Lack of a Relationship between Induced Changes in Oxygen Consumption and Changes in Lactate Levels*

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To determine whether the levels of oxygen consumption (VO₂) required to relieve an existing oxygen debt are variable, increases in VO₂ produced by increases in oxygen delivery (DO₂) were evaluated longitudinally in septic patients with lactic acidosis and related to changes in lactate levels. Interventions were performed in 17 patients and consisted of fluid administration (n = 11), packed red blood cell transfusion (n = 19), or dobutamine infusion (n = 14). Interventions associated with a decreased lactate level or an unchanged/increased lactate level demonstrated similar increases from baseline VO₂ (49 ± 9 and 47 ± 6 ml/min·m², respectively) and similar postintervention absolute VO₂ values (187 ± 13 and 189 ± 10 ml/min·m², respectively) (both p > 0.6). When all interventions were considered, correlations were not observed between changes in lactate levels and changes in VO₂ (r = 0.21, p > 0.00) or between changes in lactate levels and the postintervention VO₂ values (r = 0.06, p > 0.45). These observations demonstrate that optimal levels of VO₂ are variable and suggest that therapeutic interventions should be tailored to a patient's individual tissue needs and guided by an assessment of an oxygen debt (eg, lactate levels) rather than absolute VO₂ measurements.

(Chest 1991; 100:1012-15)

\[ \text{DO}_2 = \text{oxygen delivery; Prbc = packed red blood cells; VO}_2 = \text{oxygen consumption} \]

The demonstration of pathologic oxygen supply dependency in sepsis¹-³ suggests the existence of inadequate tissue oxygenation caused by an imbalance between oxygen demand and oxygen uptake. Indeed, investigators¹-³ have shown that elevations in oxygen consumption (VO₂) following increases in oxygen delivery (DO₂) occur predominantly in patients with lactic acidosis, a marker of inadequate tissue oxygenation. In contrast, DO₂-induced increases in VO₂ are not observed in patients with normal lactate levels. Along a similar line of reasoning, Bihari and colleagues⁴ suggested that their findings of greater increases in VO₂ with prostacyclin in nonsurvivors compared with survivors of acute respiratory failure were due to the presence of a "covert" oxygen debt in the nonsurvivors. These results have prompted the therapeutic strategy of performing DO₂ challenges to increase VO₂ to relieve the existing tissue oxygen debt.

Unfortunately, the levels to which DO₂ and VO₂ should be raised remain undetermined and controversial. Several investigators⁵,⁶ have attempted to identify a critical level of VO₂ by plotting random DO₂ and VO₂ data points obtained from groups of patients. This method, however, relies on pooled data, which ignores intersubject variation in tissue oxygen needs. Furthermore, random DO₂ changes may actually be secondary to changes in VO₂. Finally, the segmental graphic method used to define the breakpoint DO₂ at which VO₂ plateaus could have easily been replaced by a simpler linear regression analysis, because few data points were obtained at the higher DO₂ values.⁵,⁶

Shoemaker and colleagues⁷ have advocated increasing DO₂ and VO₂ to above specific supranormal values (600 ml/min·m² and 170 ml/min·m², respectively), which represent median values observed from survivors of critical surgical illnesses. However, metabolic needs are difficult to predict and vary greatly among critically ill patients.⁸,⁹ Therefore, optimal levels of VO₂ needed to meet the existing oxygen demand may differ among patients and may even vary at different times during the course of a patient's illness.

To test the hypothesis that optimal VO₂ levels are variable, DO₂-induced increases in VO₂ were evaluated longitudinally in septic patients with lactic acidosis and related to changes in lactate levels to determine whether the increases in VO₂ both met the ongoing metabolic needs and relieved the existing oxygen debt.

**Methods**

*Patient Population*

Data were obtained from patients with lactic acidosis who also met the criteria for the sepsis syndrome as defined by Bone and colleagues:¹ (1) positive blood cultures and/or clinical evidence of infection; (2) rectal temperature >38.3°C or <35.5°C; (3) tachycardia (heart rate greater than 90 beats per min); and (4) tachypnea (respiratory rate >20 breaths per minute while spontaneously breathing).

