial.

Setting: An ICU in a university hospital.

Patients: Adult patients with hyperdynamic septic shock after fluid resuscitation.

Interventions: Patients were assigned to receive either dopamine (2.5 to 25 μg/kg/min) or norepinephrine (0.5 to 5.0 μg/kg/min). If hemodynamic and metabolic abnormalities were not corrected with the maximum dose of one drug, the other was added.

Measurements and results: The aim of therapy was to achieve and maintain for at least 6 h all of the following: (1) systemic vascular resistance index >1,100 dynes·cm⁻²·m⁻² and/or mean systemic blood pressure ≥80 mm Hg; (2) cardiac index ≥3 L/min/m²; (3) oxygen delivery >550 ml/min/m²; and (4) oxygen uptake >150 ml/min/m². With the use of dopamine 10 to 25 μg/kg/min, 5 of 16 patients (31 percent) were successfully treated, as compared with 13 of 16 patients (93 percent) by norepinephrine at a dose of 1.5 ± 1.2 μg/kg/min (p<0.001). Ten of 11 patients who did not respond to dopamine and remained hypotensive and oliguric were successfully treated with the addition of norepinephrine.

Conclusions: At the doses tested, norepinephrine was found, in the present study, to be more effective and reliable than dopamine to reverse the abnormalities of hyperdynamic septic shock. In the great majority of the study patients, norepinephrine was able to increase mean perfusing pressure without apparent adverse effect on peripheral blood flow or on renal blood flow (since urine flow was reestablished). At the same time, oxygen uptake was increased.

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Septic shock that persists after blood volume expansion is often hemodynamically characterized by hypotension, systemic vasodilatation, and high cardiac index (CI). Metabolically, hyperdynamic septic shock is characterized by a reduced oxygen uptake and an abnormal flow dependence of index of O₂ uptake (IVO₂) on index of O₂ delivery (IDO₂) even at a normal or high delivery rate. According to hemodynamic monitoring, and after fluid challenge, inotropic agents with vasoconstrictive properties are commonly used to reverse hyperdynamic septic shock. Early studies showed that norepinephrine could be effective, but because of the lack of routine hemodynamic monitoring and the fears of excessive vasoconstriction, this drug is not widely used. Indeed, the inappropriate use of potent vasopressor agents leads to tissue hypoperfusion and severe ischemia of vital organs. Newer catecholamines were made available for the treatment of shock states and among them, dopamine is widely recommended for the treatment of septic shock because it increases systemic blood pressure by a combined action on myocardial performance and systemic vascular resistance. However, in many patients, dopamine fails to restore adequate hemodynamic conditions, and norepinephrine has been found to be beneficial. So far, to our knowledge, there has been no conclusive study comparing the two drugs. This prospective, randomized, double-blind study was performed to compare the ability of norepinephrine and dopamine to reverse hemodynamic abnormalities of human hyperdynamic septic shock. Since hemodynamic management of septic shock is also aimed at improving the oxygen supply to organs, the effects of both drugs on oxygen metabolism were also studied.
METHODS

This prospective, randomized, double-blind study included 32 consecutive patients presenting with hyperdynamic septic shock. The study received approval of the Ethics Committee of our Institution, and written informed consent was obtained from a close relative. Hyperdynamic septic shock was defined as follows: (1) systolic blood pressure (SBP) of less than 90 mm Hg; (2) CI of more than 4.0 L/min/m²; (3) decreased organ perfusion as evidenced by altered mental status (prior to sedation) and/or oliguria (less than 30 mL/h); (4) arterial blood lactate levels greater than 2.5 mmol/L; and (5) bacteremia, or in patients undergoing concomitant broad spectrum antibiotic treatment, an identified source of infection. All patients had a body temperature greater than 38.5°C.

