Diaspirin cross-linked hemoglobin improves oxygen extraction capabilities in endotoxic shock

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Creteur, Jacques, Haibo Zhang, Daniel De Backer, Qinhua Sun, and Jean-Louis Vincent. Diaspirin cross-linked hemoglobin improves oxygen extraction capabilities in endotoxic shock. J Appl Physiol 89: 1437–1444, 2000.—We studied the effects of diaspirin cross-linked hemoglobin (DCLHb), a cell-free hemoglobin derived from human erythrocytes, on blood flow distribution and tissue oxygen extraction capabilities in endotoxic shock. Eighteen pentobarbital sodium-anesthetized, mechanically ventilated dogs received 2 mg/kg of E. coli endotoxin, followed by saline resuscitation to restore cardiac filling pressures to baseline levels. The animals were randomly divided into three groups: six served as control, six received DCLHb at a dose of 500 mg/kg (group 1) and six DCLHb at a dose of 1,000 mg/kg (group 2). Cardiac tamponade was then induced by saline injection in the pericardial sac to progressively reduce cardiac index and thereby allow study of tissue oxygen extraction capabilities. DCLHb had a dose-dependent vasopressor effect but did not significantly alter cardiac index or regional blood flow. During cardiac tamponade, critical oxygen delivery was $12.8 \pm 0.7$ ml·kg$^{-1}$·min$^{-1}$ in the control group, but $8.6 \pm 0.9$ and $8.2 \pm 0.7$ ml·kg$^{-1}$·min$^{-1}$ in groups 1 and 2, respectively (both $P < 0.05$ vs. control group). The critical oxygen extraction ratio was $39.1 \pm 3.1\%$ in the control group but $58.7 \pm 12.8\%$ and $60.2 \pm 9.0\%$ in groups 1 and 2, respectively. We conclude that DCLHb can improve whole body oxygen extraction capabilities during endotoxic shock in dogs.

Sepsis; hypoxia; oxygen availability; dog experiment

SEPSIS IS A CLINICAL SYNDROME distinguished by systemic inflammation, profound cardiovascular alterations and widespread tissue injury. Microcirculatory dysfunction is recognized to be a significant component of the ubiquitous injury in sepsis (19). An increased release of many mediators, including nitric oxide (NO), a short-life effector molecule involved in the regulation of vascular tone and blood flow distribution, has been largely implicated in this process (43). Hypotension complicating excessive vasodilatation, or myocardial depression, depresses microcirculatory red blood cell (RBC) flow. Endothelial alterations, interstitial edema, leukocyte activation, and RBC entrapment can worsen these microcirculatory abnormalities. The consequence of these abnormalities is a decrease in the perfused capillary density (19), creating conditions that may limit oxygen availability to the cells. Furthermore, several studies (9, 15, 23, 26) have demonstrated an increased stiffness of RBC in sepsis, which is caused by several mechanisms including oxidation by oxygen free radicals (21, 27), ATP depletion, and increase in intracellular calcium (30), thus rendering the erythrocytes less deformable for penetrating the microcirculation (20, 41).

Hemoglobin solutions were initially developed with the hope of finding an alternative to the problems associated with blood transfusion, including time-consuming and expensive cross-matching, limited shelf life and supplies, and disease transmission. Nevertheless, a new, broader concept of “hemoglobin therapeutics” developed with the realization that hemoglobin solutions are not only RBC substitutes but also have a number of additional properties. One of these is that hemoglobin solutions may penetrate the microcirculation more easily than the RBC due to their small particle size and low viscosity. Their slightly right-shifted $O_2$ dissociation curve, compared with human blood, may also increase oxygen unloading. Other important properties of hemoglobin solutions are their specific vasopressor effects, mostly related to NO-binding properties (10, 35, 37–39) and their high colloid osmotic pressure (24). Several studies have indicated that resuscitation fluids containing hemoglobin improve oxygen transport to the tissues compared with nonhemoglobin solutions (14, 18). Diaspirin crosslinked hemoglobin (DCLHb), derived from old human erythrocytes, is one of these modified hemoglobin solutions. DCLHb is prepared by cross-linking between the $\alpha$-subunits of hemoglobin within the hemoglobin tetramer by means of a reaction with the diaspirin compound, bis(3,5-dibromosalicyl)fumarate and then purifying the solution by heat pasteurization to inactivate any contaminating viruses.

