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Markers of tissue hypoperfusion in pediatric septic shock

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Abstract *Objective:* To describe measurements of global oxygenation parameters, markers of splanchnic hypoperfusion and those of metabolic activity related to cellular energy production among critically ill children with septic shock.
Design: Clinical study of a series of cases.
Patients and participants: 11 previously healthy children with septic shock admitted to the pediatric intensive care unit (ICU) of a university hospital.
Interventions: None.
Measurements and results: Oxygen consumption, oxygen delivery (DO_2), serum bicarbonate, arterial pH, gastric intramucosal pH (pHi), gastroarterial carbon dioxide tension gradient, serum lactate, pyruvate, lactate to pyruvate ratio (L/P), ketone body ratio, and the esterified to free carnitine ratio were measured serially at 0, 6, 12, 24, 36, and 48 h after admission to the pediatric ICU. All children survived. One patient failed to show supranormal DO_2 (> 570 ml/min per m^2). Normalization of serum bicarbonate and lactate were associated with patient recovery. One patient presented an increasingly abnormal L/P ratio with normal lactate levels, suggesting an increased utilization of pyruvate rather than an increased cytosolic redox potential. Although values of gastric pHi < 7.30 were observed in 43 % of samples, serial measurements in individuals showed significant variability and unpredictable trends. Free fatty acid concentrations, ketone body production, and carnitine levels remained within the normal range.
Conclusions: In this study, trends in serum bicarbonate and lactate somewhat characterized the recovery of children with septic shock. Based on our data, it is unclear how other markers may have been used to modify therapy.

Key words Sepsis · Lactate · Pyruvate · Ketone bodies · Carnitine · Gastric mucosa · Child

Introduction

Sepsis is a leading cause of multiple organ dysfunction (MODS) and death in critically ill children [1, 2, 3]. It is characterized by the systemic inflammatory response syndrome (SIRS) [4], an abnormal redistribution of circulatory blood flow and a modified substrate utilization associated with hypermetabolism [5].

Early detection of physiologic abnormalities is the basis for monitoring in the intensive care unit (ICU) [6]. Various markers have been proposed in order to modify therapy with the underlying assumption that inadequate oxygenation and tissue hypoperfusion are central to the pathogenesis of MODS. Pulmonary artery catheters provide information on systemic hemodynamics at the global level. Nevertheless, increased oxygen-

Table 1 Diagnostic criteria for the systemic inflammatory response syndrome *SIRS,* sepsis, severe sepsis, and septic shock [2] ($PaCO_2$ arterial carbon dioxide tension)

SIRS (at least two of the following criteria):
(a) Temperature > 38 °C or < 36 °C rectal
(b) Heart rate > 90th percentile for age
(c) Tachypnea with a respiratory rate > 90th percentile for age or $PaCO_2$ < 4.3 kPa (< 32 torr)
(d) White blood cell count > 12×10^9/l (> 12 000 cells/mm^3) or < 4×10^9/l (< 4000 cells/mm^3) or > 10 % immature (band) forms
Sepsis
SIRS caused by an infection (positive culture from any site, clinical evidence of infection)
Severe sepsis: sepsis plus one of the following criteria
(a) decreased consciousness (Glasgow Coma Score < 15 without disease of the central nervous system)
(b) arterial blood lactate > 1.6 mmol/l (> 1.6 mEq/l)
(c) urine output < 1 ml/kg per h for 2 consecutive h with a urinary catheter
Septic shock
Presence of hypotension with two distinct measurements of blood pressure < 3rd percentile for age after administration of ≥ 20 ml/kg of crystalloids or colloids plus (a) the requirement for inotropic or vasopressor support (excluding dopamine ≤ 5 μg/kg per min) or (b) any of the previously defined diagnostic criteria for severe sepsis

ation parameters may characterize survivors of sepsis [7, 8]. The value of serum lactate as evidence of anaerobic metabolism and critical oxygen delivery has been questionned [6]. However, persistently increased blood lactate levels may also help to identify nonsurvivors of severe sepsis [9]. It has been proposed that the redox potential of cytosol and that of liver mitochondria may be evaluated by the lactate to pyruvate (L/P) ratio and the ketone body ratio, 3-hydroxybutyrate to acetoacetate ratio (3OHB/AA), respectively. These are excellent indicators of the adequacy of cellular oxygenation in vitro [5, 10], but they have not been extensively studied in humans with sepsis [11]. In fact, there are few data on the production of ketone bodies and related carnitine metabolism in this population. Finally, it has been recently reported that gastric tonometry may predict mortality among adults with sepsis [9, 12, 13] and that the measurement of interstitial partial pressure of carbon dioxide (PCO_2) may reflect regional splanchnic hypoperfusion and/or hypoxia [12, 13]. Unfortunately, the experience in critically ill children has been much less encouraging [14, 15, 16, 17].