Hemodynamic and Metabolic Studies

Heart rate was monitored continuously. Arterial pressure was monitored via an arterial catheter (radial artery). All patients had their pulmonary artery catheterized with a Swan-Ganz catheter. Serial measurements of heart rate (HR), mean blood pressure (MBP), central venous pressure (CVP), mean pulmonary artery pressure (MPAP) and pulmonary capillary wedge pressure (PCWP) were made. All pressures were measured at end-expiration with the patient in the supine position. Transducers were referenced to the midaxillary line. In all patients, cardiac output was recorded in triplicate by the thermodilution technique, using ice chilled (<2°C) 10 ml 5 percent dextrose injections performed at end-expiration. Oxyhemoglobin saturation and oxygen content were measured in systemic and pulmonary arterial blood using an oximeter (IL 282, Instrumentation Laboratories, Lexington, Mass). Derived hemodynamic variables were calculated as follows: systemic vascular resistance index (SVRI) (dynes-cm²/m²) = (SBP-CVP)/CVP · CI × 60; VO₂ (mL/min/m²) = (a-V)O₂ · CI × 10 where (a-V)O₂ = arteriovenous oxygen difference; DO₂ (mL/min/m²) = arterial O₂ content (CaO₂) · CI × 10; O₂ extraction rate (O₂ ext) (%) = CaO₂ - mixed venous O₂ content (CvO₂)/CaO₂. Urine was collected via an indwelling bladder catheter. Lactate samples were drawn from the arterial catheter.

Therapeutic Protocol

Patients received broad-spectrum antibiotic coverage. None of these patients received corticosteroids. Because of severe hypoxia due to acute pneumonia in 18 patients and adult respiratory distress syndrome in the remaining patients, respiratory support was needed in all patients. Adult respiratory distress syndrome was characterized by bilateral homogeneous pulmonary opacifications on chest radiographic examination, and marked arterial hypoxemia lower than 60 mm Hg at FiO₂ = 0.50. Tidal volume, respiratory rate, and FiO₂ were adjusted to maintain normal pH and PaCO₂ value and to keep PaO₂ above 70 mm Hg.

All patients received volume expansion that was started before the pulmonary artery catheter was in place. Indication of volume expansion was a CVP of less than 12 mm Hg. Fluid resuscitation consisted of colloid and crystalloid solutions, and blood hematocrit was maintained greater than 33 percent with blood transfusion. Once the pulmonary artery catheter was in place, left ventricular preload was established from PCWP and was considered optimal when, at a given level, additional fluid infusion was no longer accompanied by an increase in CI. Fluid resuscitation was also discontinued when PaO₂ showed a marked decrease (more than 15 percent), which was the case in seven patients. To be included in the study, after optimal ventilatory management and fluid resuscitation, the patients had to present all of the following: (1) SBP of less than 90 mm Hg; (2) SVRI of less than 1,000 dyne·sec·cm⁻²·m⁻²; (3) CI greater than 4.0 L/min/m²; (4) persistent oliguria (less than 30 mL/h); and (5) arterial blood lactate level greater than 2.5 mmol/L. When patients fulfilled these inclusion criteria, a continuous infusion of either dopamine or norepinephrine was started via a separate central venous line and an automatic pump. Dopamine was used as an original solution containing 40 mg/ml and norepinephrine, 2 mg/ml. For each patient, two drug dilutions were prepared. One contained dopamine diluted so that an infusion rate of 2 ml/min allowed us to deliver 2.5 μg/kg/min to the patient. Two-milliliter increments were allowed up to a maximum dose of 25 μg/kg/min (infusion rate, 20 ml/min). The other solution contained norepinephrine diluted so that an infusion rate of 2 ml/min allowed us to deliver to the patient 0.5 μg/kg/min. Two-milliliter increments were allowed up to a maximum dose of 5 μg/kg/min (infusion rate, 20 ml/min). Then each patient received either dopamine or norepinephrine, according to the randomization code. Dopamine was started at a dose of 2.5 μg/kg/min and norepinephrine was started at a dose of 0.5 μg/kg/min (i.e., 2 ml/min for each patient). Then catecholamine doses were increased by 2 ml/min or multiples of 2-ml/min increments after 5- to 10-minute intervals when hemodynamic abnormalities were not corrected. A maximal infusion rate of 20 ml/min was used (dopamine, 25 μg/kg/min; norepinephrine, 5 μg/kg/min). At no time was the physician in charge of the patient aware of the drug being infused. The aim of therapy was to achieve and maintain for at least 6 consecutive hours all of the following: (1) SVRI greater than 1,100 dyne·sec·cm⁻²·m⁻² and/or MBP greater than 80 mm Hg; (2) CI greater than 4.0 L/min/m²; (3) DO₂ greater than 550 ml/min/m²; and (4) Vo₂ greater than 150 ml/min/m². If the therapeutic goals were not fulfilled with the use of the maximal dose, the catecholamine dose infusion was continued, the other drug was added, and doses were progressively increased as described above. Once hemodynamic stabilization was obtained, drug titration was modified, when needed, according to the hemodynamic assessments performed every 2 h. Fluids were given to maintain PCWP at the previously determined optimal level. Catecholamines were continued until recovery or death.