We sought to define the effects of two different doses of DCLHb in an endotoxic shock model in the anesthetized dog. In the first part of the study, we studied the
Experimental protocol. After surgical preparation, the dog was placed in the supine position and allowed to stabilize for 30 min. The pericardial cavity was opened using a 5-ml syringe to ensure a slightly negative intrapericardial pressure before control measurements (B1) were obtained. The animals then received a slow intravenous bolus of 2 mg/kg E. coli endotoxin (055:B5, control no. 3120–10–7, Difco, Detroit, MI), and a second set of measurements (B2) was obtained 30 min later. A normal saline infusion was then started and titrated to restore pulmonary occlusion pressure to baseline. A third set of measurements was obtained after 30 min (B3). The saline infusion was then kept at a constant rate of 20 mg·kg⁻¹·h⁻¹ throughout the study. The dogs were randomly divided into three groups: endotoxin alone (n = 6), endotoxin and DCLHb at a dose of 500 mg/kg (n = 6), and endotoxin and DCLHb at a dose of 1,000 mg/kg (n = 6). In the two latter groups, DCLHb was infused 10 min after the B3 measurements. A fourth set of measurements (B4) was obtained 30 min later. Cardiac tamponade was then induced by repeated injections of normal saline, heated to 37°C, into the pericardial sac. Measurements were repeated every 20 min thereafter in all animals. When mean arterial pressure had declined to 20% of the baseline level, the dog was considered to be in a decompensatory state, the data collection was ended, and the dog was killed. A timeline describing the experiment is shown in Fig. 1.

Measurements and calculations. All pressures were determined from a strip-chart recorder (2600S recorder; Gould, Cleveland, OH) at end expiration. Cardiac index (ml·min⁻¹·kg⁻¹) was measured by the thermodilution technique (cardiac output computer, COM-2, Baxter) using three to five 5-ml injections of D 5% in iced water. Each injection was started at end inspiration. A temperature probe was used online to control for variations in injectate temperature. Regional blood flow was estimated simultaneously in the common hepatic artery, portal vein, and left renal artery by a previously calibrated blood flowmeter (model T208, Transonic systems, Ithaca, NY).

Exhaled gases were directed through a mixing chamber for sampling to measure expired O₂ fraction (FEO₂) and PETCO₂. The oxygen analyzer (P.K. Morgan, Chatham, UK) and the capnometer (47210A, Hewlett Packard, Waltham, MA) were calibrated before the experiment. Expired minute volume
was measured with a spirometer (Haloscale Wright, Edroton, London, UK).

Arterial and mixed, hepatic, and portal venous blood samples were simultaneously withdrawn for immediate determination of blood gases and lactate concentration (ABL 500, Radiometer, Copenhagen, Denmark; lactose/glucose analyzer 2300 Stat Plus, Yellow Springs Instruments, Yellow Springs, OH). Hemoglobin concentration and oxygen saturation were measured simultaneously (OSM 3 hemoximeter, calibrated for dog blood, Radiometer). Whole body oxygen delivery (DO₂) was calculated as the product of arterial oxygen content and cardiac index. Whole body oxygen consumption (VO₂) was measured from the expired gases, as previously described (47). Hepatic and portal DO₂ were calculated as the product of their regional blood flow and the regional oxygen content of the hepatic artery and the portal vein, respectively. Liver DO₂ was calculated as the sum of the hepatic artery and the portal vein VO₂ (34). Oxygen extraction ratio (ERO₂) was derived from the ratio of VO₂ to DO₂.

Statistics. In each animal, the determination of the whole body and liver critical DO₂ (DO₂crit) was obtained from a plot of VO₂ vs. DO₂ using the method described by Samsel and Schumaker (33). DO₂crit was defined as the point of intersection of two best-fit regression lines, as determined by a least sum of squares technique. Paired sets of linear regressions were calculated for all possible combinations of points separated into low (supply-dependent) and high (supply-independent) DO₂ groups. Points were constrained to fall on either regression line but not on both. The pair of regressions with the lowest sum of standard errors of estimate was taken as the set that best fit the data. The values of DO₂ and VO₂ at the intersection point were then calculated using the two regression equations and were called DO₂crit and VO₂crit, respectively. Because VO₂ and DO₂ were derived from independent techniques of measurement, ERO₂ at critical point (ERO₂crit) was calculated by dividing VO₂crit by DO₂crit. An example is shown in Fig. 2. Statistical analysis included a repeated measurements ANOVA followed by Dunnett’s test. The difference in the slopes of VO₂/DO₂ were tested by ANCOVA. P < 0.05 was considered statistically significant. All values are expressed as mean ± SD.

