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Serial Measurement of Arterial Lactate Concentrations as a Prognostic Indicator in Relation to the Incidence of Disseminated Intravascular Coagulation in Patients with Systemic Inflammatory Response Syndrome

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Abstract To demonstrate the prognostic value of measuring blood lactate concentrations and to investigate the mechanisms of lactate production in patients with systemic inflammatory response syndrome (SIRS), we conducted a prospective cohort study. Among 22 patients with SIRS, there were 9 survivors and 13 nonsurvivors. Serial arterial lactate concentrations were measured on the day of admission to the intensive care unit (day 0), then on days 1–4. The subjects of this study consisted of 14 patients with SIRS, 6 with severe sepsis, and 2 with septic shock. On admission, the lactate concentrations did not differ between the two groups, but remained high in the nonsurvivors throughout the study period, while they progressively decreased in the survivors. The incidence of disseminated intravascular coagulation (DIC) was significantly higher in the nonsurvivors than in the survivors. The nonsurvivors had persistently higher DIC scores and lower platelet counts than the survivors. The changes in lactate concentration over time were statistically different between the patients with DIC and those without DIC. The findings of this study clearly demonstrated that serial arterial lactate measurements can predict a poor outcome in patients with SIRS, severe sepsis, or septic shock. DIC might play an important role in the pathogenesis of lactate production in these newly defined critically ill patients.

Key words Lactate · Outcome · Mortality · Systemic inflammatory response syndrome · Sepsis · Disseminated intravascular coagulation

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Introduction

Critically ill patients with lactic acidosis have a high hospital mortality rate and are at great risk of the development of multiple organ dysfunction syndrome (MODS).[1] The blood lactate level is an especially good indicator of prognosis in patients with severe sepsis and septic shock.[2–4] Lactic acidosis has been broadly characterized into two groups: type A, caused by tissue hypoxia, and type B, caused by other disorders such as liver disease.[1] The distinction between type A and B lactic acidosis is based on the presence or absence of clinical evidence of tissue hypoperfusion.[1] However, the classification is sometimes confusing to apply to sepsis, a condition defined by some as type A and by others as type B.[1,5,6]

In 1992, the American College of Chest Physicians/Society of Critical Care Medicine (ACCP/SCCM) consensus conference defined the responses noted to occur in association with sepsis, trauma, and other severe clinical insults as systemic inflammatory response syndrome (SIRS).[7] In this context, sepsis was newly defined as SIRS with infection. We recently demonstrated that disseminated intravascular coagulation (DIC) is deeply involved in the pathogenesis of SIRS, being the main determinant for the outcome.[8–10] DIC with widespread fibrin in the microvasculature can lead to the occlusion of capillaries, contributing to tissue hypoperfusion and hypoxia.[11]

Until now few studies have investigated the role of measuring lactate to predict outcome, and the pathogenesis of lactate production in these newly defined critically ill patients. Thus, the aims of this study were to test the hypotheses that serial measurements of arterial lactate concentration can predict outcome in patients with SIRS, and that microthromboses through DIC play an important role in tissue hypoperfusion, contributing to hyperlactatemia. To test these hypotheses, we measured arterial lactate concentrations and studied their

changes in relation to patient outcome and the incidence of DIC.

Patients and Methods

Patients

With the approval of our Institutional Review Board, we studied 22 consecutive patients admitted to the intensive care unit (ICU) between October 1997 and December 1998. They were classified into subgroups of survivors ($n = 9$) and nonsurvivors ($n = 13$). All surgical and medical patients who met more than two SIRS criteria on the day of admission to the ICU were included in the present study. Patients aged under 12 years old or over 90 years old were excluded. The severity of illness was evaluated according to the Acute Physiology and Chronic Health Evaluation (APACHE) II score.[12]