Statistics

Data are reported as mean ± SD. Repeated measures analysis of variance and the Student-Newman-Keuls' test were used to evaluate differences between groups with respect to change over time. Within-group variabilities were tested using two-way analysis of variance and means were then compared by Duncan's multiple range test. A two-sided p value of <0.05 was considered statistically significant.

RESULTS

Thirty-two patients were included in the study. Table 1 shows that at the time of inclusion in the study, no difference was observed between the two groups with regard to clinical data of the 32 patients. Table 2 shows that at the time of inclusion to the study, no...
Table 2—Hemodynamic and Metabolic Data of the Patients Who Responded to Norepinephrine or Dopamine + Norepinephrine*

<table>
<thead>
<tr>
<th></th>
<th>Norepinephrine</th>
<th>Dopamine + Norepinephrine</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Baseline†</td>
<td>Nor‡</td>
</tr>
<tr>
<td>MBP, mm Hg</td>
<td>54 ± 10</td>
<td>89 ± 13¶</td>
</tr>
<tr>
<td>HR, beat/min</td>
<td>113 ± 21</td>
<td>112 ± 18</td>
</tr>
<tr>
<td>CI, L/min/m²</td>
<td>5.3 ± 1.3</td>
<td>5.5 ± 1.2</td>
</tr>
<tr>
<td>PCWP, mm Hg</td>
<td>12 ± 3</td>
<td>14 ± 4</td>
</tr>
<tr>
<td>SVR, dyn.sec/cm²-m¹</td>
<td>659 ± 221</td>
<td>1,150 ± 350¶</td>
</tr>
<tr>
<td>MPA, mm Hg</td>
<td>24 ± 5</td>
<td>28 ± 5</td>
</tr>
<tr>
<td>O₂ ext</td>
<td>0.28 ± 0.10</td>
<td>0.28 ± 0.10</td>
</tr>
<tr>
<td>IDo₂, ml/min/m²</td>
<td>810 ± 231</td>
<td>840 ± 225</td>
</tr>
<tr>
<td>IVo₂, ml/min/m²</td>
<td>208 ± 70</td>
<td>232 ± 85†</td>
</tr>
<tr>
<td>Urine output, ml/h</td>
<td>22 ± 7</td>
<td>153 ± 51¶</td>
</tr>
<tr>
<td>Lactate, mmol/L</td>
<td>4.8 ± 1.6</td>
<td>4.4 ± 1.8</td>
</tr>
</tbody>
</table>

*CI = cardiac index; HR = heart rate; IDo₂ = oxygen delivery; IVo₂ = oxygen uptake; MBP = mean blood pressure; MPA = mean pulmonary artery pressure; O₂ ext = oxygen extraction; PCWP = pulmonary capillary wedge pressure; SVRI = systemic vascular resistance index.
†Sixteen patients randomized to receive norepinephrine.
‡Fifteen patients who responded to norepinephrine (stabilization and after 6 h).
§Sixteen patients randomized to receive dopamine.
∥Ten patients who did not respond to dopamine, 25 µg/kg/min, and subsequently received norepinephrine (stabilization and after 6 h).
¶p<0.0001 vs “baseline.”
**p<0.001 vs “baseline.”
††p<0.05 vs “baseline.”

A significant difference was observed between the two groups with regard to hemodynamic and metabolic parameters (baseline values). With the use of dopamine, 10 to 25 µg/kg/min, only 5 of 16 patients (31 percent) were successfully treated and fulfilled the therapeutic goals (Table 3) as compared with 15 of 16 patients (93 percent) with norepinephrine (p<0.001) at a dose of 1.5 ± 1.2 µg/kg/min (Table 2). One patient in each group did not respond to a combination of dopamine, 25 µg/kg/min, and norepinephrine, 5 µg/kg/min.