RESULTS

Effects of endotoxin alone. Endotoxin administration resulted in sharp decreases in mean arterial pressure, cardiac filling pressures, cardiac index, and whole body DO₂ (Fig. 3). Blood lactate levels increased (Fig. 4). There was no significant difference between the three groups in the total amount of intravenous fluids required (3.9 ± 0.8 liters in the control group vs. 3.5 ± 0.7 and 3.4 ± 0.8 liters in the DCLHb groups).

After initial fluid resuscitation, mean arterial pressure remained low, but cardiac index, systemic DO₂,
Liver D\(\text{O}_2\) crit was slightly lower in the DCLHb-treated groups, respectively, than in the control group (39.1 \(\pm\) 0.9 ml·kg\(^{-1}\)·min\(^{-1}\)) vs. 42.8 \(\pm\) 1.7 ml·kg\(^{-1}\)·min\(^{-1}\)) in the control group (Fig. 4). Mean arterial pressure at whole body ER \(\text{O}_2\) crit was higher in the two DCLHb-treated groups, respectively, than in the control group, but these differences were not significant (Table 1). Relative portal, hepatic artery, and renal blood flows were not affected by the infusion of DCLHb (Fig. 5). DCLHb infusion had no influence on the blood hemoglobin concentration, which somewhat decreased in the three groups throughout the study (Table 2). During cardiac tamponade, the administration of DCLHb was followed by a significant decrease in whole body \(\text{D}_{O2\text{crit}}\) (12.8 \(\pm\) 0.7 ml·kg\(^{-1}\)·min\(^{-1}\)) in the control group and low- and high-dose DCLHb groups, respectively (Fig. 6). In the absence of significant differences in whole body \(\text{V}_{O2\text{crit}}\), whole body \(\text{ER}_{O2\text{crit}}\) was significantly higher in the two DCLHb groups (58.7 \(\pm\) 12.8 ml·min\(^{-1}\)) than in the control group (39.1 \(\pm\) 3.1 ml·min\(^{-1}\)); Fig. 6). Liver \(\text{D}_{O2\text{crit}}\) was slightly lower in the DCLHb-treated groups than in the control group, but these differences did not reach statistical significance (Fig. 6). During cardiac tamponade, the DCLHb-treated groups maintained significantly lower arterial lactate levels than the control group (Fig. 4). Mean arterial pressure at whole body \(\text{D}_{O2\text{crit}}\) was quite similar in the three groups (44 \(\pm\) 6, 46 \(\pm\) 8, and 47 \(\pm\) 4 mmHg, in the control and the two DCLHb-treated groups, respectively).

**DISCUSSION**

The main findings of our study are that DCLHb infusion in endotoxemic shock can exert a vasopressor effect without affecting cardiac output and regional blood flow and can increase oxygen extraction capabilities.

Many studies have reported a rise in blood pressure after administration of hemoglobin solutions in animals (2, 13, 18, 22, 29, 37–39, 44) and in humans (14, 17, 28). These vasopressor effects are primarily due to the scavenging of NO by hemoglobin (8, 12, 32, 35, 39, 45). Sharma et al. (39) demonstrated, in anesthetized rats, that the administration of the NO precursor L-arginine significantly attenuated the systemic hemodynamic effects of DCLHb. They also showed that DCLHb, when administered in N\(^{\text{a}}\)-nitro-L-arginine methyl ester (N\(^{\text{a}}\)-NAME, a NOS inhibitor)-pretreated rats, accentuated the decrease in blood flow to the gastrointestinal system, spleen, mesentery and pancreas, skin, and musculoskeletal system (9). Further-

