Hyperlactatemia and Pulmonary Lactate Production in Patients With Fulminant Hepatic Failure

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Study objectives: To determine whether the lungs of patients with fulminant hepatic failure release lactate, and if so, whether this release relates to systemic lactate concentration or acid base status. Another objective was to examine the accuracy of lactate flux calculations in critically ill patients.

Design: Prospective observational study.

Setting: The ICU of a major teaching hospital.

Patients: Twelve patients with fulminant hepatic failure; 30 other critically ill patients in whom a pulmonary artery catheter was in place.

Interventions: None.

Measurement and results: The precision of whole-blood lactate measurements was assessed in 30 patients with critical illnesses of variable etiology who had a wide range of arterial lactate concentrations. The reliability of lactate measurements decreased with increasing lactate concentration. In each patient with liver failure, pulmonary lactate flux was calculated on three occasions using the Fick principle. Arterial blood lactate concentration was consistently higher than venous concentrations, indicating lactate release by the lungs (mean difference, 0.15 mmol/L; 95% confidence interval, 0.09 to 0.21; p < 0.001). Mean pulmonary lactate production for the 12 patients was 83 mmol/h (range, 22 to 210 mmol/h). No patient had significant acute lung injury. Correlations were found among the arterial lactate concentration and both the arteriovenous (AV) lactate difference (p < 0.025) and pulmonary lactate production (p < 0.05), but not with acid-base status or cardiac output. The reliability of individual AV lactate difference calculations and pulmonary lactate flux calculations was poor.

Conclusion: The lungs release lactate in patients with fulminant hepatic failure at a rate proportional to the degree of systemic hyperlactatemia. However, the measurement errors associated with pulmonary lactate flux calculations using the Fick principle are large, so individual measurements should be interpreted with caution. (CHEST 1999; 116:471–476)

Key words: acidosis; acute liver failure; critical illness; lactate; lung; measurement error; reproducibility of results

Abbreviations: ALI = acute lung injury; AV = arteriovenous; p = Spearman rank correlation coefficient; SBC = standard bicarbonate concentration

Lactate metabolism in critically ill patients is incompletely understood. Elevated or increasing blood lactate concentrations are associated with adverse outcomes, but recent studies have clearly shown that an elevated blood lactate concentration does not always indicate tissue hypoxia. Hyperlactatemia can occur in critically ill patients without systemic acidosis, because of increased aerobic pro-

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measurement of pulmonary lactate flux requires the detection of a small arteriovenous (AV) lactate concentration difference across the lungs and is potentially subject to considerable measurement error. It is unclear whether pulmonary lactate flux calculations in critically ill patients are sufficiently accurate for use in clinical studies.

We observed incidentally that in patients with fulminant hepatic failure, in whom hepatic lactate metabolism is significantly impaired, the systemic arterial lactate concentration was consistently slightly higher than lactate concentration in pulmonary arterial blood, despite the absence of clinically significant ALI. Based on this finding, the present study was carried out with the following objectives: (1) to investigate prospectively whether a lactate flux exists across the lungs of patients with fulminant hepatic failure; (2) to determine whether a relationship exists between pulmonary lactate flux and systemic hyperlactatemia or acidosis; and (3) to estimate the repeatability of pulmonary lactate flux calculations in critically ill patients.

**Materials and Methods**

The study had regional hospital ethical approval, and informed consent was obtained from patients' relatives prior to the study, which comprised two parts. First, the relationship between the arterial whole-blood lactate concentration and the repeatability of lactate measurements was prospectively assessed in a mixed group of critically ill patients. Second, pulmonary lactate production was prospectively measured in patients with fulminant hepatic failure.

**Repeatability of Blood Lactate Measurements in Critically Ill Patients:** The repeatability of whole-blood lactate measurements over the range of concentrations commonly observed in the intensive care setting was investigated using arterial blood samples taken from a mixed group of 30 critically ill patients admitted to the general ICU. In each case, a 2-mL sample of blood was drawn from the arterial catheter into a heparinized syringe. The sample was immediately placed in iced water and analyzed within 5 min of collection. Following thorough mixing, whole-blood lactate was measured five times on each sample. The means (SDs) of the five measurements were calculated and plotted against one another for each of the 30 patients in order to determine the relationship between the whole-blood lactate concentration and the precision of measurement.