Definitions and Treatment

SIRS, sepsis, severe sepsis, and septic shock were defined according to the definitions of the ACCP/SCCM consensus conference.[7] Infection was defined as any localization with clinical evidence of infection, and the identification of microorganisms in bacteriologic samples that showed positive growth at least twice. The diagnosis of DIC was performed on the basis of the Disseminated Intravascular Coagulation Diagnosis Standards published in 1988 by the Japanese Ministry of Health and Welfare, described elsewhere.[9] Briefly, the basic disorder, the clinical condition, and the results of examinations including platelet counts, prothrombin time, fibrinogen, and fibrin/fibrinogen degradation products were quantified on a score basis, the maximum being 13 and the minimum, 0. If the score was ≥ 7, a diagnosis of DIC was established. DIC was diagnosed cautiously in patients with liver diseases and blood-related disorders. A diagnosis of DIC was made in one patient with fulminant hepatitis, due to persistent low platelet counts <20000 and high levels of fibrin/fibrinogen degradation products $\geq 50\,\mu g/ml$. The Lung Injury Score was obtained according to the report by Murray et al.,[13] and those patients showing a score ≥ 2.5 were diagnosed as having acute respiratory distress syndrome (ARDS). Dysfunction of the major organs was defined as follows: for the central nervous system, progressive coma independent of direct cerebral insult or sedation; for the cardiovascular system, hemodynamics requiring inotropic support; for the pulmonary system, a Lung Injury Score of ≥ 1.0; for the hepatic system, a serum bilirubin concentration of $\geq 5\,mg/dl$ ($85.5\,\mu mol/l$) or aspartate aminotransferase (AST) and alanine aminotransferase (ALT) activities of more than twice the normal values; for the renal system, oliguria of 500 ml of urine/24 h or a creatinine concentration of $\geq 2\,mg/dl$ ($176.8\,\mu mol/l$); for the intestine, stress ulcer requiring transfusion; for hematology, DIC. Those patients with more than two organs dysfunctioning were defined as having MODS. Survivors were defined as patients discharged from the hospital.

DIC treatment consisted of anticoagulant therapy and blood supplements. Platelet concentrates were infused when the platelet counts were less than 30×10^9 cells/l. Standard treatment protocols of our ICU were applied to those patients with ARDS, dysfunction of other organs, sepsis, or septic shock.

Measurement and Protocol

Blood samples were collected using an arterial catheter, immediately after admission to the ICU (day 0), and every 4 h thereafter until day 4. Arterial lactate concentration was measured by an ABL System 520 (Radiometer, Copenhagen, Denmark) as soon as the blood was collected. The normal arterial lactate level was 0.2–1.8 mmol/l (95% confidence range). Simultaneously, platelet counts and other coagulofibrinolytic markers for the diagnosis of DIC were measured every 24 h. The SIRS criteria and DIC score were also determined every day.

Statistical Analysis

All measurements are expressed as mean ± SEM. The StatView 4.5 statistical software package (Abacus Concepts, Berkeley, CA, USA) was used for all statistical calculations. A two-tailed unpaired Student's *t*-test or the Chi-squared test with Yates' corrections as necessary were used to compare differences between the two groups. Changes over time were analyzed using a two-way analysis of variance (ANOVA) for repeated measurement. A P value of less than 0.05 was considered significant.

The sensitivity and specificity for the prediction of death were calculated by preparing a 2×2 table. A receiver operating characteristic (ROC) curve was constructed for lactate using several cutoff points for the levels of lactate on days 0 and 1. The value in the top left corner of the square in the ROC curve was then defined as the optimal cutoff point.

Results

Characteristics of the Patients

The 22 patients consisted of 14 with SIRS, 6 with severe sepsis, and 2 with septic shock. Table 1 shows the clini-

cal data of the patients. The incidence of DIC was significantly higher in the nonsurvivors than in the survivors (85% *vs* 33%, $P = 0.014$). The development of MODS and the number of dysfunctioning organs were markedly higher in the nonsurvivors than in the survivors ($P = 0.007$). We could not find any difference in the systolic blood pressure on admission between the two groups. There were no statistical differences in the maximum number of the SIRS/sepsis criteria met by the patients or the duration of SIRS/sepsis in days between the survivors and nonsurvivors. The underlying diseases of the patients, DIC diagnosis, and their outcomes are presented in Table 2.