**Table 1. Selected hemodynamic parameters**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>B1</th>
<th>B3</th>
<th>B4</th>
<th>Near (\text{D}_{O2\text{crit}})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temperature, °C</td>
<td>38.2 ± 0.8</td>
<td>38.9 ± 0.7</td>
<td>38.5 ± 1.1</td>
<td>37.7 ± 0.9</td>
</tr>
<tr>
<td>CO, l/min</td>
<td>140 ± 10</td>
<td>143 ± 17</td>
<td>146 ± 20</td>
<td>132 ± 17</td>
</tr>
<tr>
<td>PAOP, mmHg</td>
<td>5.7 ± 1.2</td>
<td>7.1 ± 1.3</td>
<td>6.6 ± 0.8</td>
<td>2.9 ± 0.8</td>
</tr>
<tr>
<td>MAP, mmHg</td>
<td>97.5 ± 12.8</td>
<td>66.3 ± 15.1</td>
<td>57.7 ± 12.1</td>
<td>44.2 ± 6.1</td>
</tr>
<tr>
<td>(\text{SVRi}), (\text{dyne}·\text{s}·\text{cm}^{-5}) (\text{kg}^{-1})</td>
<td>2.6 ± 1.9</td>
<td>5.3 ± 1.4</td>
<td>5.2 ± 1.2</td>
<td>8.1 ± 0.8</td>
</tr>
<tr>
<td>(\text{PVRi}), (\text{dyne}·\text{s}·\text{cm}^{-5}) (\text{kg}^{-1})</td>
<td>58.5 ± 24.6</td>
<td>41.8 ± 17.4</td>
<td>28.0 ± 13.4</td>
<td>45.2 ± 20.3</td>
</tr>
</tbody>
</table>

\(\text{Values are means} \pm \text{SD. DCLHb} \times 1, \text{DCLHb} 500 \text{mg/kg (group 1); DCLHb} \times 2, \text{DCLHb} 1,000 \text{mg/kg (group 2); CO, cardiac output; MAP, mean arterial pressure; RAAP, right atrial pressure; PAOP, pulmonary arterial occlusive pressure; SVRi, systemic vascular resistance index; PVRi, pulmonary vascular resistant; Qsport, portal blood flow; Qhepart, hepatic artery blood flow; Qren, renal blood flow.}\)
more, plasma cGMP concentrations decreased after the administration of both DCLHb and L-NAME. In addition, Rooney et al. (32) showed, in dogs hemodiluted with oxyhemoglobin, that the administration of the NO donor sodium nitroprusside could reverse the vasoconstriction and increase the cardiac output. Ulatowski et al. (45) demonstrated that a cross-linked hemoglobin solution selectively reduced blood flow to the kidneys.