We hypothesized that physiologic abnormalities noted during pediatric septic shock and MODS are associated with patient recovery and death. The purpose of the study was to characterize over time global oxygenation parameters, markers of splanchnic hypoperfusion, and those of metabolic activity related to cellular energy production among critically ill children with septic shock. Oxygen consumption, oxygen delivery, gastric intramucosal pH, gastroarterial PCO_2 gradient, serum lactate, L/P ratio, 3OHB/AA, plasma free fatty acids, and esterified to free carnitine ratio were measured serially during the first 48 h after admission to the pediatric ICU for septic shock.

Patients and methods

Population characteristics

The study was approved by the ethics committee of Sainte-Justine Hospital. Informed consent was obtained from the parents for inclusion in the study. This study was conducted prospectively in a 22-bed, multidisciplinary pediatric ICU of a university hospital. All children aged between 1 and 18 years old, who had been admitted to the pediatric ICU at Sainte-Justine Hospital from 15 February 1995 to 15 March 1997 were screened for the study. Patients were eligible only if they required mechanical ventilation for septic shock. Those children who developed septic shock after ICU admission were not eligible. Children under 1 year of age and those with the following comorbid states were also excluded: inborn errors of metabolism, Reye-like syndrome, use of valproic acid, prior renal or hepatic dysfunction, diabetes mellitus, and malnutrition defined as weight [18] or tricipital skinfold thickness < 10th percentile for age and sex [19].

Clinical data

Age, sex, physiologic variables, therapeutic interventions, Pediatric Risk of Mortality (PRISM) score [20], length of ICU stay, and ICU mortality were noted. The expected rate of mortality for our study population was calculated according to the following formula: p (ICU death) = exp(r)/(1 + exp[R]), where $r = 0.207 \times$ PRISM–$0.005 \times$ age (months)–$0.433 \times$ operative status (postoperative = 1, nonoperative = 0)–4.782. Operational diagnostic criteria for SIRS, sepsis, severe sepsis, and septic shock are presented in Table 1. Diagnostic criteria for MODS used in this study have been previously defined [2]. Weight was obtained on a metabolic balance (Scale-Tronix 2001, White Plains, N.Y., USA). Tricipital skinfold thickness was measured with a skinfold caliper (Lange HB 859–1-2, Cambridge Scientific Industries, Cambridge, Md., USA). The mean of three consecutive measurements was compared to normal values [19]. Oxygen consumption and delivery (VO_2, DO_2), gastric intramucosal pH (pHi), gastro-arterial PCO_2 gradient ($\Delta PtCO_2$-$PaCO_2$), serum lactate, pyruvate, 3-hydroxybutyrate, acetoacetate, and plasma free fatty acids (FFA), total carnitine, and esterified carnitine were measured on study entry and then 6, 12, 24, 36, and

Table 2 Characteristics of patients (*ARDS* adult respiratory distress syndrome, *CSF* cerebrospinal fluid, *TTP* thrombotic thrombocytopenic purpura)

Patients[a]	Age (months)	Sex	PRISM	Diagnosis	Culture (sites)
1 ◆	19	M	7	Severe chickenpox	Negative
2 ▽	174	F	3	Peritonitis/Meckel Pancreatitis/ARDS	Negative
3 X	187	F	33	Chorioamniotitis/ARDS	*Escherichia coli* (blood + vagina)
4 ▲	67	F	20	Meningococcemia/ARDS	*Nesseria meningitidis* (blood)
5 □	48	F	20	Sepsis-associated hemophagocytosis	Respiratory syncytial virus (nasopharyngeal)
6 ■	145	F	24	Toxic shock	*Streptococcus A* (pus)
7 O	25	F	5	Meningitis	*Streptococcus pneumoniae* (blood and CSF)
8 ▼	29	F	7	Meningococcemia	*Nesseria meningitidis* (blood and CSF)
9 △	39	F	19	Meningococcemia	*Nesseria meningitidis* (blood)
10 ◆	188	F	17	Community-acquired pneumonia	Negative
11 ◇	75	M	46	TTP/ARDS	Negative