These two patients died within a few hours of intractable septic shock despite the addition of epinephrine (5 µg/kg/min). Ten of the 11 patients who did not respond to dopamine, 25 µg/kg/min, were successfully treated with the addition of norepinephrine (1.7 ± 1.8 µg/kg/min) (Table 2). In patients who received norepinephrine first, there were significant increases in MBP, SVRI, IVo₂, and urine flow (Table 2). These changes were maintained over 6 h. A significant decrease in blood lactate levels was also observed (Table 2). In the

Table 3—Hemodynamic and Metabolic Data of the Responders (Five Patients, 10 to 25 µg/kg/min) and the Nonresponders (Ten Patients, 25 µg/kg/min) to Dopamine*

<table>
<thead>
<tr>
<th></th>
<th>Responders (n = 5)</th>
<th>Nonresponders (n = 10)</th>
<th>Dopamine, 10 to 25 µg/kg/min</th>
<th>Responders (n = 5)</th>
<th>Responders + 6 hours (n = 5)</th>
<th>Dopamine, 25 µg/kg/min, Nonresponders (n = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MBP, mm Hg</td>
<td>54 ± 4</td>
<td>51 ± 10</td>
<td>94 ± 12†</td>
<td>96 ± 5†</td>
<td>59 ± 10</td>
<td></td>
</tr>
<tr>
<td>HR, beat/min</td>
<td>110 ± 20</td>
<td>109 ± 18</td>
<td>117 ± 14</td>
<td>110 ± 17</td>
<td>122 ± 23</td>
<td></td>
</tr>
<tr>
<td>CI, L/min/m²</td>
<td>5.8 ± 1</td>
<td>5.0 ± 1.1</td>
<td>6.8 ± 2.1‡</td>
<td>6.1 ± 1.3</td>
<td>5.5 ± 1</td>
<td></td>
</tr>
<tr>
<td>PCWP, mm Hg</td>
<td>14 ± 3</td>
<td>16 ± 7</td>
<td>19 ± 6‡</td>
<td>15 ± 5</td>
<td>19 ± 4‡</td>
<td></td>
</tr>
<tr>
<td>SVR, dyn.sec/cm²-m¹</td>
<td>642 ± 147</td>
<td>601 ± 197</td>
<td>1,003 ± 455†</td>
<td>1,270 ± 350†</td>
<td>659 ± 217</td>
<td></td>
</tr>
<tr>
<td>MPA, mm Hg</td>
<td>24 ± 6</td>
<td>25 ± 4</td>
<td>36 ± 7†</td>
<td>28 ± 9</td>
<td>28 ± 6</td>
<td></td>
</tr>
<tr>
<td>O₂ ext</td>
<td>0.19 ± 0.06</td>
<td>0.26 ± 0.09</td>
<td>0.21 ± 0.05</td>
<td>0.20 ± 0.09</td>
<td>0.26 ± 0.02</td>
<td></td>
</tr>
<tr>
<td>IDo₂, ml/min/m²</td>
<td>932 ± 110</td>
<td>659 ± 182‡</td>
<td>1,052 ± 288</td>
<td>947 ± 205</td>
<td>697 ± 175</td>
<td></td>
</tr>
<tr>
<td>IVo₂, ml/min/m²</td>
<td>169 ± 71</td>
<td>182 ± 65</td>
<td>221 ± 54</td>
<td>193 ± 51</td>
<td>188 ± 65</td>
<td></td>
</tr>
<tr>
<td>Urine output, ml/h</td>
<td>20 ± 2</td>
<td>17 ± 4</td>
<td>202 ± 25†</td>
<td>196 ± 36†</td>
<td>8.2 ± 10</td>
<td></td>
</tr>
<tr>
<td>Lactate, mmol/L</td>
<td>4.7 ± 2.2</td>
<td>4.9 ± 3.7</td>
<td>4.3 ± 2.15</td>
<td>2.3 ± 1.1†</td>
<td>4.2 ± 2.0</td>
<td></td>
</tr>
</tbody>
</table>

*CI = cardiac index; HR = heart rate; IDo₂ = oxygen delivery; IVo₂ = oxygen uptake; MBP = mean blood pressure; MPA = mean pulmonary artery pressure; O₂ ext = oxygen extraction; PCWP = pulmonary capillary wedge pressure; SVRI = systemic vascular resistance index.
†p<0.001 vs all other groups.
‡p<0.02 vs “responders, before dopamine.”
§p<0.005 vs “before dopamine.”
∥p<0.01 vs “before dopamine.”