Table 1. Clinical characteristics of the patients

	Survivors ($n = 9$)	Nonsurvivors ($n = 13$)	P value
Age (years)	53 ± 8	49 ± 6	0.681
Sex (male/female)	6/3	5/8	0.385
APACHE II score	24 ± 12	30 ± 2	0.062
SIRS/severe sepsis/ septic shock	5/4/0	9/2/2	0.203
DIC (yes/no)	3/6	11/2	0.014
ARDS (yes/no)	2/7	4/9	0.656
MODS (yes/no)	7/2	13/0	0.304
MODS (no.)[a]	2.8 ± 0.4	4.7 ± 0.3	0.007
Systolic BP (mmHg)[b]	130 ± 10	117 ± 10	0.405
SIRS/sepsis criteria[c]	3.4 ± 0.2	3.6 ± 0.1	0.266
SIRS/sepsis day[d]	3.7 ± 0.4	4.3 ± 0.3	0.275
CHDF (yes/no)	5/4	12/1	0.132
Hepatic failure (yes/no)	3/6	11/2	0.045

Plus-minus values are expressed as mean ± SEM. APACHE, Acute Physiology and Chronic Health Evaluation; ARDS, acute respiratory distress syndrome; MODS, multiple organ dysfunction syndrome; BP, blood pressure; SIRS, systemic inflammatory response syndrome; DIC, disseminated intravascular coagulation; CHDF, continuous venovenous hemodiafiltration

[a] Numbers of dysfunctioning organs

[b] Systolic blood pressure on admission to intensive care unit

[c] Maximum numbers of the SIRS/sepsis criteria that patients met

[d] Duration of SIRS/sepsis days

Changes in Arterial Lactate Concentrations, Platelet Counts, and DIC Scores

The lactate concentrations on admission to ICU and the peak lactate levels on day 0, then on days 1–4 after admission were analyzed. Figure 1 shows the time course of arterial lactate concentrations in the survivors and nonsurvivors. The differences in lactate concentrations on admission to the ICU and on day 0 between the survivors and nonsurvivors did not reach statistical significance. However, the arterial lactate concentrations remained high in the nonsurvivors, and progressively decreased in the survivors, so that the differences were significant on every day after day 0 of the investigation. Repeated-measures ANOVA between the groups was $P = 0.0152$. The patients were further subdivided into two groups according to whether DIC developed ($n = 14$) or not ($n = 8$). The time course of the changes in peak lactate concentration between the two groups also showed statistical significance ($P = 0.043$). The lactate levels in the patients with DIC remained high up to day

Table 2. Underlying diseases of the patients

Patients	Underlying diseases	DIC (yes/no)
Survivors		
1	Pulmonary thromboembolism	Yes
2	Mediastinitis post thoracic aortic aneurysm repair	No
3	Massive bleeding post gastric cancer surgery	Yes
4	Status epilepticus	No
5	Hypovolemic shock caused by hemopneumothorax	No
6	Mediastinitis after esophageal perforation, chronic renal failure	No
7	Hepatic failure caused by ornithine transcarbamylase defect	No
8	Aplastic anemia, pneumonia	Yes
9	Acute respiratory distress syndrome, sepsis	No
Nonsurvivors		
10	Acute renal failure, uremic lung	No
11	Tumor thrombosis of the inferior vena cava	Yes
12	Esophageal cancer and massive bleeding	Yes
13	Fulminant hepatitis	Yes
14	Liver transplantation	No
15	Myelodysplastic syndrome, bone marrow transplantation	Yes
16	Myelodysplastic syndrome, veno-occulusive disease, acute renal failure	Yes
17	Aspiration pneumonia, acute respiratory distress syndrome	Yes
18	Aortitis syndrome, acute renal failure	Yes
19	Liver cirrhosis, varix rupture, acute renal failure	Yes
20	Liver cirrhosis, acute renal failure	Yes
21	Osteosarcoma, intoxication of methotrexate	Yes
22	Massive bleeding post gastrointestinal tract surgery	Yes