[a] The symbols refer to individual patients identified in Figs. 1 to 4

48 h later. The data collection was stopped before 48 h if the patient could be weaned from mechanical ventilation and extubated.

Oxygenation indices

A 5 or 7 French pulmonary artery catheter (Arrow International, Reading, Penna., USA) was inserted by the attending physician. An arterial line was placed in all patients. Pressure transducers (Baxter, Irvine, Calif., USA). were calibrated before each set of measurements. Cardiac output was measured randomly throughout the respiratory cycle [21] by rapid injection of 5 or 10 ml of saline at room temperature. All patients received continuous infusions of fentanyl and midazolam, and five children were given continuous vecuronium. The mean of three consecutive measurements was used for calculation of cardiac index; oxygenation parameters were then calculated using simultaneously drawn mixed venous and arterial blood gases according to the following formula: arterial O_2 content = (hemoglobin g/dl × systemic arterial O_2 saturation × 1.34) + (arterial O_2 tension × 0.003); DO_2 = (cardiac index l/min per m^2 × systemic arterial O_2 content); VO_2 = mixed venous arterial O_2 content–systemic arterial O_2 content, using mixed venous and systemic arterial saturation [22]. Systemic arterial O_2 saturation was measured using a blood gas analyser (Nova Stat Profile 5, Nova Biomedical, Watham, Mass., USA).

L/P ratio

Blood samples were immediately deproteinized by precipitation of 200 µl titrated whole blood with 400 µl of trichloric acid 2 %. These were transported on ice and centrifuged at 2200 rpm, 4 °C for 10 min. Supernatants were then neutralized with bicarbonate and frozen at –80 °C. Lactate and pyruvate were determined by an enzymatic method as previously reported [23].

Marker of splanchnic hypoperfusion

A 16 French gastric tonometer (TRIP-NGS catheter, Tonometrics, Worchester, Mass., USA) was introduced orally; adequate positioning into the stomach was verified by radiography. No patients were fed enterally, but all children received ranitidine, 0.5 mg/kg per dose intravenously every 6 h. The silicone balloon was flushed many times with phosphate buffer solution (Omega, Montreal, Canada) and then filled with 2.5 ml of this solution. It was allowed to equilibrate for 240 min. Then, the first 1 ml was discarded and 1.5 ml was put on ice. Measurement of CO_2 was done using a blood gas analyser (Nova Stat Profile 5, Nova Biomedical, Watham, Mass., USA). The pHi was calculated according to the modified Henderson-Hasselbach equation: $pHi = 6.1 + {}_{\log 10}[\text{bicarbonate arterial} \div (F \times PCO_2)]$, where F is a constant accounting for both the solubility of CO_2 and the equilibration time. Using this method, Takala et al. have reported a bias ranging from –1.4 to 2.0 torr for high and low control values of CO_2, respectively [24].

Other markers of intermediary metabolism

For 3-hydroxybutyrate and acetoacetate measurements, samples were deproteinized by adding 500 µl of perchloric acid (0.9 mmol/l) to 500 µl of whole blood. These measurements were done in duplicate. They are based on a fully enzymatic endpoint spectrophotometric method. The concentrations of ketone bodies are calculated from the amount of nicotinamide-adenine dinucleotide to the reduced form (NADH) converted during the time required to complete the reaction using the absorption coefficient of NADH at 340 nm [25, 26]. Quantification of FFA was performed in duplicate by an vitro enzymatic colorimetric method (Wako Chemicals, Dallas, Tex., USA). Plasma total and free carnitine concentrations were determined in duplicate by radioenzymatic assay as previously reported by us [27].