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Norepinephrine or Dopamine in Septic Shock? (Martin et al)
10 patients who did not respond to dopamine, 25 μg/kg/min, and remained markedly hypotensive and oliguric, a similar pattern of evolution was observed (Table 2) when norepinephrine was added. A significant increase in MBP, SVRI, MPAP, PCWP, and urine flow was observed, but no significant decrease in blood lactate levels was seen during the study period. In this group of patients, IVO₂ did not change. Table 3 shows the hemodynamic and metabolic data of the 5 patients successfully treated with dopamine, 10 to 25 μg/kg/min. Significant increases in MBP, SVRI, MPAP, PCWP, and urine flow were observed. No change in IDO₂ and IVO₂ was noted. After 6 h of therapy, increases in MBP, SVRI, and urine flow were maintained, but MPAP and PCWP returned to baseline values. A significant decrease in blood lactate levels was observed. At the time of inclusion in the study, no difference was seen between responders and non-responders to dopamine with the exception of IDO₂ which was greater in the responders (Table 3). Fifteen patients were discharged from the hospital; 9 were primarily given norepinephrine, and 6 were given dopamine.

**DISCUSSION**

The main result of the present study is that, at the dosages tested, norepinephrine was more efficient and reliable than dopamine to reverse the hemodynamic abnormalities seen in hyperdynamic septic shock. Norepinephrine was also capable of being active when high-dose dopamine (25 μg/kg/min) failed. The traditional treatment of hemodynamic abnormalities of septic shock includes restoration of intravascular volume by fluid infusion and the use of adrenergic drugs if hypotension persists despite adequate volume resuscitation. Dopamine is the most common first choice and its use has been widely advocated. However, several studies have shown that an adequate tissue perfusion pressure cannot be obtained in many patients with the use of dopamine, even at doses as high as 80 μg/kg/min.¹⁷-¹⁹ In these studies, norepinephrine was found to be beneficial, with improvement in arterial blood pressure, urine flow, oxygen delivery, and consumption. However, excessive vasoconstriction with impaired tissue oxygenation is a potential risk when using norepinephrine. To avoid such a deleterious effect, it has been suggested that the rational use of norepinephrine should be based not only on the reversal of hypotension, but also on the achievement of appropriate physiologic end-points on DO₂ and VO₂.²⁰,²¹ Therapeutic goals and physiologic end-points used in the present study were defined from values previously obtained in survivors of life-threatening critical illnesses.²²-²⁵ The aim of therapy was to achieve and maintain optimal hemodynamic and oxygen metabolism patterns and, at the same time, to restore a normal tissue perfusion pressure. The attempt to normalize blood pressure at the expense of CI and DO₂, by using high doses of vasopressors, leads to poor survival.²⁶ Restoring and maintaining high CI values are not sufficient per se since survivors and nonsurvivors of septic shock may have a normal or high CI even within a few hours of death.²⁷,²⁸ However, previous studies have suggested that maintaining a high CI may be an important goal of therapy since patients who eventually died were reported to exhibit evolution from a hyperdynamic to a hypodynamic state.²⁹-³⁷ To fulfill the therapeutic goals, fluid infusion was selected as the first priority in order to correct blood volume defect. Following volume loading, the patients had high CI and low SVRI, a hemodynamic profile perfectly suited to the use of a potent vasopressor agent. Norepinephrine was able to reverse hemodynamic abnormalities in 93 percent of the patients and dopamine in only 31 percent. Vasopressor infusion should not be considered in patients with high SVRI since elevated cardiac afterload obtained by placing a strain on the myocardium could be deleterious in case of severe cardiac dysfunction. This point is crucial: a potent vasopressor such as norepinephrine must be used only to restore normal values of SVRI and/or systemic arterial blood pressure in patients with severe and documented vasodilation. Although there are some methodologic problems with the use of SVRI as the sole measurement of peripheral resistance,³² it was found in the present study that adjusting vasopressor infusion rate according to this parameter was beneficial. Potentially deleterious effects of vasoconstriction were avoided as shown by the improvement in urine output and blood lactate levels.

