

# Oxygen Consumption and Lactate Release by the Lung After Cardiopulmonary Bypass and During Septic Shock

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## ABSTRACT

**Objective:** *We sought to determine whether a correlation exists between lung lactate release and lung oxygen consumption by studying adult intensive care patients, either after cardiopulmonary bypass (CPB) or with septic shock.*

**Methods:** *A prospective observational study of six post cardiopulmonary bypass patients and seven patients with septic shock was performed in an intensive care unit of a major teaching hospital. Pulmonary oxygen consumption was estimated by subtracting oxygen consumption calculated using the reverse Fick equation ( $\dot{V} O_{2Fick}$ ) from that measured by indirect calorimetry ( $\dot{V} O_{2meas}$ ). Pulmonary lactate release was derived from the difference between arterial and mixed-venous lactate, multiplied by cardiac output.*

**Results:** *Pulmonary oxygen consumption comprised a substantial component of total oxygen consumption (CPB-median: 20.6%; interquartile range (IQR): 15.4 - 27.3%; septic shock-median: 32.3%; IQR: -4.0 - 35.4%). Lung lactate release occurred both after CPB (median: 27.5mmol/hr; IQR: 24.8-64.1 mmol/hr) and with septic shock (median: 55.4 mmol/hr; IQR: 24.3 - 217.6 mmol/hr). Although no correlation was found between lung lactate release and pulmonary oxygen consumption, lactate release correlated with  $\dot{V} O_{2meas}$  and  $\dot{V} O_{2Fick}$  in septic patients ( $p < 0.005$ ).*

**Conclusions:** *We conclude that lung oxygen consumption and lactate release are substantial in conditions associated with lung inflammation. Lactate release and lung oxygen consumption may not share a common pathogenesis, however there is an association between lung lactate release and systemic oxygen consumption in sepsis. (Critical Care and Resuscitation 1999; 2: 181-187)*

**Key words:** Critical illness, lactate, lung, oxygen consumption, sepsis

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Hyperlactataemia in sepsis is poorly understood and both animal and human studies have failed to fully clarify its pathogenesis and the source of lactate release. The lung, however, has been shown to be a possible source of lactate during sepsis and lung inflammation. In a dog model of sepsis, for example, the lung activity changed from uptake to release of lactate after induction of endotoxaemia. Muscle and liver lactate fluxes were

neutral and lactate uptake occurred in the gut and kidneys before and after endotoxaemia.<sup>1</sup> Human studies have also shown net lactate release by the lungs and have demonstrated a correlation between lung lactate release and lung injury score in patients with acute lung injury and/or sepsis.<sup>2,3</sup> The source of lung lactate during sepsis and lung inflammation is unknown. Lactate release may be caused by increased metabolic activity of

the lung itself or of infiltrating activated white cells, rather than resulting from hypoxia and anaerobic metabolism.<sup>2</sup>

Similarly, pulmonary oxygen consumption has been shown to increase, both in animal models<sup>4</sup> and in human studies, with sepsis and/or lung inflammation.<sup>5-7</sup> It is possible that increased lung oxygen consumption and lactate release share a common pathogenesis. Therefore, we sought to determine whether lactate release by the lung varies with the severity of lung inflammation and to determine whether there is a correlation between pulmonary oxygen consumption and pulmonary lactate release. We attempted to detect such a correlation by determining lung lactate release and lung oxygen consumption in patients after cardiopulmonary bypass and during septic shock.

## MATERIALS AND METHODS

### Patient Selection.

Two groups of patients with conditions expected to induce lung inflammation were studied, 1) patients immediately after cardiopulmonary bypass and 2) patients with septic shock. Septic shock was defined according to published criteria.<sup>8</sup> Post cardiopulmonary bypass patients were studied within the first four post-

operative hours. Several patients with septic shock had pneumonia, and all fulfilled published criteria for either acute lung injury or acute respiratory distress syndrome.<sup>9</sup> Six post cardiac bypass patients had a total of 14 measurements, and 7 septic shock patients had a total of 17 measurements (Table 1). Measurements were performed according to the following protocol.