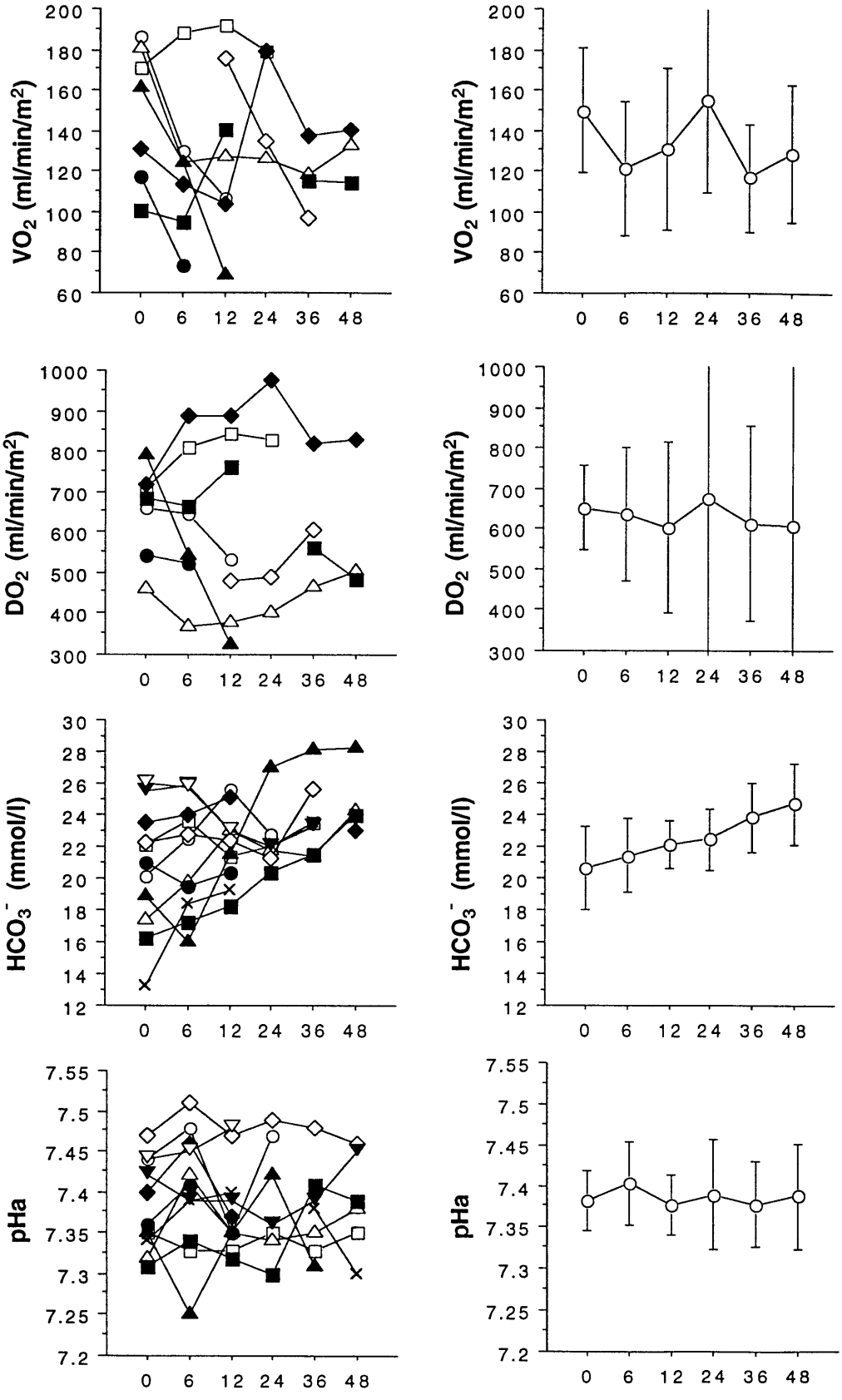

Fig. 1 Global markers of tissue hypoperfusion. Oxygen consumption (VO_2), oxygen delivery (DO_2), arterial pH (*pHa*), and serum bicarbonate in children with septic shock (individual measurements are shown on *left*, mean ± 95% confidence interval is presented on *right*). VO_2 and DO_2 were measured in 7 children only, who required a pulmonary artery catheter. Levels of serum bicarbonate normalized over time in all patients recovering from sepsis, while those of VO_2, DO_2 and pHa displayed large variances. Three children (*closed circle*, *closed triangle*, *open diamond*) showed decreasing VO_2 values to less than 100 ml/min per m^2 at the end of the study. Another patient (*open triangle*) survived without ever reaching supranormal DO_2 (> 570 ml/min per m^2) [8]