Table 2. Blood gases and hemoglobin

<table>
<thead>
<tr>
<th></th>
<th>B1</th>
<th>B3</th>
<th>B4</th>
<th>Near Dclhba</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin, g/dl</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>14.2 ± 1.5</td>
<td>12.9 ± 1.4</td>
<td>12.7 ± 1.1</td>
<td>11.8 ± 1.1</td>
</tr>
<tr>
<td>DCLHb × 1</td>
<td>14.3 ± 1.9</td>
<td>12.5 ± 1.7</td>
<td>12.6 ± 1.4</td>
<td>11.6 ± 1.7</td>
</tr>
<tr>
<td>DCLHb × 2</td>
<td>15.0 ± 1.5</td>
<td>12.5 ± 2.1</td>
<td>12.8 ± 2.5</td>
<td>12.2 ± 2.8</td>
</tr>
<tr>
<td>Methemoglobin, %</td>
<td>0.2 ± 0.1</td>
<td>0.3 ± 0.2</td>
<td>0.3 ± 0.1</td>
<td>0.4 ± 0.2</td>
</tr>
<tr>
<td>Control</td>
<td>0.4 ± 0.2</td>
<td>0.3 ± 0.1</td>
<td>0.6 ± 0.4</td>
<td>0.7 ± 0.5</td>
</tr>
<tr>
<td>DCLHb × 1</td>
<td>0.3 ± 0.1</td>
<td>0.4 ± 0.3</td>
<td>0.8 ± 0.2</td>
<td>1.1 ± 0.6*</td>
</tr>
<tr>
<td>pH</td>
<td>7.37 ± 0.05</td>
<td>7.22 ± 0.04</td>
<td>7.22 ± 0.05</td>
<td>7.15 ± 0.1</td>
</tr>
<tr>
<td>Control</td>
<td>7.39 ± 0.09</td>
<td>7.21 ± 0.06</td>
<td>7.23 ± 0.08</td>
<td>7.18 ± 0.08</td>
</tr>
<tr>
<td>DCLHb × 1</td>
<td>7.40 ± 0.02</td>
<td>7.22 ± 0.04</td>
<td>7.23 ± 0.04</td>
<td>7.17 ± 0.09</td>
</tr>
<tr>
<td>Pao2, Torr</td>
<td>78.2 ± 10.1</td>
<td>60.7 ± 12.5</td>
<td>59.3 ± 9.7</td>
<td>52.2 ± 11.2</td>
</tr>
<tr>
<td>Control</td>
<td>79.3 ± 12.3</td>
<td>61.9 ± 9.5</td>
<td>57.2 ± 7.5</td>
<td>48.2 ± 9.2</td>
</tr>
<tr>
<td>DCLHb × 1</td>
<td>75.3 ± 11.2</td>
<td>59.3 ± 12.2</td>
<td>58.7 ± 11.3</td>
<td>47.5 ± 9.2</td>
</tr>
<tr>
<td>SaO2, %</td>
<td>93.6 ± 2.8</td>
<td>85.2 ± 2.9</td>
<td>83.0 ± 3.3</td>
<td>70.1 ± 4.0</td>
</tr>
<tr>
<td>Control</td>
<td>94.0 ± 2.8</td>
<td>86.8 ± 4.8</td>
<td>82.8 ± 7.5</td>
<td>66.2 ± 11.2</td>
</tr>
<tr>
<td>DCLHb × 1</td>
<td>92.6 ± 2.1</td>
<td>85.5 ± 5.2</td>
<td>84.3 ± 4.8</td>
<td>65.3 ± 9.9</td>
</tr>
</tbody>
</table>

Values are mean ± SD. pH, arterial pH; Pao2, arterial partial pressure of O2; PaCO2, arterial partial pressure of CO2; SaO2, arterial O2 saturation; Svo2, venous O2 saturation. *P < 0.05 vs. control.

Fig. 5. Changes in regional blood flow during incremental changes in IPP in the 3 groups of animals. Qportal, portal vein blood flow; Qhepar, hepatic artery blood flow. Values are means ± SD.
and its hemoglobin concentration) and the measured hemoglobin concentration after DCLHb infusion. Using this approach, we found that the blood volumes of the dogs after DCLHb infusion were virtually unchanged (98 ± 5 and 96 ± 3% of baseline blood volumes for the DCLHb 500 mg/kg- and DCLHb 1,000 mg/kg-treated groups, respectively). The lack of intravascular volume expansion after DCLHb infusion in our model might be the capillary leak phenomenon secondary to the endotoxin infusion which could minimize the oncotic effects of DCLHb by extravascular leak of a certain quantity of DCLHb molecules. Finally, it is not surprising that the hemoglobin level did not increase after DCLHb infusion because the concentration of the infused DCLHb was lower than the hemoglobin blood dog concentration before DCLHb infusion. In nonseptic rats, Sharma et al. (37, 39) and Gulati and colleagues (10) showed that the infusion of DCLHb was followed by an increase in cardiac output and that regional blood flow measured by a radioactive microsphere technique was either increased or not affected. In septic rats, Mourelatos et al. (25) showed that DCLHb immediately increased blood pressure but did not affect cardiac output or regional perfusion; in fact, after 24 h, DCLHb even increased regional perfusion to the brain, heart, and stomach, but not to the liver and the kidney. On the contrary, in septic cats, Ulatowski et al. (45) showed that the infusion of another cross-linked hemoglobin (bovine fumaryl bb-cross-linked hemoglobin) selectively reduced blood flow in the intestines and kidneys by a mechanism consistent with NO scavenging. In a swine model of endotoxic shock, Aranow et al. (2) reported that the infusion of cross-linked human hemoglobin did not impair renal or mesenteric blood flows but did decrease gut mucosal perfusion, when compared with a dextran-treated group. These differences can probably be explained by the different experimental models used. Our data suggest that DCLHb infusion does not alter cardiac output and regional blood flow, provided that generous fluid administration is simultaneously given. The use of pentobarbital sodium as anesthetic agent in our dogs may also have minimized the vasopressor effect of DCLHb because pentobarbital sodium has been demonstrated to attenuate systemic vascular responses to multiple vasopressors (1, 7).