*Hemodynamic Monitoring*

All intravascular pressures were measured with the patient in the supine position using the midaxillary level as the zero reference point. Mean arterial blood pressure was obtained from an indwelling arterial catheter. Heart rate was obtained from the electrocardiogram (ECG). Right atrial, pulmonary artery, and pulmonary artery wedge pressures were obtained from a percutaneously placed pulmonary artery catheter and measured at end-expiration from a strip chart recorder.
Cardiac output was measured by the thermodilution technique using cold (<3°C) 5 percent dextrose in water and a closed system (CO-set system; Marquette Laboratories). Three to five measurements were averaged to obtain each cardiac output value. All values were within 10 percent of each other.

Arterial and mixed venous blood samples were obtained for determination of blood gas values (ABL 3; Radiometer, Copenhagen, Denmark), hemoglobin saturation, and hemoglobin concentration. Arterial lactate samples were placed on ice and immediately measured by reflectance spectrophotometry (Etktachem 700, Eastman Kodak, Rochester, NY); normal values are 0 to 11.3 mg/dl.

\( \text{DO}_2 \) (ml/min/m²) and \( \text{Vo}_2 \) (ml/min/m²) were calculated as: \( \text{CI} \times \text{Hb} \times \text{SaO}_2 \times 1.39 \times 10 \) and \( \text{CI} \times \text{Hb} \times (\text{SaO}_2 - \text{SVO}_2) \times 1.39 \times 10 \), respectively, where CI represents the cardiac index (L/min/m²), Hb represents the hemoglobin concentration (g/dl), and \( \text{SaO}_2 \) and \( \text{SVO}_2 \) represent the measured \( \text{O}_2 \) saturation (percent) of the arterial blood and mixed venous blood, respectively.

**Protocol**

Increases in \( \text{DO}_2 \) were achieved by either the administration of fluids (250 ml of human plasma fraction [Plasmanate] or 500 ml of normal saline solution), two units of packed red blood cells (Prbc), or dobutamine infusions (5 µg/kg/min or an increase of 5 µg/kg/min above the previous infusion rate). Physiologic parameters and lactate levels were obtained immediately before and within one hour after each intervention.

Only interventions that produced significant increases in \( \text{DO}_2 \) (≥20 percent above baseline) were included for analysis. A significant increase in \( \text{Vo}_2 \) was arbitrarily defined as a 10 percent increase above baseline, whereas a plateau in \( \text{Vo}_2 \) was arbitrarily defined as a change of less than 5 percent from baseline. A 10 percent change in the arterial lactate level was considered significant.

During the interventional period, no change in therapy, including the infusion rate of adrenergic agents, level of inspired oxygen concentrations, or magnitude of positive end-expiratory pressure (PEEP) were allowed. Data were excluded if temperatures varied by more than 1°C.

Optimal \( \text{Vo}_2 \) levels are defined as those that meet the ongoing metabolic needs as well as the prior oxygen debt and should, therefore, result in a fall in the lactate level. Hence, interventions were divided into two subsets based on whether the changes in \( \text{Vo}_2 \) were associated with a decreased lactate level or with an unchanged/increased lactate level.

**Statistical Analysis**

An unpaired \( t \) test was used to compare differences between groups. A linear regression analysis was used to evaluate correlations between parameters. A \( p \) value less than 0.05 was considered significant. All data are expressed as mean ± SEM.

**Results**

Studies were obtained from 17 patients, eight women and nine men. The average age was 52 ± 4.9 years (range, 22 to 87 years) and the mortality rate was 53 percent. Pulmonary infections were present in 13 patients, kidney infections in two, catheter-related infections in two, and a pleural space infection in one. The infecting organisms were Gram negative in two patients, Gram positive in five, viral in one, *Pneumocystis carinii* in four, and *Mycobacterium tuberculosis* in one patient; cultures were negative in the remaining four patients. Liver failure, defined by a serum bilirubin level above normal, was not present in any patient.