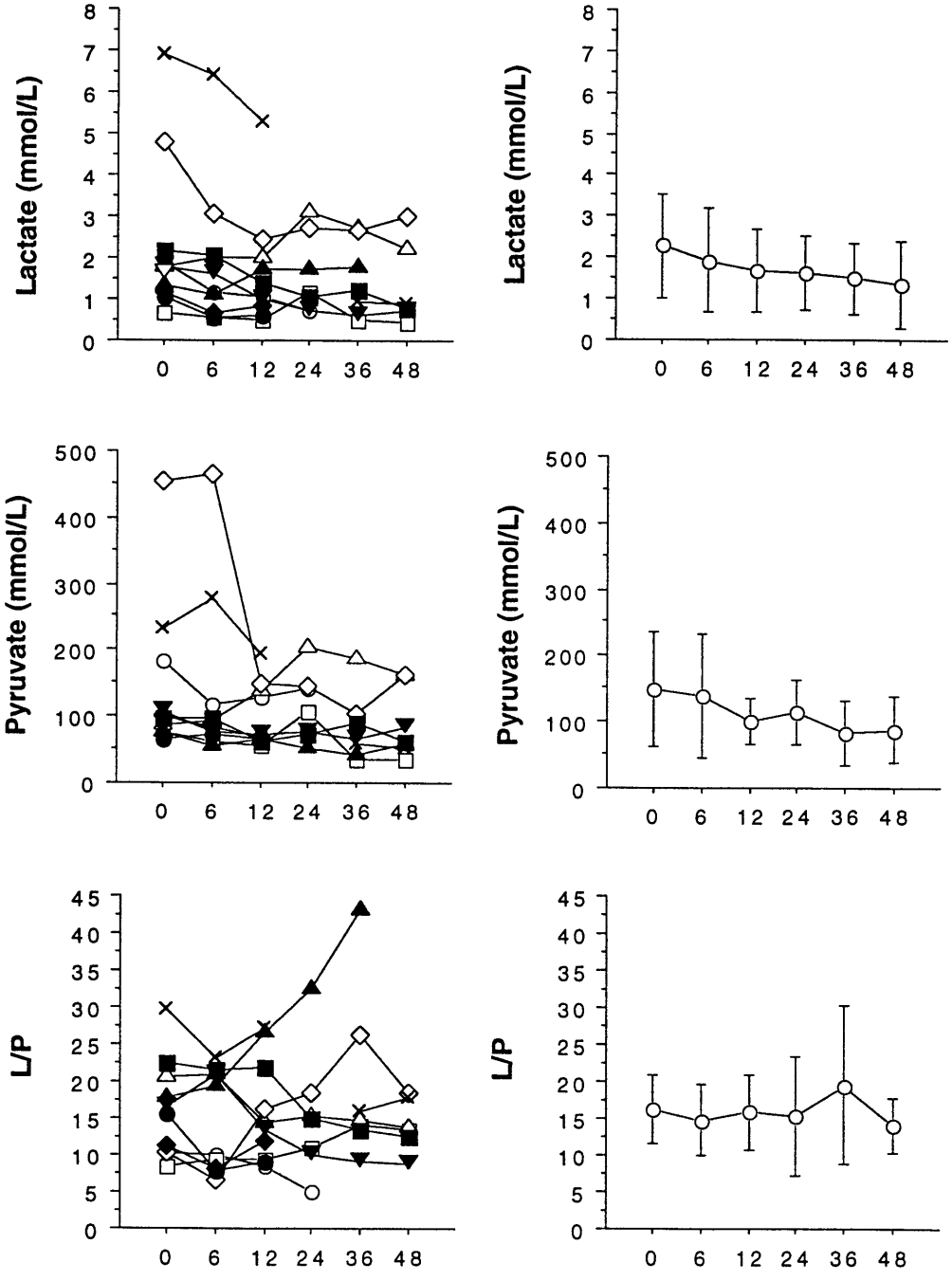

Fig. 2 Measurements of serum lactate, pyruvate, and lactate to pyruvate ratio in children with septic shock (individual measurements are shown on *left*, mean ± 95 % confidence interval is presented on *right*). The figure shows that serum lactate levels rapidly normalized over time in all individuals. The lactate to pyruvate (*L/P*) ratio displayed significant variability over the study period. One child (*closed triangle*) presented increasingly abnormal values of L/P ratio at normal lactate levels while he was recovering from sepsis

