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Muscle lactate concentration during experimental hemorrhagic shock

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Abstract

Purpose. Blood lactate concentration does not correspond well to oxygen transport variables during circulatory shock. Prolonged washout of lactate from tissues during shock has been reported. This study was designed to test the hypothesis that the discrepancy between serum lactate and oxygen metabolism is caused by the failure of lactate to wash out from the tissues and that tissue lactate may reflect the oxygen metabolism better.

Methods. Using a canine model of hemorrhagic shock, lactate concentration measured in a muscle biopsy specimen and in arterial blood was compared with the cumulative deficit in oxygen consumption.

Result. The cumulative deficit in oxygen consumption correlated with the concentration of lactate in muscle ($r = 0.67$, $P < 0.01$) but not with that in blood. During shock, all muscle lactate levels were greater than those in serum, and a linear relationship was demonstrated between arterial(X) and muscle(Y) lactate levels ($Y = 2.45X - 2.72$, $r = 0.82$, $P < 0.001$). The muscle/serum lactate concentration ratio increased from 1 to 2.5 as the blood volume decreased.

Conclusion. In the setting of experimental hemorrhagic shock, only tissue lactate levels reflected the true deficit in oxygen metabolism. The difference between lactate levels in muscle and serum represented the severity of the shock.

Key words: Hemorrhagic shock, Cumulative deficit in oxygen consumption, Lactate concentration, Washout of lactate, Muscle/serum lactate concentration ratio

Introduction

Low perfusion of the tissues leads to inadequate cellular perfusion and maldistribution of blood flow, followed by impairment of tissue oxygen extraction [1] and tissue hypoxia [2]. The cumulative deficit in oxygen consumption is one of the most reliable predictors of lethal and nonlethal organ failure in patients with shock [3–5]. If the oxygen supply is rapidly restored, cellular function will return to normal. When the reduction in oxygen supply is prolonged, pyruvate cannot be aerobically metabolized in the mitochondria and instead is converted anaerobically to lactate. Thus, the accumulation of lactate is often observed in hypovolemic shock. The blood lactate concentration is often used to estimate the severity of circulatory shock [6–10], but it does not accurately reflect the cumulative deficit in oxygen consumption [11,12]. It is the increase of serum lactate from baseline values, and not the absolute value, that corresponds to changes in oxygen transport variables [13]. The delay of the rise in serum lactate levels was reported as an impairment in "lactate washout" from the tissues to the vascular system [14,15].

We hypothesized that the discrepancy between blood lactate and oxygen metabolism is caused by the restricted washout of lactate from the tissues and that directly measured lactate in the tissues might reflect oxygen metabolism. In this study, we measured the concentration of lactate directly in muscle tissue and evaluated the relationships among muscle lactate concentration, serum lactate concentration, and oxygen transport variables.

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Methods

This study was performed in accordance with the regulations of the Animal Care and Use Committee of Kyoto Prefectural University of Medicine.

Animal preparation

Experiments were conducted on six mongrel dogs of both sexes weighing 7.2 to 13.2kg (mean, 10.2kg). Anesthesia was induced by the intramuscular injection

of 150 mg of ketamine hydrochloride. After the animal had been intubated intratracheally, anesthesia was maintained by inhalation of 0.5% isoflurane with 30% oxygen. Ventilation was controlled to maintain an end-tidal CO_2 tension of 35 to 40 mmHg. The rectal temperature was monitored and maintained at 38°C during the experiment. Catheters were inserted into the external jugular vein, the internal jugular artery, and the femoral vein. A 5F triple-lumen balloon-tip thermodilution catheter (132–5F, Baxter Health Care, Edwards Division, Irvine, CA, USA) was inserted into the pulmonary artery. Correct position of the catheter was confirmed by the pressure wave form of the distal port. Pancuronium, 4 mg, was administered intravenously to prevent muscle contraction. After all surgical preparations had been completed, each animal was allowed to rest for 1 h to stabilize vital signs.