The interval between initial and final hemodynamic and lactate measurements was 4.5 ± 1.4, 6.3 ± 1.4, and 1.9 ± 0.5 hours for fluid administration, Prbc transfusions, and dobutamine infusions, respectively.

Significant increases in \( \text{Vo}_2 \) occurred with 32 interventions. Figure 1 shows individual data associated with a decrease in the lactate level. Large variations were observed for the increases in \( \text{Vo}_2 \) (range, 33 to 115 ml/min/m²; mean, 49 ± 9 ml/min/m²) as well as for the postintervention \( \text{Vo}_2 \) values (range, 165 to 280 ml/min/m²; mean, 187 ± 3 ml/min/m²).

Figure 2 presents individual data that were accompanied by a subsequent unchanged or an increase in the lactate level. The increases in \( \text{Vo}_2 \) (range, 17 to 91 ml/min/m²; mean, 47 ± 6 ml/min/m²) as well as the postintervention \( \text{Vo}_2 \) values (range, 87 to 277 ml/min/m²; mean, 189 ± 10 ml/min/m²) were similar to those observed for the interventions associated with a fall in the lactate level (\( p > 0.40 \) for both mean values).

In nine patients in whom multiple interventions were performed, variable postintervention \( \text{Vo}_2 \) levels were observed on different occasions during the hospital course. In five of these patients, interventions were associated with either a decreased lactate level or an unchanged/increased lactate level.

When all interventions associated with a significant

![Figure 1](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21635/)  
**Figure 1.** Individual data on changes in oxygen delivery (\( \text{DO}_2 \)) and oxygen consumption (\( \text{Vo}_2 \)) associated with a subsequent decrease in the lactate level.

![Figure 2](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21635/)  
**Figure 2.** Individual data on changes in oxygen delivery (\( \text{DO}_2 \)) and oxygen consumption (\( \text{Vo}_2 \)) associated with a subsequent unchanged or an increase in the lactate level.
Figure 3. Linear regression between changes in lactate levels and significant changes in oxygen consumption (\( \dot{V}O_2 \)) with all interventions.

increase in \( \dot{V}O_2 \) were considered, correlations could not be demonstrated between changes in lactate levels and changes in \( \dot{V}O_2 \) \( (r=0.21, \ p>0.60, \ \text{Fig} \ 3) \) or between changes in lactate levels and the postintervention \( \dot{V}O_2 \) values \( (r=0.08, \ p>0.45, \ \text{Fig} \ 4) \).

Plateaus in \( \dot{V}O_2 \) were observed after 12 interventions and individual data are presented in Figure 5. The levels at which \( \dot{V}O_2 \) failed to increase were variable \( \text{range}, \ 144 \text{ to } 280 \text{ ml/min-m}^2; \ \text{mean} \ 190 \pm 11 \text{ ml/min-m}^2 \) and were associated with a decreased lactate level after seven interventions or an unchanged/increased lactate level after five interventions. Varying plateau levels of \( \dot{V}O_2 \) were observed in three patients in whom multiple interventions were performed at different times during the hospital course.

Because catecholamines may independently increase metabolic demand or enhance lactate production,\(^{11,12} \) the analysis of the data was performed without the dobutamine interventions and the results were unchanged.

**Discussion**

This study shows that in septic patients, considerable intersubject variation occurs in the optimal level of \( \dot{V}O_2 \) required to relieve an existing tissue oxygen debt. Indeed, changes in lactate levels did not correlate with either changes in \( \dot{V}O_2 \) or the absolute postintervention \( \dot{V}O_2 \) levels. Hence, attainment of any specific \( \dot{V}O_2 \) value does not ensure the reversal of an ongoing oxygen debt. Finally, inrasubject variation in optimal \( \dot{V}O_2 \) levels may also occur during the course of an illness, probably due to frequently changing metabolic needs.