### Protocol

All patients were intubated, sedated and had pulmonary artery catheters and arterial catheters in situ. All patients were receiving controlled mechanical ventilation, with a fractional inspired oxygen concentration ( $F_{I}O_2$ ) of less than 0.6 and 5 cmH<sub>2</sub>O of positive end expiratory pressure. We ensured that there was no air leak from around the endotracheal cuff or from chest drains. During the study period, no changes in  $F_{I}O_2$  or ventilatory parameters occurred, and tracheal suctioning and nursing care were withheld. Patients were haemodynamically stable and no fluid therapy or alteration in inotropic support was required. Post cardiopulmonary bypass patients were normothermic, having temperatures above 36.0 °C. The study was approved by the Ethics Committee of our institution and prior informed consent was obtained from the patients or their relatives.

**Table 1. Characteristics of patients included in the study**

Patient	Age/ sex	No. of Observations	Diagnosis	Apache II Score	Day of study (ICU day)	Inotropic Support**	CI (L/min/ m <sup>2</sup> )	Arterial lactate, Average (mmol)	LIS†	Out- come*
1	75/F	2	CABG		1	Dop 5.0	2.3	2.55		S
2	72/M	2	CABG		1	-	2.1	3.50		S
3	72/M	2	CABG		1	M 0.25	3.2	1.60		S
4	78/F	3	CABG		1	M 0.25	2.4	1.47		S
5	82/F	2	CABG		1	M 0.25	2.8	1.05		S
6	71/M	3	CABG		1	M 0.25	3.5	2.60		S
7	46/M	2	pneumonia, ALI, septic shock	17	4	NA 2.0	8.2	2.02	2.3	S
8	71/F	2	pneumonia, ALI, septic shock	19	2	Dop 4.0	2.7	1.41	2.0	D
9	63/M	3	pneumonia, ALI, septic shock	21	4	NA 20.0	6.7	10.66	1.3	D
10	80/M	2	peritonitis, ALI, septic shock	17	3	Adr 6.0 NA 6.0	4.1	1.63	0.67	S
11	58/F	4	peritonitis, ALI, septic shock	16	2	Adr 10.0 NA 70.0	4.5	7.33	0.33	S
12	82/M	2	pneumonia, ARDS, septic shock	25	1	Dob 5.0	2.7	1.38	2.67	S
13	51/M	2	pneumonia, ALI, septic shock	20	1	NA 11.0	2.3	2.92	1.67	S

\* S = Survived, D = Died, CABG = Coronary artery bypass graft, ALI = Acute lung injury, ARDS = Acute respiratory distress syndrome.

\*\* Dop = dopamine (µg/kg/min), M = milrinone (µg/kg/min), NA = noradrenaline (µg/min), Adr = adrenaline (µg/min), Dob = dobutamine (µg/kg/min).

† LIS = Lung injury score (No injury 0; Mild to moderate injury (ALI) 0.1 – 2.5; Severe injury (ARDS) > 2.5)

*Measurements*

Indirect calorimetry measurements were performed with the Engström Metabolic Computer (Gambro Engström AB, Bromma, Sweden) used in conjunction with the Engström Erica Ventilator. The metabolic computer measures total body oxygen consumption by analysing the inspired and expired oxygen concentrations and expired carbon dioxide concentration (Engström Eliza CO<sub>2</sub> analyser), as well as inspired minute volume. Expired minute volume is derived using the reversed Haldane transformation factor, which then enables oxygen consumption to be determined. The Engström Metabolic Computer has been validated in the laboratory and found to be accurate to within 5% of expected  $\dot{V}O_2$  values.<sup>10,11</sup>

After a period of stable indirect calorimetry oxygen consumption measurements, values over a ten minute period were averaged. During this time oxygen consumption was also determined by the reverse Fick method, a method that excludes oxygen consumption occurring within the lung. This involved taking arterial and mixed venous blood samples and measuring cardiac output by the thermodilution technique. Injections of 10 ml of room temperature 5% dextrose were performed randomly within the respiratory cycle and were repeated until triplicate results within 10% of each other were obtained. Arterial and mixed venous blood samples were analysed (CIBA -Corning 800 series blood gas analyser) for oxygen tension, oxygen saturation (via co-oximetry), haemoglobin concentration and lactate. When a discrepancy occurred between simultaneously drawn arterial and mixed venous haemoglobin concentrations, the average value was used for the calculation of oxygen content.