Cardiac output and blood gas measurements

Cardiac output (CO) was measured by the thermodilution technique using a cardiac output computer (9520A, Baxter Health Care). The oxygen content of the blood was measured with a hemoxymeter (OSM3, Radiometer A-S, Copenhagen, Demmark). The gas tension of the arterial blood was measured using the automatic blood gas analyzer (Stat Profile 5, Novametrix Medical System, Wallingford CT, USA). Oxygen consumption was calculated from measurements of cardiac output using the Fick equation: $CO \cdot Ca\text{-}vO_2$, where $Ca\text{-}vO_2$ represents the difference in oxygen content between arterial and mixed venous blood.

Shoemaker et al. [5] explained the oxygen consumption deficit and the cumulative oxygen consumption deficit ($def.O_2$) as follows. The oxygen consumption deficit was calculated as the difference between the measured oxygen consumption and the needed (baseline) oxygen consumption. $Def.O_2$ was calculated as the integrated area under the oxygen consumption deficit–time curve. In the present study, $def.O_2$ was simply estimated as the sum of the oxygen consumption deficit determined every 10 min during the hemorrhagic period as follows (Fig. 1):

$$\text{def.O}_2 = \sum\left\{\Delta VO_2(\text{baseline-}t)\cdot 10\,\text{min}\right\},$$

where ΔVO_2(baseline-t) represents the deficit of oxygen consumption at time t.

Measurement of lactate concentration

Muscle samples were taken from the quadriceps muscle. Immediately after sampling, the muscle was weighed and homogenized for 2 min (5000 rev·min^{-1}) and centrifuged (6000 rev·min^{-1}) for 15 min at 0°C. Protein was removed with 10% trichloroacetic acid. The lactate concentration of the supernatant fluid was measured by the enzymatic electrode method using a lactate analyzer (YSI27, Yellow Springs Instrument Co., Yellow Springs, OH, USA). The results were adjusted for the weight of muscle and were expressed as mmol·kg^{-1} wet weight. The serum lactate concentration was measured immediately after blood sampling using the same assay method.

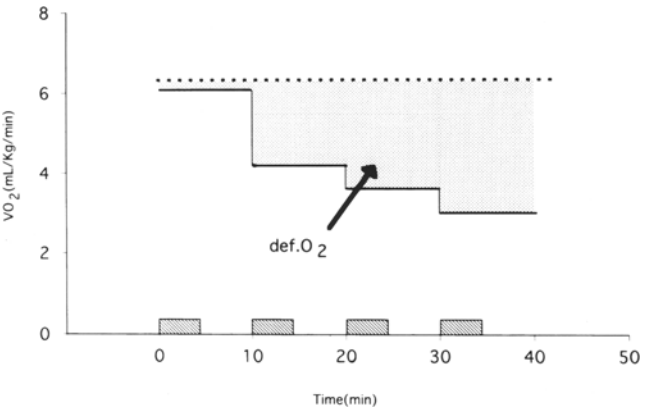

Fig. 1. Cumulative deficit in oxygen consumption (*def.O_2*) in an illustrative case. The *stippled area* represents $def.O_2$ and is the difference between the steady state of oxygen uptake (*dashed line*) and the measured oxygen uptake (*solid line*) for the duration of the experiment. The *cross-hatched area* represents blood shedding, 10 ml·kg^{-1}

Experimental protocol

After baseline data had been obtained, hemorrhagic shock was induced by shedding an amount of blood equivalent to 10 ml·kg^{-1} body weight (BW) over 5 min, followed by 5 min rest. During the rest, muscle and blood samples were obtained to determine lactate, $def.O_2$, and gas tension of arterial blood. This procedure was repeated four times, and a total of 40 ml·kg^{-1} blood was removed. No fluid replacement was given.

Statistical analysis

Correlation analysis was performed between the following three pairs; (1) muscle lactate *vs* serum lactate, (2) $def.O_2$ *vs* muscle lactate, and (3) $def.O_2$ *vs* serum lactate. Data within each parameter were compared with the respective baseline values using a analysis of variance followed by Bonferroni's correction for multiple comparisons. All data were presented as means ± SEM. A level of $P < 0.05$ was accepted as statistically significant.