In septic rats, Sielenkämper et al. (40) demonstrated a beneficial effect of DCLHb on tissue oxygen utilization. When oxygen supply dependency was induced by progressive hemodilution, these authors observed that DCLHb infusion increased oxygen uptake and reversed lactic acidosis. In our study, when cardiac tamponade dramatically reduced cardiac output and arterial pressure, DCLHb was also able to improve cellular oxygen...
availability, as reflected by the lower arterial lactate concentrations found in the DCLHb-treated groups during cardiac tamponade. Because DCLHb did not alter cardiac output and hemoglobin concentration, calculated whole body DO₂ was similar in the three groups of dogs throughout the study. Therefore, the improvement in cellular oxygen availability had to be due to an improvement in oxygen extraction capabilities and/or local microvascular perfusion, as indicated by the lower whole body DO₂ crit and higher ERO₂ crit found in the DCLHb groups. Hemoglobin solutions may influence O₂ transport in the microcirculation by several mechanisms, including interaction with NO, colloid osmotic effects, and a right-shifted O₂ dissociation curve.

In sepsis (19), systemic hypotension and/or myocardial depression, coupled to local microcirculatory alterations (including interstitial edema, endothelial alterations, and leukocyte or RBC entrapment), depress microcirculatory RBC flow. DCLHb binds NO, an endogenous mediator that contributes to regulating vascular tone (16). DCLHb may have acted primarily on the microcirculation through increasing the tissue perfusion pressure or by scavenging NO. The similar arterial pressure at DO₂ crit in the three groups rules out the vasopressor effects as an important mechanism. The NO scavenging effect was also unlikely to play an important role. On the same animal model of endotoxic shock, our laboratory previously demonstrated that the infusion of N⁵-monomethyl-L-arginine, a NO synthase inhibitor, did not improve oxygen extraction capabilities (46). On the contrary, the administration of the NO donor 3-morpholinosydnonimine increased oxygen extraction capabilities. Thus we believe that neither the increase in tissue perfusion pressure nor the NO scavenging effects were implicated in the improvement in oxygen extraction capabilities. Finally, the absence of blood flow redistribution rules out the hypothesis that the improvement in whole body oxygen extraction capabilities could have been due to a possible interorgan blood flow redistribution towards more hypoxic tissues.

The rightward shift of the O₂ dissociation curve of DCLHb (higher P₅₀), compared with human blood (4, 40) may facilitate oxygen offloading in the microcirculation and, therefore, improve tissue oxygenation (40, 42). However, there is no clear evidence, as yet, that right-shifting the O₂ dissociation curve is important to restoring tissue oxygenation. Using a low flow in a pump-perfused left hindlimb dog model, Curtis et al. (5) showed that raising hemoglobin P₅₀ increases tissue skeletal muscle PO₂ but does not affect the ERO₂ crit. Schumaker et al. (36) showed that, in canine steady-state exercise, hemoglobin P₅₀ is not a significant determinant of tissue oxygen extraction capacity during normoxia or moderate hypoxia. Finally, we do not think that, in our study, the DCLHb P₅₀ was an important determinant in the improvement in oxygen extraction capabilities because the value of dog blood P₅₀, which is between 28.8 and 33.1 mmHg (31, 36), is close to the DCLHb P₅₀, which is ~32 mmHg.

Therefore, we suppose that DCLHb improved tissue oxygenation by its rheological properties. Due to their small particle size and low viscosity, DCLHb molecules penetrate microvessels better than RBC, which must navigate through capillaries with small luminal diameters. These advantageous rheological properties may be particularly important in sepsis, in which both microcirculatory alterations and alterations in RBC stiffness (15) can hinder RBC microcirculatory penetration.

In summary, with its rheological properties, oxygen carrying abilities, and vascular effects, DCLHb may be an interesting option to increase cellular oxygen availability in septic shock.

REFERENCES