*Calculations*

Oxygen consumption as determined by the reverse Fick method was calculated as follows:

$$\dot{V}O_{2Fick} = CO \times (CaO_2 - C\bar{v}O_2) \times 10$$

Where

$\dot{V}O_{2Fick}$  = Oxygen consumption using the reverse Fick method (mL/min)

CaO<sub>2</sub> = Arterial oxygen content (mL/100mL)

C $\bar{v}$ O<sub>2</sub> = Mixed venous oxygen content (mL/100mL)

CaO<sub>2</sub> = 1.31 x Hb x SaO<sub>2</sub> + 0.003 x PaO<sub>2</sub>

C $\bar{v}$ O<sub>2</sub> = 1.31 x Hb x S $\bar{v}$ O<sub>2</sub> + 0.003 x P $\bar{v}$ O<sub>2</sub>

Hb = Haemoglobin concentration (g/100mL)

SaO<sub>2</sub> = Arterial oxygen saturation (%)

PaO<sub>2</sub> = Arterial O<sub>2</sub> partial pressure (mmHg)

S $\bar{v}$ O<sub>2</sub> = Mixed venous oxygen saturation (%)

P $\bar{v}$ O<sub>2</sub> = Mixed venous O<sub>2</sub> partial pressure (mmHg)

0.003 = Oxygen solubility per mmHg per 100 mL of blood

1.31 = mL of oxygen per gram of haemoglobin, as determined by Gregory<sup>12</sup>

Pulmonary oxygen consumption ( $\dot{V}O_{2pulm}$ ) was calculated as the difference between indirect calorimetry measured oxygen consumption ( $\dot{V}O_{2meas}$ ) and Fick oxygen consumption ( $\dot{V}O_{2Fick}$ ):

$$\dot{V}O_{2pulm} = \dot{V}O_{2meas} - \dot{V}O_{2Fick}$$

Lung lactate release was calculated as the difference between arterial lactate (Lactate<sub>Art</sub>) and mixed venous lactate (Lactate<sub>MV</sub>), multiplied by cardiac output (CO) and expressed as mmol/hr.

$$\text{Lung lactate release} = (\text{Lactate}_{Art} - \text{Lactate}_{MV}) \times CO$$

*Statistical Analysis.*

The values obtained with our measurements were not normally distributed. Non-parametric descriptive statistics were therefore used. Correlation was performed using the Spearman correlation test. A Mann-Whitney U test was used to compare measurements between the two groups of patients. StatView software (Abacus Concepts, Berkeley, CA) was used for statistical analysis. Values are expressed as medians along with the 25th and 75th percentiles as the interquartile range (IQR). A p<0.05 was considered statistically significant.

RESULTS

*Pulmonary lactate release*

Lactate release from the lungs was a consistent finding in both groups of patients. The median values for lung lactate release in the post-cardiac bypass and septic shock groups were 27.5 mmol/hr (IQR:24.8 - 64.1 mmol/hr) and 55.4 mmol/hr (IQR:24.3 - 217.6 mmol/hr) respectively (Figure 1).