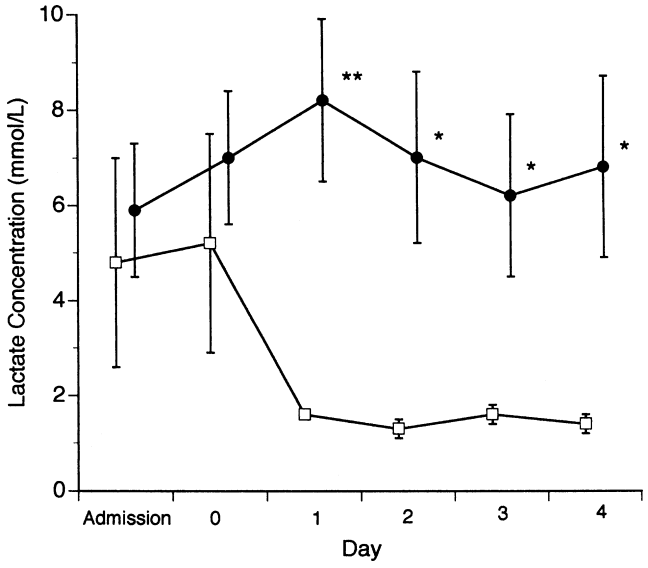

Fig. 1. Changes in arterial peak lactate concentrations in the survivors (*white squares*) and nonsurvivors (*black circles*). Two patients died, one on day 2 and one on day 3. *Admission*, admission to the intensive care unit (ICU). $*P < 0.05$, $**P < 0.01$ *vs* survivors

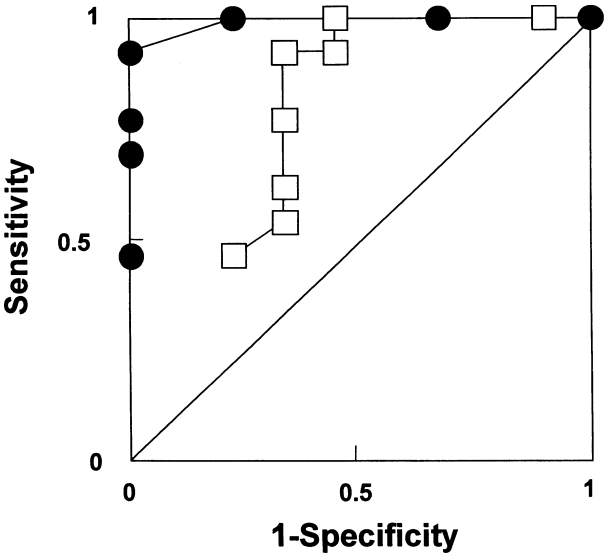

Fig. 3. Receiver operating characteristic (ROC) curves of lactate on days 0 (*open squares*) and 1 (*closed circles*). The value in the top left corner of the square in each ROC curve was defined as the optimal cutoff point

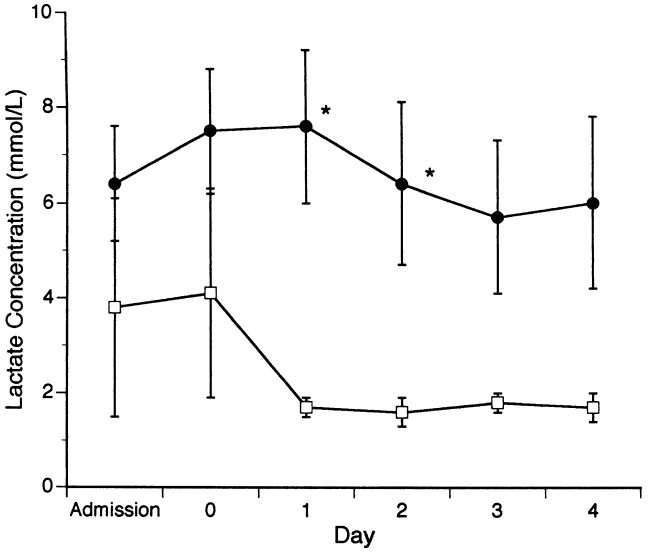

Fig. 2. Changes in arterial peak lactate concentrations in patients without disseminated intravascular coagulation (DIC) (*white squares*) and in patients with DIC (*black circles*). *Admission*, admission to the ICU. $*P < 0.05$ *vs* patients without DIC

4, but the values in those without DIC markedly decreased, as shown as Fig. 2. To predict death in patients with SIRS, we decided upon an optimal cutoff lactate level on day 1. The optimal cutoff point, defined as the best prognostic value for the prediction of subsequent death in patients with SIRS, was a lactate concentration of 2.5 mmol/l. The result is shown in Fig. 3.

The changes in DIC scores and platelet counts are presented in Tables 3 and 4. There were statistical differences in the scores and platelet counts between the two groups throughout the study period. The acid-base parameters such as pH, PCO_2, and base excess are shown in Table 5.