**Pulmonary Lactate Production in Patients With Fulminant Hepatic Failure:** Twelve patients with fulminant hepatic failure were studied. Nine were female, 11 had acetaminophen toxicity, and 1 had non-A, non-B, non-C hepatitis. All patients had grade III or IV hepatic encephalopathy and were tracheally intubated, sedated (with alfentanil and propofol infusions), paralyzed (with atracurium), and ventilated. Patients were all studied within 24 h of admission to the intensive therapy unit. In all cases, a 7.5F pulmonary artery catheter was in situ, and cardiac output was monitored semi-continuously using a cardiac output computer (Vigilance; Baxter Edwards Critical-Care; Irvine, CA). Arterial BP was monitored via an indwelling radial or femoral artery catheter. Patients were studied after fluid resuscitation to a pulmonary artery wedge pressure of ≥ 10 mm Hg. No patients received enteral or parenteral nutrition during or prior to the study period, except those in whom blood glucose concentration was < 4 mmol/L. In these cases, dextrose was administered IV to maintain blood glucose concentrations at 4–6 mmol/L.

Whole-blood lactate concentration was measured using an analyzer (YSI 2300 Stat Plus; Yellow Springs Instrument Co; Yellow Springs, OH), which employs a technique based on membrane-bound enzyme electrode methodology. L-lactate oxidase is immobilized in a thin membrane placed over an electrochemical probe and catalyzes the conversion of L-lactate to pyruvate and hydrogen peroxide, the latter then being oxidized at the platinum anode. A stainless-steel electrode completes the circuits, and a silver chloride electrode is used as the reference electrode. The validity and precision of this rapid method of lactate measurement in comparison with slower traditional methods has been previously demonstrated.12,13 Instrument performance was checked daily against standards according to the manufacturer’s recommendations. The machine also self-calibrates after every five samples or every 15 min. With this method, normal whole-blood lactate concentration is ≤ 1 mmol/L.

To calculate pulmonary lactate flux, 2-mL samples of arterial and mixed venous blood were drawn simultaneously into heparinized syringes, and the cardiac output was recorded (this represented a running average over approximately 3 min). Mixed venous blood was drawn over at least 30 s from the distal port of the pulmonary artery catheter. Care was taken to ensure that samples were not contaminated with saline from flush systems or diluted with excess heparin, and all were analyzed within 5 min of collection. Pulmonary lactate flux was calculated from the Fick principle as the product of cardiac output and the AV whole-blood lactate concentration difference. In each patient, three pulmonary lactate fluxes were calculated over a 90-min period, during which time gas exchange did not alter significantly and no other therapeutic interventions or changes were made. PaO2, PacO2, H+ concentration, and standard bicarbonate concentration (SBC) were determined with an analyzer (IL BGE, 1400 series; Instrumentation Laboratories; Lexington, MA), using the arterial samples. At the beginning of the study period, an ALI score was calculated for each patient using the method described by Murray et al,14 and the alveolar-to-arterial oxygen tension gradient and the ratio of PaO2 to the fraction of inspired oxygen were determined. For these calculations, alveolar oxygen pressure was calculated using the simplified alveolar gas equation with the respiratory quotient measured using a metabolic monitor (Deltatrac; Datex; Helsinki, Finland).

**Statistical Analysis**

**AV Lactate Gradient:** The overall significance of the AV lactate concentration difference in the 12 patients was determined using a paired Student’s t Test. The difference between the arterial and mixed venous lactate concentrations was further illustrated using the Bland and Altman method.15 The relationship between the mean lactate concentration and the AV lactate concentration difference was investigated by calculating the product-moment correlation coefficient between these variables.