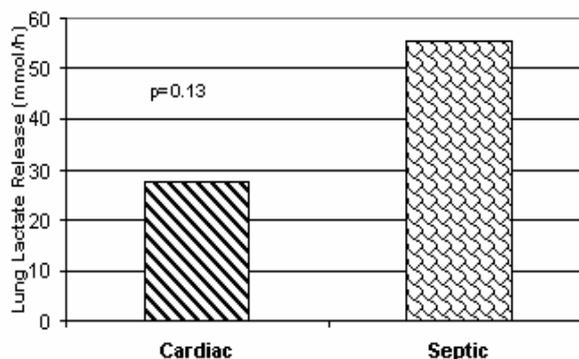


Figure 1. Median values for lung lactate release for post cardiac and septic shock patients

There was no significant difference in lactate release between the two groups ( $p = 0.13$ , Mann-Whitney U test) and in the septic group, no correlation existed between lung lactate release and the lung injury score ( $\rho = -0.57$ ,  $p = 0.16$ ).

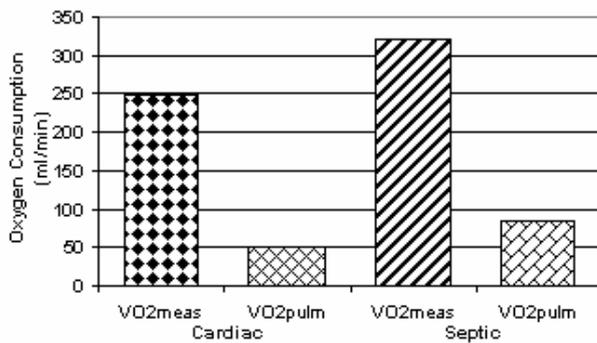
**Oxygen consumption:**

In the post-cardiac bypass group, the median values for  $\dot{V}O_{2meas}$  and  $\dot{V}O_{2Fick}$  were 240 mL/min (IQR:218 – 292 mL/min) and 191 mL/min (IQR:176 – 208 mL/min). The median pulmonary oxygen consumption was calculated at 50 mL/min (IQR:42 - 66mL/min).

The septic shock group had median values for  $\dot{V}O_{2meas}$  and  $\dot{V}O_{2Fick}$  of 320 mL/min (IQR:271 - 493 mL/min) and 290 mL/min (IQR:224 – 348 mL/min) and a median  $\dot{V}O_{2pulm}$  of 85 mL/min (IQR: -14 – 236 mL/min).

There was no significant difference in the pulmonary oxygen consumption between the two groups (Mann-Whitney U test,  $p = 0.81$ ) though  $\dot{V}O_{2meas}$  and  $\dot{V}O_{2Fick}$  were both significantly greater in the septic group ( $p = 0.0013$  and  $p = 0.0045$ , respectively).

Pulmonary oxygen consumption as a percentage of whole body oxygen consumption ( $\dot{V}O_{2pulm}/\dot{V}O_{2meas}$ ) was similar in the septic shock patients (32.3%; IQR: - 4.0 - 35.4%) and the post-cardiac bypass patients (20.6%; IQR:15.4 - 27.3%), ( $p = 0.97$ ) (Figure 2). In the septic group, pulmonary oxygen consumption did not correlate with the lung injury score ( $\rho = 0.32$ ;  $p = 0.43$ ).

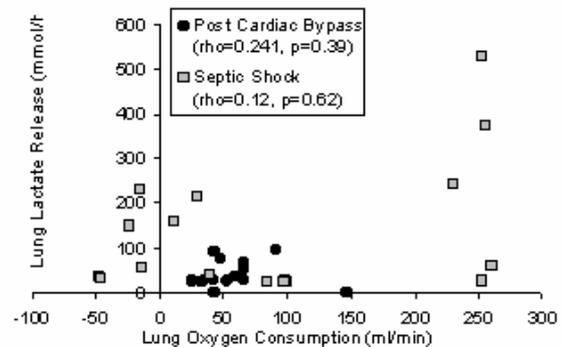


**Figure 2.** Median values for pulmonary oxygen consumption ( $\dot{V}O_{2pulm}$ ) and total oxygen consumption ( $\dot{V}O_{2meas}$ ) for post cardiac bypass and septic shock patients.