Statistical analysis

Descriptive statistics are presented as mean ± 95 % confidence interval. Coefficients matrix of correlation between mesurements of the different markers under study were established using the values obtained upon admission. Statistical significance was established at 0.05.

Results

Eleven previously healthy children were admitted to the pediatric ICU for septic shock. Characteristics of these patients are presented in Table 2. All patients required mechanical ventilation and met criteria for septic shock. Nine children (80 %) also developed MODS [2]. The mean age was 91 ± 69 months, the PRISM score was 17 ± 11 (expected mortality of 50 %), and the length of

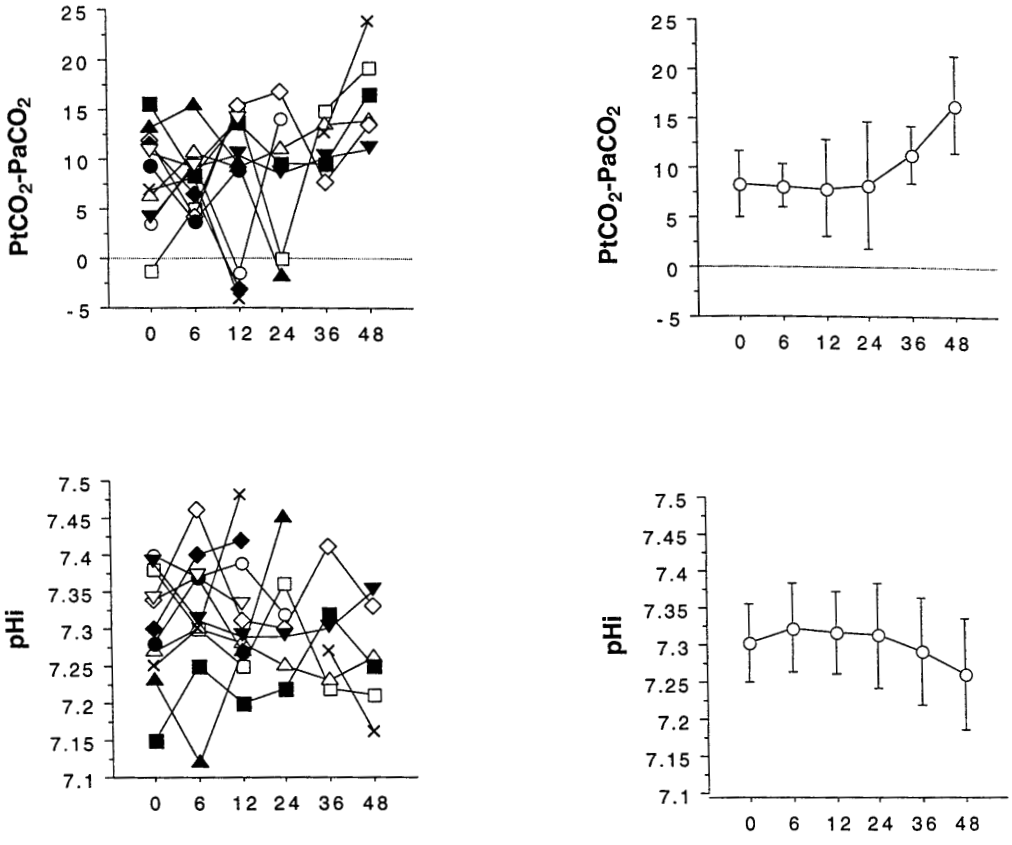

Fig. 3 Regional markers of tissue hypoperfusion. Gastric pHi and gastro-arterial PCO_2 gradient ($\Delta PtCO_2$-$PaCO_2$) in children with septic shock (individual measurements are shown on *left*, mean ± 95 % confidence interval is presented on *right*). The figure shows significant variability and unpredictable trends in serial measurements in individual patients

ICU stay was 8 ± 7 days. The use of dopamine or dobutamine alone (15 μg/kg per min) was required in 3 children, dopamine and dobutamine (15–20 μg/kg per min, 10–15 μg/kg per min, respectively) were required in 2 patients, and 6 children were treated with three vasopressors (dopamine 15–25 μg/kg per min, dobutamine 10–43 μg/kg per min, and epinephrine 0.2–0.7 μg/kg per min). All patients were survivors from pediatric ICU.