**Pulmonary Lactate Flux:** For each patient, the mean of the three pulmonary lactate flux calculations was determined. The relationship between this and the other measured physiologic variables was investigated by calculating the Spearman rank correlation coefficient (ρ). The repeatability of AV lactate difference and pulmonary lactate flux calculations was calculated, with the assumption that the amount of lactate released by the lungs did not change over the 90-min study period, so that variability in pulmonary lactate flux within each patient was attributable to measurement error alone. Overall repeatability of pulmonary lactate flux measurements in the 12 patients was then estimated.
by calculating the within-patient SD, using analysis of variance. Repeatability was calculated as 2.77 SD, which represents the amount by which two measurements might differ because of measurement errors at a confidence level of 95%. Thus, the larger the repeatability the less accurate the measurement of interest. This method of estimating and expressing repeatability has been described in full elsewhere.18 The relationship between the repeatability of pulmonary lactate flux calculations in individual patients and the arterial lactate concentration was investigated by calculating the correlation (r) between the precision (SD) of the three calculations of pulmonary lactate flux for each patient and the mean lactate concentration. A p value < 0.05 was considered statistically significant.

RESULTS

None of the fulminant hepatic failure patients had clinically significant ALI or evidence of sepsis at the time of the study. The median prothrombin time was 108 s (range, 70 to 200 s). Seven patients received dextrose infusion during the study period. Data for individual patients are shown in Table 1.

Repeatability of Arterial Whole-Blood Lactate Measurements: For the 30 critically ill patients, the reliability of individual whole-blood lactate measurements decreased significantly as the mean lactate concentration increased (Fig 1). This relationship appeared linear over the wide range of lactate concentrations studied and was described by the equation y = 0.014x + 0.022 (r = 0.81; p < 0.001).

Pulmonary Lactate Production in Patients With Fulminant Hepatic Failure: Considering pooled data from all 12 patients, a small but significant bias between the arterial and mixed venous lactate concentrations was found (mean [SD] arterial lactate concentration, 2.80 [1.60]; mean mixed venous lactate, 2.65 [1.50] mmol/L; p < 0.014; mean bias, 0.15 [95% confidence interval, 0.09 to 0.21] mmol/L), indicating that the lungs were releasing lactate into the circulation (Fig 2). Mean arterial lactate concentration correlated with the AV lactate difference (r = 0.61; p < 0.01).

Pulmonary lactate flux varied widely both within and between patients (Table 1, Fig 3), but indicated a net release of lactate by the lungs in all cases (mean [SEM] lactate release, 83 [21] mmol/h). Mean arterial lactate concentration correlated with the mean AV lactate concentration difference for each patient (p = 0.63; p < 0.025), and with the mean pulmonary lactate production (p = 0.57; p < 0.05). There were no correlations between mean pulmonary lactate flux and cardiac output, systemic acidemia (H⁺ concentration), or systemic acidosis (SBC). Mean arterial lactate concentration did not correlate with either the H⁺ concentration, the SBC, or the cardiac output.

The repeatability of AV lactate flux calculations was 0.41 mmol/L, and the repeatability of pulmonary lactate flux calculations was 202 mmol/h. The precision (SD) of pulmonary lactate flux calculations for each patient correlated with the mean arterial lactate concentration (p = 0.60; p < 0.05), as shown in Figure 3.

DISCUSSION

This study has demonstrated a significant gradient for blood lactate across the lungs of patients with fulminant hepatic failure consistent with lactate release into the systemic circulation. In view of the small difference between arterial and venous blood lactate concentrations, a primary objective was to determine the repeatability of lactate measurements in critically ill patients and estimate the accuracy of lactate flux calculations made using the reverse Fick method. With the enzymatic method of measure-