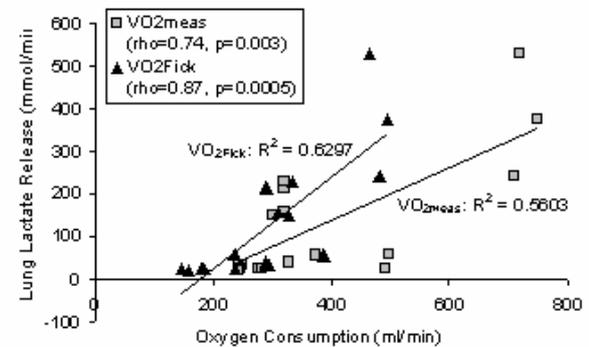
**Relationship between oxygen consumption and lung lactate release:**

No relationship between pulmonary oxygen consumption and lung lactate release was found for each of the two groups. The correlation coefficient for post-

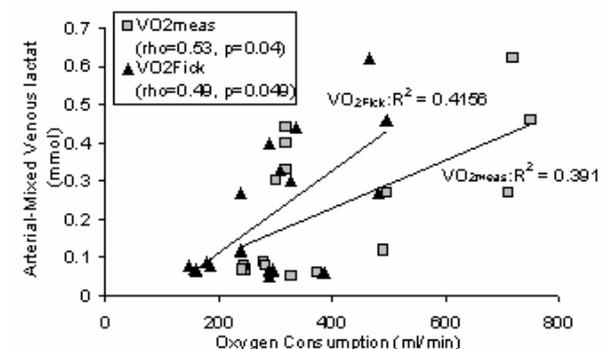
cardiac bypass patients was 0.24;  $p = 0.39$ , and for those with septic shock it was 0.12;  $p = 0.62$  (Figure 3).



**Figure 3.** Simultaneous measurements of lung oxygen consumption ( $\dot{V}O_{2pulm}$ ) and lung lactate release in post-cardiac bypass patients and septic shock patients.



**Figure 4.** Correlation between lung lactate release and calorimetric derived ( $\dot{V}O_{2meas}$ ) and Fick derived ( $\dot{V}O_{2Fick}$ ) oxygen consumption in septic shock patients.



**Figure 5.** Correlation between arterial mixed venous lactate gradients and calorimetric derived ( $\dot{V}O_{2meas}$ ) and Fick derived ( $\dot{V}O_{2Fick}$ ) oxygen consumption in septic shock patients.

In the septic group, lung lactate release was significantly related to both calorimetric derived oxygen consumption,  $\dot{V}O_{2meas}$  ( $\rho = 0.74$ ;  $p = 0.003$ ) and Fick derived oxygen consumption,  $\dot{V}O_{2Fick}$  ( $\rho = 0.87$ ;  $p = 0.0005$ ), (Figure 4). The arterial-mixed venous lactate

difference, which is independent of cardiac output, also correlated with  $\dot{V}O_{2\text{meas}}$  ( $\rho = 0.53$ ;  $p = 0.04$ ) and  $\dot{V}O_{2\text{Fick}}$  ( $\rho = 0.49$ ;  $p = 0.049$ ) (Figure 5). No correlation between oxygen delivery ( $\dot{D}O_2$ ) and the arterial-mixed venous lactate difference was found ( $\rho = 0.20$ ;  $p = 0.42$ ).

In the cardiac bypass group, lung lactate release correlated with neither  $\dot{V}O_{2\text{meas}}$  ( $\rho = 0.40$ ,  $p = 0.15$ ), nor  $\dot{V}O_{2\text{Fick}}$  ( $\rho = 0.49$ ,  $p = 0.08$ ). Similarly no correlation existed for the arterial-mixed venous lactate difference and  $\dot{V}O_{2\text{meas}}$  ( $\rho = 0.23$ ,  $p = 0.41$ ) or  $\dot{V}O_{2\text{Fick}}$  ( $\rho = 0.29$ ,  $p = 0.29$ ). The arterial-mixed venous lactate difference did, however, correlate with  $\dot{D}O_2$  ( $\rho = 0.548$ ,  $p = 0.048$ ).