VO_2, DO_2, arterial pH (pHa), and levels of serum bicarbonate are presented in Fig. 1. The figure shows that large variations were observed for both VO_2 and DO_2. We noted unexpected values of $VO_2 < 100$ ml/min per m^2 at the end of the study in 3 patients. However, supranormal levels of DO_2 (> 570 ml/min per m^2) [8] were observed in 7 of 8 patients, accounting for 56 % (18/32) of DO_2 measurements. Only 23 % (13/57) of pHa measurements were lower than 7.35; this was secondary to high minute ventilation induced by mechanical ventilation (data not shown). Overall, the steadily increasing values of serum bicarbonate reflected well patients' recovery from septic shock. Levels of serum lactate and pyruvate and the L/P ratio are presented in Fig. 2. The figure shows that serum lactate levels rapidly normalized over time in all individuals. We noted abnormal levels of lactate in 29 % (15/53) of samples and of L/P in 27 % (14/53) (normal lactate < 1.8 mmol/l, L/P 16 ± 5 [28]). Increasingly abnormal values for the L/P ratio were noted at normal lactate levels in 1 patient who was recovering, suggesting increased pyruvate utilization. Nevertheless, upon admission, the L/P ratio was significantly inversely correlated with VO_2 ($r^2 = -0.8$; $p = 0.02$) and with pHi ($r^2 = -0.5$; $p = 0.03$). Regional markers of splanchnic hypoperfusion are presented in Fig. 3. The figure shows that both $\Delta PtCO_2$-$PaCO_2$ and gastric pHi displayed significant variability over time with unpredictable trends in individual measurements within the first 24 h. We noted abnormal levels of pHi in 72 % (38/53) of samples and of $\Delta PtCO_2$-$PaCO_2$ in 78 % (41/53) of samples (normal pHi < 7.35 [14, 15], $\Delta PtCO_2$-$PaCO_2$ < 7 mmHg [29]). Moreover, 58 % (31/53) of pHi measurements were less than 7.32 and 43 % (23/53) were lower than 7.30 [17]. Five patients (45 %) presented a gastric pHi < 7.30 on admission and 7 children (63 %) had two or more pHi values of < 7.30 during the study period. Markers of intermediary metabolism are presented in Fig. 4. The figure shows that most values for the ketone body ratio remained within the normal range (3.5 ± 1.2 mmol/l) [28]. The total production of ketone bodies and FFA also appeared appropriate. There was no evidence of carnitine deficiency in