Results

There were no significant differences in the partial pressure of arterial oxygen (PaO_2). $CO \cdot BW^{-1}$ decreased

Table 1. Changes in variables measured during the experiment

Time (min)	0 (baseline)	10	20	30	40
Total bleeding ($ml \cdot kg^{-1}$)	0	10	20	30	40
MAP (torr)	130 ± 10	115 ± 8	71 ± 7**	44 ± 5**	28 ± 8**
PaO_2 (torr)	112 ± 12	114 ± 9	108 ± 7	108 ± 13	110 ± 7
CO/BW ($ml \cdot min^{-1} \cdot kg^{-1}$)	137 ± 28	103 ± 28	76 ± 24	61 ± 27**	31 ± 16**
VO_2 ($ml \cdot kg^{-1} \cdot min^{-1}$)	9.3 ± 3.1	7.4 ± 2.3	6.2 ± 4.2*	6.5 ± 3.6*	4.3 ± 2.6**
Lac (serum) ($mmol \cdot l^{-1}$)	3.1 ± 0.5	3.2 ± 0.5	3.6 ± 0.5	4.6 ± 0.8*	6.4 ± 1.5*
Lac (muscle) ($mmol \cdot kg^{-1}$)	2.8 ± 1.1	6.1 ± 3.4*	6.3 ± 2.9*	8.5 ± 3.2*	12.3 ± 4.1**
M/S ratio	0.9 ± 0.4	1.8 ± 0.7*	1.7 ± 0.5	1.8 ± 0.5*	2.5 ± 0.9*

MAP, Mean arterial pressure; PaO_2, arterial PO_2; CO/BW, cardiac output per kilogram body weight; VO_2, oxygen consumption; Lac, lactate concentration; M/S ratio, muscle lactate concentration/serum lactate concentration. Data are means ± SD. $*P < 0.05$, $**P < 0.01$ *vs* baseline values.

to 25% of the baseline value after the shedding of $40 ml \cdot kg^{-1}$ of blood. Muscle and serum lactate increased significantly after the shedding of blood (Table 1).

A significant correlation ($r = 0.82$, $P < 0.001$) was observed between the lactate concentrations in muscle and serum (Fig. 2). Muscle lactate concentration was higher than serum lactate where the serum lactate level was more than $4 mmol \cdot l^{-1}$. This deviation became higher as the serum lactate level increased. The correlation between $def.O_2$ and muscle lactate concentration while the cardiac output was less than 70% of baseline is shown in Fig. 3. $Def.O_2$ was correlated with muscle lactate concentration ($r = 0.67$, $P < 0.01$) but not with arterial lactate concentration. The changes in muscle/serum lactate concentration ratio (M/S ratio) and cumulative deficit in oxygen consumption in this experiment are shown in Fig. 4. M/S ratio increased from 1 to 2.5 over 40 min and $def.O_2$ increased to $170 ml \cdot kg^{-1}$.

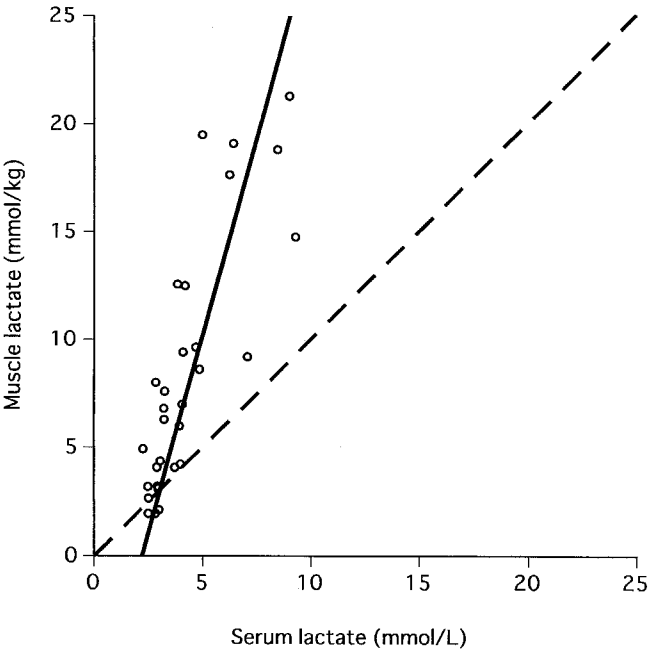

Fig. 2. Correlation of lactate concentration in muscle with that in serum for all observations. $n = 30$, $r = 0.82$, $P < 0.001$. The *dashed line* is the line of identity