Although several investigators\(^ {7,13} \) have proposed that \( \dot{V}O_2 \) may be a discriminating parameter predictive of outcome, several studies have failed to demonstrate differences in \( \dot{V}O_2 \) between survivors and nonsurvivors of sepsis or postoperative surgical illnesses.\(^ {8,14,15} \) Interestingly, Tuchschmidt and his colleagues\(^ 6 \) observed that despite similarity in the mean \( \dot{V}O_2 \) levels after the initial resuscitation period, lactate levels had decreased in the survivors, but not in the nonsurvivors, suggesting that the obtained \( \dot{V}O_2 \) level had relieved the existing oxygen debt only in the survivors and that higher \( \dot{V}O_2 \) values were probably required in the nonsurvivors to meet their tissue oxygen needs. The existence of variable optimal \( \dot{V}O_2 \) levels also explains why several studies have failed to observe a fall in lactate levels despite \( \text{DO}_2 \)-induced increases in \( \dot{V}O_2. \)

Failure to identify a singular optimal \( \dot{V}O_2 \) level is not surprising, because \( \dot{V}O_2 \) only measures the amount of oxygen used and not the adequacy of tissue oxygenation. Indeed, the optimal level of \( \dot{V}O_2 \) is dependent on the existing oxygen debt caused by the previous as well as any ongoing imbalance between the oxygen demand and the oxygen uptake. Hence, variations in optimal \( \dot{V}O_2 \) levels between patients or within the same patient during the course of an illness are due to differences in the magnitude of the oxygen debt. Indeed, Shoemaker and colleagues\(^ 4 \) observed that the calculated oxygen debt was variable in patients with postoperative surgical illnesses. Differences in

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**Figure 4.** Linear regression between changes in lactate levels and postintervention oxygen consumption (\( \dot{V}O_2 \)) values with all interventions.

**Figure 5.** Individual data demonstrating plateaus in oxygen consumption (\( \text{DO}_2 \)) after an induced increase in oxygen delivery (\( \text{DO}_2 \)) associated with either a decreased (solid line) or an unchanged increased lactate level (dashed line).
the oxygen debt are due to variations the oxygen demand caused by differences in body temperature, nutritional support, work of breathing, level of sedation, muscle activity, and levels of endogenous and exogenous catecholamines. Variability in oxygen uptake due to differences in cardiac output and oxygen extraction also contribute to a changing oxygen debt.

This study also demonstrates that when examined individually, plateau levels of VO₂ can be observed in septic patients with lactic acidosis. Plateau levels either indicate that tissue oxygen requirements are being met, as reflected by a subsequent decrease in the lactate level, or the inability of tissues to receive or use oxygen. However, as reflected by a lack of a decline in the lactate level. The variability observed in the plateau VO₂ levels probably explains the inability of investigators to convincingly detect a singular plateau VO₂ level from group data.

Evidence in the literature attests to the importance of changes in serial lactate levels in critically ill patients as a means of estimating severity of illness, response to therapy, and prognosis. However, reliance on lactate levels as a guide to the state of tissue oxygenation may carry certain limitations. One, the lactate level reflects the balance between lactate production and lactate clearance, mainly occurring in the liver. However, impaired lactate clearance was probably not significant in this study, because liver dysfunction was not present in any patient. Alternatively, enhanced lactate production can occur from catecholamine stimulation. Although data in this study suggest that lactate levels were not influenced by dobutamine infusions, a metabolic effect from endogenous catecholamines cannot be discounted.

Failure of the lactate level to decline may also be due to a tissue lactate "washout" phenomenon. Finally, reversibility of tissue oxygen deficits and a decline in the lactate level may depend on the length of time at which specific VO₂ levels are sustained. Long-term monitoring of VO₂ and lactate levels was not performed in this study to test these possibilities.

The existence of variable optimal VO₂ levels suggests that therapy aimed at reversal of oxygen deficits should be tailored to individual tissue needs and guided by an assessment of oxygen debt (eg, changes in lactate levels) rather than an absolute VO₂ value. Specifically, DO₂ challenges should be pursued until either VO₂ plateaus or the arterial lactate level decreases. Because of the temporal variability in the optimal VO₂ level that may occur within the same patient, assessment of the DO₂/VO₂ relationship associated with lactate measurements should be performed frequently. Further studies are needed to determine if such a strategy is associated with enhanced survival.

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REFERENCES