Discussion

According to the previous report, blood lactate concentrations >5 mmol/l at the time of admission to ICU were associated with patient mortality rates of 59% after 3 days and 83% after 30 days.[14] Furthermore, a blood lactate concentration greater than 4 mmol/l portended a poor prognosis in critically ill patients.[15] The average blood lactate concentration of the nonsurvivors in the present study was about 6 mmol/l, while the optimal cutoff point for the prediction of death in patients with SIRS was 2.5 mmol/l. These results suggest that regardless of the definitions of critical illness, hyperlactatemia of approximately 3–6 mmol/l without a tendency to decrease is highly predictive of a poor outcome. To our knowledge, only one other study has examined the ability of blood lactate concentrations to predict outcome in newly defined severe sepsis.[16] Our study, for the first time, demonstrated that blood lactate concentrations were significantly higher in nonsurvivors than in survivors with newly defined SIRS, severe sepsis, or septic shock. Although the definition of SIRS is sensitive, it is specific enough to diagnose

Table 3. Disseminated intravascular coagulation score change

	Day 0	Day 1	Day 2	Day 3	Day 4	ANOVA
						0.004
Survivors	4.1 ± 0.8	3.8 ± 0.6	3.0 ± 0.6	3.6 ± 0.8	3.3 ± 0.7	
Nonsurvivors	7.6 ± 0.5*	7.7 ± 0.6*	7.8 ± 0.8**	7.2 ± 0.8*	7.3 ± 0.7*	

ANOVA, analysis of variance. Values are expressed as mean ± SEM
* $P < 0.01$, ** $P < 0.001$ *vs* survivors

Table 4. Changes in platelet counts ($\times 10^9$/l)

	Day 0	Day 1	Day 2	Day 3	Day 4	ANOVA
						0.016
Survivors	15.1 ± 4.1	13.0 ± 3.2	11.6 ± 2.8	10.7 ± 2.6	10.2 ± 2.3	
Nonsurvivors	5.0 ± 0.9*	3.5 ± 0.3**	3.5 ± 0.8**	3.7 ± 0.6*	3.4 ± 0.5*	

Values are expressed as mean ± SEM
* $P < 0.05$, ** $P < 0.01$ *vs* survivors

Table 5. Changes in pH, PCO_2 (mmHg), and base excess (mmol/L)

	Admission	Day 0	Day 1	Day 2	Day 3	Day 4
pH						
Survivors	7.36 ± 0.04	7.38 ± 0.04	7.45 ± 0.01	7.44 ± 0.01	7.43 ± 0.02	7.42 ± 0.01
Nonsurvivors	7.38 ± 0.03	7.40 ± 0.03	7.43 ± 0.02	7.42 ± 0.03	7.44 ± 0.03	7.39 ± 0.04
PCO_2						
Survivors	40 ± 4	39 ± 8	38 ± 1	39 ± 1	39 ± 1	39 ± 1
Nonsurvivors	33 ± 2	32 ± 2	33 ± 2	35 ± 2	34 ± 2	34 ± 2
Base excess						
Survivors	−1.5 ± 3.1	−3.2 ± 2.6	2.7 ± 1.1	2.8 ± 0.9	2.0 ± 1.2	1.5 ± 0.9
Nonsurvivors	−3.7 ± 2.0	−4.1 ± 1.7	−1.9 ± 1.4	−0.4 ± 1.8	−0.9 ± 1.8	−3.5 ± 2.6

Values are expressed as mean ± SEM

patients in a critical condition. Therefore, we believe that the specificity to predict poor outcome would be elevated further using the optimal lactate cutoff point determined in the present study. This result is the first significant finding of our study on patients with SIRS.

We found no significant differences in lactate levels between the two groups at the time of ICU admission, but the differences became significant on day 1. This result coincided with that of a previous study by Joynt et al.[16] who observed that lactate levels were lower in survivors than in nonsurvivors 48 h after the start of the study. Using definitions of severe sepsis and septic shock that were different from ours, Vincent and coworkers[2,6,17] recommended that measurements of lactate levels should be repeated regularly. We agree with their opinion because our study also indicated that the serial analysis of blood lactate concentration is more informative than a single value to predict outcome in patients with SIRS or sepsis.