Discussion

This study showed that tissue (muscle) lactate concentration reflects the cumulative oxygen consumption deficit ($def.O_2$) during hemorrhagic shock. However, a recent study [16] reported that hyperlactacidemia generally occurs in settings in which tissues are well perfused, and serum lactate levels do not correlate well with changes in oxygen metabolism [11,12]. During shock, the muscle lactate concentration exceeded that in serum, resulting in increases in the M/S ratio of lactate. The M/S ratio by itself paralleled the increasing $def.O_2$ and represented the severity of the shock. To interpret those findings, we will discuss anaerobic metabolism and the restricted washout of lactate from the tissues to the blood vessels during shock.

In shock states, maldistributed or inadequate tissue perfusion impairs tissue oxygen extraction and causes a deficit in oxygen consumption. $Def.O_2$ is taken as a determinant of the severity of circulatory failure [3–5,17]. Shock arising from blood loss is characterized by decreased circulation in nonvital organs, including muscle, resulting in anaerobiosis and increased lactate production [18]. Accordingly, serum lactate concentration has been used as an indicator of the severity of circulatory failure [6–10]. Lactate production should parallel the increasing $def.O_2$. However, serum lactate, as shown in the present study, does not represent $def.O_2$ or tissue lactate levels during advanced stages of circulatory failure. This might be caused by the deterioration in lactate washout from the tissues because of low tissue perfusion, as described by Leavy et al. [14] and Levine

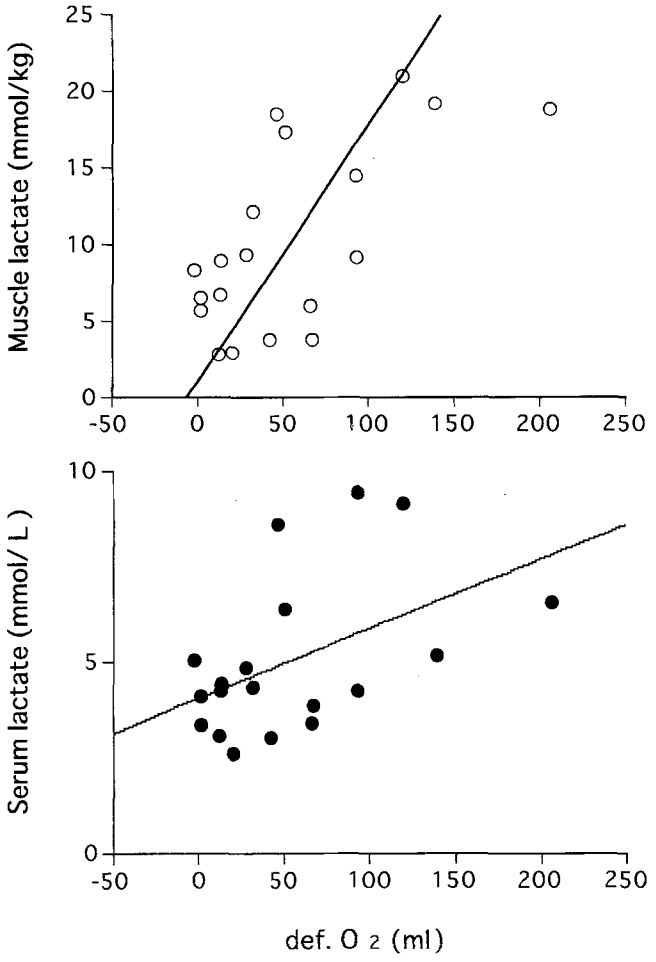

Fig. 3. Correlation analyses (muscle lactate concentration *vs* the cumulative deficit in oxygen consumption [def.O_2] and serum lactate *vs* def.O_2) were performed where cardiac output was below 70% of baseline (n = 19). *Top*: muscle lactate *vs* def.O_2; $r = 0.67$, $P < 0.01$. *Bottom*: serum lactate *vs* def.O_2; not significant