Other studies have demonstrated the beneficial effects of norepinephrine on renal function during septic shock.¹⁷-¹⁹,³³,³⁴ In patients with hypotension and hypovolemia, e.g., during hemorrhagic shock, the use of vasopressor should be avoided for the following reasons: despite the constant improvement in blood pressure, renal blood flow decreases and renal vascular resistance rises.¹³ The situation is different in hyperdynamic septic shock. It is speculated that urine flow decreases mainly as a result of lowered glomerular perfusion pressure. Since norepinephrine has a greater effect on efferent than on afferent arteriolar resistance³⁶ and increases the filtration fraction, normalization of renal vascular resistance could effectively reestablish urine flow. Schaer et al³⁶ have demonstrated that when CI is normal or elevated, norepinephrine increases renal vascular resistance but renal blood flow remains stable or even increases. The increase in urine output observed in most of the study patients could also be explained by a decrease in antidiuretic hormone release which, through different mecha-
nisms, favors water retention. Cardiac and sinoaortic baroreceptors are sensitive to pressure and in case of low intravascular pressure they induce an activation of the sympathetic system and an increase antidiuretic hormone secretion. Restoration of adequate systemic and central pressures in patients with septic shock probably resulted in an inhibition of vasopressin secretion.

Given the positive correlation between VO₂ and survival in septic shock, increasing and maintaining VO₂, even to supranormal values, is one of the major goals of therapy. In the present study, the patients receiving norepinephrine exhibited an increase in VO₂, unaccompanied by an increase in DO₂. This could be a direct effect of the adrenergic drug on the oxidative metabolism. However, the decrease in lactate blood levels observed in the present study does not support this hypothesis, and oxygen was preferentially used in the mitochondria, as the affinity of the extramitochondrial oxidase system is lower than the mitochondrial oxygen transport chain (cytochrome A₃).

An explanation for the increase in VO₂ and the decrease in lactate levels could be the correction of splanchinic ischemia with an efficient hepatic lactate uptake. Indeed, increase in splanchic blood flow has been demonstrated in patients with hyperdynamic septic shock after the use of norepinephrine. Another explanation is that under the influence of norepinephrine, vascular reactivity was restored and blood flow was directed toward the areas of greatest oxygen demand, thus optimizing oxygen extraction.

In conclusion, this study confirms that norepinephrine can be useful to reverse the hemodynamic and metabolic abnormalities of severe hyperdynamic septic shock states. At the doses tested, norepinephrine was found to be more effective and reliable than dopamine for that purpose and can be used even when the latter has failed. In the study patients, norepinephrine fulfilled the therapeutic goals in 93 percent of the patients, and dopamine fulfilled the goals in only 31 percent (p<0.001). Thus, norepinephrine can be considered as a useful drug for the treatment of hyperdynamic septic shock. During therapy, careful attention should be paid to SVRI (which should be maintained in the lower part of the normal range) and to DO₂ (which should be kept greater than 550 ml/min/m²).

References
1 Siegel JI, Greenspan M, Del Guercio LR. Abnormal vascular tone, defective oxygen transport and myocardial failure in human septic shock. Ann Surg 1987; 165:504-17
22 Shoemaker WC, Czer LSC. Evaluation of the biologic importance of various hemodynamic and oxygen transport variables: which variables should be monitored in postoperative shock? Crit Care Med 1979; 7:424-31
24 Shoemaker WC, Appel PL, Bland R. Use of physiologic monitoring to predict outcome and to assist in clinical decisions.
30 Baumgartner JD, Vaney C, Perret C. An extreme form of the hyperdynamic syndrome in septic shock. Intens Care Med 1984; 10:245-49
44 Vincent JL. The relationship between oxygen demand, oxygen uptake and oxygen supply. Intens Care Med 1990; 16(suppl 2):S145-8