Table 1—Tests Performed in 12 Patients With Fulminant Hepatic Failure*

<table>
<thead>
<tr>
<th>Patient</th>
<th>AV Lactate Difference, mmol/L</th>
<th>Cardiac output, L/min</th>
<th>Pulmonary lactate flux, mmol/h</th>
<th>Arterial lactate concentration, mmol/L</th>
<th>H⁺ Concentration, mmol/L</th>
<th>SBC, mmol/L</th>
<th>P/F, kPa</th>
<th>A-a Gradient, kPa</th>
<th>ALI score</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.19 (0.11)</td>
<td>8.6 (0.6)</td>
<td>94 (53)</td>
<td>2.98 (0.01)</td>
<td>28.9</td>
<td>31.0</td>
<td>57</td>
<td>8</td>
<td>0.5</td>
</tr>
<tr>
<td>2</td>
<td>0.09 (0.10)</td>
<td>7.5 (0.6)</td>
<td>42 (47)</td>
<td>1.18 (0.12)</td>
<td>33.8</td>
<td>25.5</td>
<td>61</td>
<td>8</td>
<td>0.7</td>
</tr>
<tr>
<td>3</td>
<td>0.05 (0.20)</td>
<td>9.0 (1.4)</td>
<td>34 (95)</td>
<td>2.08 (0.31)</td>
<td>36.1</td>
<td>25.5</td>
<td>57</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>0.31 (0.12)</td>
<td>10.5 (0.9)</td>
<td>196 (54)</td>
<td>3.89 (0.17)</td>
<td>35.8</td>
<td>27.7</td>
<td>51</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>0.09 (0.02)</td>
<td>5.4 (0.5)</td>
<td>29 (7)</td>
<td>2.14 (0.08)</td>
<td>27.9</td>
<td>29.9</td>
<td>75</td>
<td>3</td>
<td>0.75</td>
</tr>
<tr>
<td>6</td>
<td>0.04 (0.03)</td>
<td>10.2 (0.8)</td>
<td>22 (19)</td>
<td>1.95 (0.16)</td>
<td>24.8</td>
<td>30.8</td>
<td>45</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>0.07 (0.08)</td>
<td>12.5 (0.5)</td>
<td>54 (61)</td>
<td>1.89 (0.16)</td>
<td>32.0</td>
<td>29.2</td>
<td>62</td>
<td>7</td>
<td>0.75</td>
</tr>
<tr>
<td>8</td>
<td>0.35 (0.32)</td>
<td>8.5 (1.2)</td>
<td>190 (140)</td>
<td>5.74 (0.20)</td>
<td>51.4</td>
<td>18.1</td>
<td>41</td>
<td>12</td>
<td>0.75</td>
</tr>
<tr>
<td>9</td>
<td>0.05 (0.05)</td>
<td>8.1 (0.2)</td>
<td>23 (22)</td>
<td>2.01 (0.02)</td>
<td>32.8</td>
<td>25.3</td>
<td>68</td>
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<td>1</td>
</tr>
<tr>
<td>10</td>
<td>0.05 (0.01)</td>
<td>10.7 (1.0)</td>
<td>30 (4)</td>
<td>1.66 (0.15)</td>
<td>34.4</td>
<td>30.4</td>
<td>47</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>11</td>
<td>0.20 (0.20)</td>
<td>6.4 (0.5)</td>
<td>73 (71)</td>
<td>1.90 (0.33)</td>
<td>25.4</td>
<td>32.6</td>
<td>59</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>12</td>
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<td>12.3 (1.2)</td>
<td>210 (114)</td>
<td>6.24 (0.39)</td>
<td>47.6</td>
<td>17.3</td>
<td>38</td>
<td>23</td>
<td>1</td>
</tr>
</tbody>
</table>

*Values given as mean (SD). P/F = ratio of PaO₂ to fraction of inspired oxygen; A-a = alveolar-arterial.
ment used, the reliability of whole-blood lactate measurements in a mixed group of critically ill patients decreased as the mean lactate concentration increased. This means that the reliability of individual AV lactate differences in hyperlactatemic patients is likely to be low. De Backer and colleagues\(^9\) also found the reliability of individual AV lactate differences was low, but they did not investigate the relationship between this and the magnitude of arterial lactate concentration. In their study of lung lactate production in patients with ALI, De Backer et al\(^9\) averaged five measurements of arterial and venous lactate concentration in each patient but did not estimate the repeatability of lung lactate flux calculations in vivo. Our approach in patients with fulminant hepatic failure was to measure lung lactate flux on three occasions over a short period, during which pulmonary status was unchanged. From these measurements, our estimation of repeatability indicated that the reliability of individual AV lactate differences was low. Individual pulmonary lactate flux calculations were also unreliable because measurement error in the AV lactate difference was amplified when values were multiplied by the cardiac output, which was uniformly high. Pulmonary lactate flux may be more reliable in patients who are less hyperdynamic, in whom measurements based on the reverse Fick method are more accurate because measurement error is propagated less.\(^{17}\)