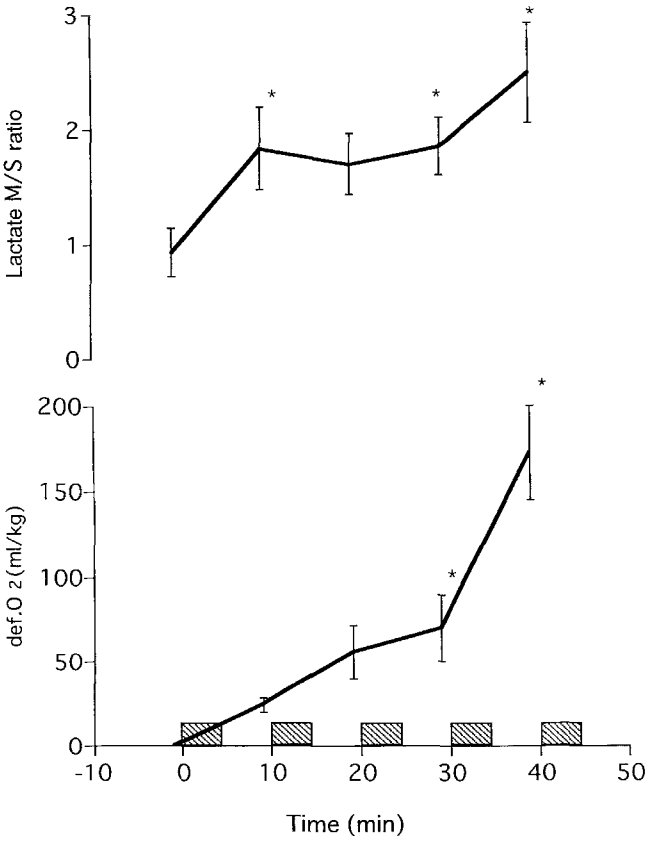

Fig. 4. *Top*: change in muscle/serum lactate concentration ratio (M/S ratio). *Bottom*: cumulative deficit in oxygen consumption (def.O_2). Values are means ± SEM. The *cross-hatched area* represents blood shedding, 10 ml·kg^{-1}. *Significantly different from the basal value ($P < 0.05$)

[19]. When the microcirculation is preserved, the lactate produced in the tissues is rapidly washed into the vascular system. In this situation, the concentration of lactate in the serum reflects that in the tissues. However, the development of shock disrupts the tissue microcirculation and impairs the washout of lactate from the tissues to the vessels.

Nevertheless, the muscle lactate levels that we measured were barely influenced by the conditions of washout and correlated best with oxygen metabolism. We infer that muscle lactate is more representative of the severity of shock than the concentration of lactate in the serum.

Crowel and Smith [3] reported that def.O_2 was a good predictor of the outcome of hemorrhagic shock. They used a canine model of hemorrhagic shock and found that a def.O_2 of 140 ml·kg^{-1} was associated with 100% mortality, whereas a deficit of 100 ml·kg^{-1} was uniformly tolerated. Adapting their reports to our results, the anticipated critical level of muscular lactate is estimated to be 20 to 25 mmol·kg^{-1} from the regression analysis in Fig. 3, and that of the M/S ratio is estimated from Fig. 4 to be 2 to 2.5. To establish such thresholds as clinically diagnostic parameters, detailed investigations of the relationships between those values and the lethality of the shock may be indispensable.

In clinical settings, the measurement of oxygen metabolism is very time-consuming and is not routinely employed for emergency cases. It requires complicated calculations derived from frequent measures of arterial and mixed venous blood gases and cardiac output. Measurement of lactate in muscle and blood is much more convenient in the management of critically ill patients. For the clinical application of these methods, further studies of factors predicting shock outcome are necessary. Furthermore, there must be less invasive methods, such as needle biopsy [20].

In conclusion, the lactate concentration in muscle tissue more accurately reflects the severity of hemorrhagic shock than does serum lactate, and the M/S ratio is a good predictor of the outcome of hemorrhagic shock because in severe shock the circulation is impaired such that lactate is not delivered to the sampling site.

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