## DISCUSSION

Release of lactate from the lungs occurred in patients early post cardiopulmonary bypass and also those with septic shock. The magnitude of lactate release from the lung was substantial, considering that basal total body lactate production is in the range of 0.9 to 1.0 mmol/kg/hr.<sup>13</sup> The source of lactate within the lungs, and indeed hyperlactataemia itself in sepsis, is not well understood, though recent studies have also suggested that the lung may be a substantial source of lactate during ARDS or endotoxaemia.<sup>1-3</sup> The conventional explanation that lactate production occurs in the lung as a result of hypoxia-induced anaerobic metabolism would seem unlikely in this highly oxygenated organ. All of the post-bypass patients in this study had clear postoperative chest x-rays, though small pockets of atelectasis could not be excluded. In addition, laboratory experiments using the perfused rat lung have shown the lung to be capable of producing lactate under aerobic conditions,<sup>14,15</sup> and that hypoxia may induce additional lactate production only at very low intracellular partial pressures of oxygen, approaching 1 mmHg.<sup>16</sup>

There is increasing evidence casting doubt upon the notion that lactate production in the resuscitated septic patient occurs as a result of inadequate oxygen delivery. Recent human studies in sepsis have failed to show a relationship between hyperlactataemia in sepsis and the dependence of oxygen consumption on oxygen delivery, raising doubt about the relevance of concepts such as 'tissue oxygen debt' and 'pathologic supply dependency'.<sup>17,18</sup> Interestingly, in our septic patients, we found that lung lactate release correlated with oxygen consumption as determined by both calorimetry and the reverse Fick method. The correlation of the Fick oxygen consumption with lactate release may be partly explained by mathematical coupling, as cardiac output is present in both calculations. However, this correlation

persisted when the arterial-mixed venous lactate difference (excluding cardiac output from the calculation) was compared with oxygen consumption. Calorimetric oxygen consumption, which is measured directly, also correlated with both lung lactate release and the arterial-mixed venous difference. These findings exclude mathematical coupling and suggest that increased oxygen consumption and lung lactate release are but two different expressions of the increased metabolic activity seen during sepsis. Of note, no correlation existed between the arterial-mixed venous lactate gradient and oxygen delivery. If lactate production in sepsis was caused by inadequate oxygen supply, one might have expected the two to be inversely correlated, with the lactate gradient diminishing as oxygen delivery increased. Assuming our data are correct, 'supranormal resuscitation' based approaches to the management of the hyperlactataemia of septic shock might be unhelpful.

In addition to greater lactate release, septic patients also demonstrated higher pulmonary oxygen consumption than did post cardiac bypass patients, although this difference was not significant. Despite both lung lactate release and lung oxygen consumption being greater in the septic group, no correlation between the two was found. Pulmonary oxygen consumption however, was seen to comprise a substantial proportion of total body oxygen consumption. The proportion of total body oxygen consumption attributable to  $\dot{V}O_{2\text{pulm}}$  in this study, was similar to that reported in other published series, which ranges from 7 - 22% in post-cardiac bypass patients,<sup>19-21</sup> and 13 - 40% in patients with sepsis or acute lung injury.<sup>5-7</sup> The reason for the increase in lung oxygen consumption during lung inflammation is unclear but may be due to the inflammatory cell infiltrate as suggested by Light.<sup>4</sup> Jolliet,<sup>7</sup> however, we could find no correlation with the degree of lung inflammation assessed by broncho-alveolar lavage inflammatory cell number, although the limited samples obtained may not have reflected inflammation of the entire lung. Recent evidence,<sup>22</sup> however, shows that white cells may be a major source of lactate. If white cells were both the source of lung lactate release and oxygen consumption, the two values might be expected to correlate. This hypothesis was not supported by our study.