As predicted by the positive correlation between precision and size of lactate measurement in the mixed group of critically ill patients, the reliability of pulmonary lactate flux calculations decreased as the mean arterial lactate concentration increased. It is possible that some of the variability in the pulmonary lactate flux observed within patients occurred because of true physiologic variability over the study period rather than measurement error alone. However, the direction of variability was random in all patients and they were otherwise stable, so we
consider it unlikely that true physiologic variability was significant. Values for blood lactate measurements can be falsely elevated by contamination with lactate-containing crystalloid solutions and falsely decreased by dilution with lactate-free crystalloid solutions in flush systems, but care was taken to avoid these factors in the present study. The use of citrate as an anticoagulant can also falsely lower blood lactate values, but heparin does not adversely affect accuracy. Previous studies of pulmonary lactate production have used plasma samples, and some made corrections for changes in hematocrit between pulmonary and systemic arterial blood, but this approach requires further laboratory measurements, which may introduce further measurement error rather than improve accuracy. The use of whole blood for analysis, as in the present study, is considered most accurate.

Despite concerns regarding the reliability of individual measurements, our data indicate that the lungs of patients with fulminant hepatic failure release lactate. The mechanism of lactate production by the lungs in this, and in other conditions, is unclear. Previous studies have demonstrated lung lactate production, but only in patients with ALI in whom lactate production correlated with lung injury scores. The present study is the first to demonstrate lung lactate production in patients without significant lung injury. Lactic acidosis might occur in hypoperfused or hypoxic lung regions, but while these may exist in the lungs of patients with ALI, lung hypoxia was unlikely in the patients in the present study in whom pulmonary blood flow was high, pulmonary shunt was low, and clinically significant lung injury was not present. An alternative mechanism of lactate production, without acidosis, occurs as a result of enhanced cellular glucose uptake and accelerated glycolysis, which may occur as part of the stress response in the absence of hypoxia. Under these circumstances, the ratio of lactate to pyruvate remains normal (approximately 10:1). The mechanism of lung lactate release could be investigated further by examining lactate-pyruvate ratios across the lungs, although such measurements would be subject to considerable measurement error.

Pulmonary lactate flux correlated with the mean arterial lactate concentration. This association could indicate that the lungs contribute significantly to systemic hyperlactatemia in fulminant hepatic failure, as has been proposed in patients with ALI. Alternatively, lung lactate release may represent part of a generalized increase in lactate production by tissues, resulting in hyperlactatemia. The majority of patients were not acidotic, and recent studies indicate that inadequate global oxygen delivery is unusual in resuscitated patients with fulminant hepatic failure, so mechanisms of lactate production other than tissue hypoxia may be implicated. This conjecture is supported by the lack of relation between blood lactate concentrations and the degree of acidemia or acidosis. The presence of metabolic alkalosis in many patients, which is common in fulminant hepatic failure, may have contributed to hyperlactatemia by accelerating glycolytic production of pyruvate at a rate which exceeds cellular capacity to metabolize it via the citric acid cycle. Exogenous glucose supply can also stimulate lactate production, which may have contributed to hyperlactatemia in those patients receiving dextrose infusions to maintain normoglycemia. Hyperlactatemia can also result from reduced lactate clearance, which is likely in patients with fulminant hepatic failure as a result of impaired hepatic lactate metabolism.

In conclusion, we have shown that the lungs of patients with fulminant hepatic failure release lactate into the systemic circulation in the absence of clinically significant ALI. Lung lactate release was associated with the degree of systemic hyperlactatemia, but not with acid-base variables. The accuracy of blood lactate measurements using a rapid enzymatic method decreased as the blood lactate concentration increased, so the repeatability of pulmonary lactate flux calculations in individual patients was low. In future studies which investigate lactate flux across organs in the critically ill, the accuracy of measurements will require careful consideration.

**REFERENCES**

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