The poorly understood aspects of hyperlactatemia are the mechanisms and the anatomic site of lactate production. Since lactate is primarily metabolized in the liver, alterations in liver function may delay lactate clearance. In the present study, the incidence of hepatic dysfunction was markedly higher in the nonsurvivors than in the survivors. However, almost total destruction of the liver must occur before the lactate level increases remarkably.[6] Moreover, it is well known that lactate can be used as a marker of tissue distress even in patients with liver dysfunction.[1,6] Treatment by continuous venovenous hemofiltration with bicarbonate dialysis, as used in our study, cannot mask the overproduction of lactate, and the blood lactate concentration remains a reliable marker of tissue hypoxia.[18] The effect of the intravenous infusion of lactated Ringer's solution on the level of serum lactate can be denied.[19] Recent studies have examined the regional production of lactate by the lung and liver in patients with sepsis.[20–22] Although the pathogenesis of regional hyperlactatemia is complex, the hypothesis that injury to the endothelial cells in the lung vasculature results in lactate release has been proposed.[20–22] Endothelial injury is frequently observed in patients with SIRS complicated by DIC,[8] which is the major contributing factor to organ dysfunction and poor outcome.

In our study, the nonsurvivors with persistent hyperlactatemia had a significantly higher incidence of DIC and lower platelet counts than the survivors. Furthermore, the DIC scores and platelet counts on day 0 demonstrated clear differences between the survivors and nonsurvivors. These differences became evident earlier than the changes in lactate levels, which were observed on day 1. The results of this study suggest two important points. First, they indirectly imply that DIC is one of the causes of lactate elevation; and second, the specificity of the definition of SIRS can be raised to predict a poor outcome in combination with lactate levels, platelet counts, and DIC scores. Only two patients suffered from septic shock, which suggests that hemodynamic instability plays a minor role in the hyperlactatemia observed in the patients in this study. The circulatory obstruction resulting from microthrombosis caused by intravascular coagulation produces organ hypoperfusion, even ischemia, and the risk of infarction is well known. This process is disseminated throughout the microcirculation, and the lungs, kidneys, and gastrointestinal tract are potentially vulnerable.[23] In addition to the decrease in oxygen transport, DIC is also the main cause of oxygen maldistribution and tissue hypoxia.[11] Furthermore, we demonstrated that DIC associated with massive thrombin activation plays a key role in the pathogenesis of MODS, and in the outcome of patients with SIRS, severe sepsis, or septic shock.[9,10] Accordingly, to combat hyperlactatemia in patients with SIRS, anticoagulant therapy combined with increased oxygen delivery could be effective. The controversy surrounding the pathophysiology of lactic acidosis in sepsis[1,5,6] may be based on the disregard for DIC.

The development of hyperlactatemia without acidosis during hypermetabolic stress has been a subject of discussion.[24,25] Stress-induced hyperlactatemia after severe clinical insults, such as infection and injury, results from overall acceleration in glycolysis caused by a cytokine-mediated increase in the cellular uptake of glucose.[24] Stress-induced hyperlactatemia is accompanied by a normal lactate/pyruvate ratio.[24] Although the lactate/pyruvate ratio was not measured in this study, stress-induced hyperlactatemia may have played a role in elevating the lactate concentrations observed in our patients. Levraut et al.[26] reported that the development of hyperlactatemia in septic patients mainly occurs due to a defect in lactate utilization. However, they did not evaluate the hepatic circulation, and the decrease in lactate clearance may be the consequence of liver hypoperfusion caused by intravascular coagulation. The present study examined not only septic patients, but also patients with SIRS. Thus, reduction in the lactate clearance may have played a minor role in the development of hyperlactatemia in our patients.

The major limitation of the present study was that we could not prove a direct pathophysiological link between DIC and hyperlactatemia. The second limitation was that only 22 patients were studied. To override these limitations, measurements of lactate/pyruvate ratios and global oxygenation data such as gastric intramucosal pH, oxygen delivery, tissue oxygen consumption, and mixed venous oxygen saturation are mandatory. The interrelationships of the three important variables, namely lactate, survival, and DIC, could be better evaluated in a larger group of patients.

We conclude that a persistent high lactate concentration in patients with SIRS, severe sepsis, or septic shock is a reliable indicator of poor outcome. The persistent lactate production was associated with a high incidence of DIC and a low platelet count. DIC associated with a low platelet count preceding the elevation of lactate levels indirectly implies that the former may be the cause of the lactate production. These results indicate that hyperlactatemia may be, at least in part, due to tissue hypoxia caused by disseminated platelet and fibrin microthrombosis. To demonstrate the direct pathophysiological relationship between DIC and hyperlactatemia, simultaneous measurements of lactate levels, DIC variables, and global oxygenation data must be conducted in a future study.

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