The substantial contribution of the lung to total body oxygen consumption calls into question, as previous studies have done,<sup>23,24</sup> the validity of using the reverse Fick method to determine total body oxygen consumption. In this study, reliance on  $\dot{V}O_{2\text{Fick}}$  to determine oxygen consumption, would have led to an underestimation of whole body  $\dot{V}O_2$  of 20% and 27%

in post-cardiac bypass and septic shock patients respectively. The calorimetric method is a more complete method including not only lung oxygen consumption via the pulmonary circulation but other minor contributions to oxygen consumption missed by the Fick method, such as that occurring through bronchial blood flow or the coronary thesbian veins which drain directly to the left heart. This latter component may explain some of the difference between the two methods, which is not due to lung oxygen consumption, though is likely to be small in magnitude compared with the pulmonary component.<sup>4</sup>

The lack of correlation between lactate release and oxygen consumption in the lung may be due to the use of inadequate methodology. Indeed, the methods available to determine oxygen consumption do have inherent weaknesses, with indirect calorimetry being the more accurate and reproducible of the two methods.<sup>6,25</sup> A variety of metabolic computers have been validated to be accurate to within 5%,<sup>10,11</sup> though they become unreliable when a high  $F_{I}O_2$  is used<sup>10,26</sup> or if air leaks are present in the breathing system. Errors in this study were limited by enrolling patients who required an  $F_{I}O_2$  of less than 0.60, by excluding air leaks and by performing regular calibration of the device. By comparison, the reverse Fick method for oxygen consumption has poor precision,<sup>27</sup> leading to repeated measurements that vary randomly and widely around the true value. The cardiac output measurement performed by thermodilution contributes the greatest error<sup>20</sup> with an inaccuracy of individual measurements of up to 10%.<sup>28</sup> Hb, oxygen saturation and oxygen partial pressure measurements all have smaller associated errors. Depending on the direction of each of these errors, a potentially large cumulative error results from the multiplication of individual variables in the reverse Fick calculation.<sup>25</sup> Such errors are the likely explanation for the occasional negative difference in calorimetric and Fick derived oxygen consumption (which would otherwise imply oxygen production by the lungs). In this study, attempts were made to minimise errors by having the one individual perform all measurements, which were performed multiple times and the average used. The blood gas analyser and co-oximeter used have good precision for Hb,  $SO_2$  and  $pO_2$  measurements with a standard deviation of 0.32 g/dL, 0.57% and 2.5 mmHg respectively.

We sought to overcome such methodologic limitations by performing more than thirty measurements. As we were looking for a strong physiological signal, we reasoned that such a signal would emerge or that a trend would develop that would encourage further measurements. This was not the case. In addition, we detected a correlation between lactate release and body

oxygen consumption both by the Fick method and calorimetry. Such measurements showed all the limitations of lung oxygen consumption calculations as discussed and yet a correlation was shown. It is reasonable to argue that if lung oxygen consumption and lung lactate release were truly correlated, our study should have demonstrated such correlation.

To our knowledge, this is the first time that lung lactate release has been demonstrated in patients immediately after cardiopulmonary bypass. This finding suggests that lactate release by the lung may be a stereotyped response to organ stress. It may also be useful for clinicians to appreciate that the pathogenesis of hyperlactataemia after cardiac surgery is still poorly understood. Our findings show that the lung may contribute to its pathogenesis. Understanding the complex events that participate in determining blood lactate concentration in these patients may assist clinicians in their assessment of post cardiac surgery patients.

In conclusion, this study shows that lungs release lactate during septic shock and immediately after cardiopulmonary bypass and that they contribute substantially to total body oxygen consumption in conditions of lung inflammation. Lung lactate release and body oxygen consumption correlate and may reflect increased general metabolic activity occurring during sepsis. However, lung lactate release and lung oxygen consumption do not correlate, suggesting they may not be due to the same process. Lung lactate release occurs immediately after bypass, challenging the notion that in non-septic patients hyperlactataemia is solely caused by insufficient oxygen delivery to tissues.

Received: 20 May 2000

Accepted: 22 June 2000

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