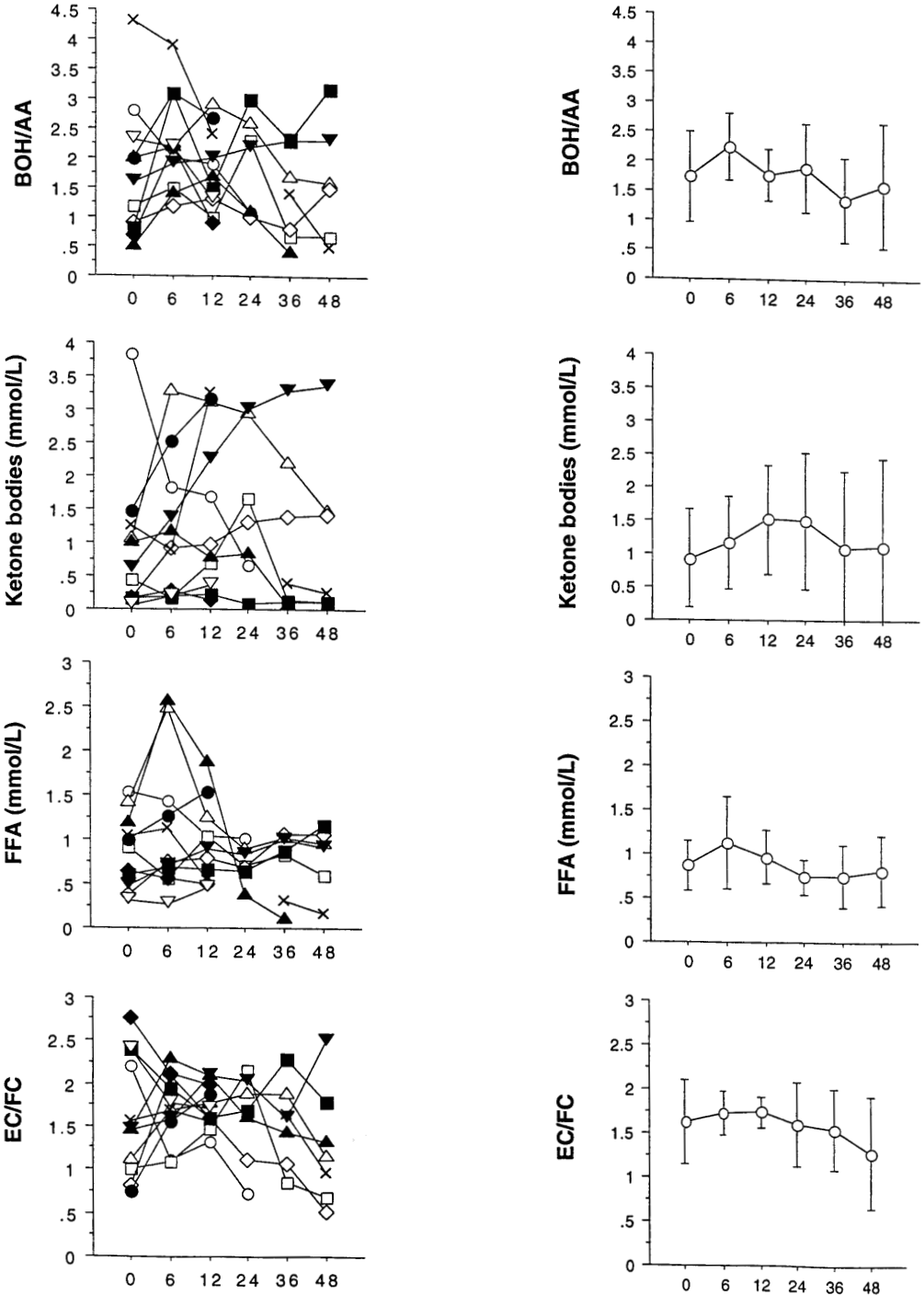

Fig. 4 Metabolic markers of intermediary metabolism: 3-hydroxybutyrate to acetoacetate ratio (*BOH/AA*), total ketone bodies, free fatty acids (*FFA*), and esterified to free carnitine ratio (*EC/FC*), in children with septic shock (individual measurements are shown on *left*, mean ± 95 % confidence interval is presented on *right*). The figure shows significant individual variability over time in all these markers of metabolic activity

this population [30]. The esterified to carnitine (EC/FC) ratio was also within the normal range (0.4 ± 0.2) and thus gave little information [30].

Discussion

The patients included in this study were severely ill as reflected by their high PRISM score and their requirement for significant cardiopulmonary support. We estimated that the expected survival rate was lower than 50 %. The lack of any death among our study population

precluded the usual prognostic analysis based on mortality. Contrary to previous reports [14, 15, 16, 17], all of our children were previously healthy and this may have contributed to a better observed than expected survival rate. Nevertheless, our data may be informative regarding the changes associated with patient improvement.

In this study, abnormal measurements of VO_2, DO_2, pHa, serum bicarbonate, lactate, L/P ratio, and pHi were frequently noted. However, only the normalization over time of serum bicarbonate and lactate seemed to be associated with patients' recovery from septic shock. Calculation of VO_2, and to a lesser extent DO_2, appeared to show significant heterogeneity. However, only 1 child spontaneously recovered without ever reaching the supranormal DO_2 threshold (> 570 ml/min per m^2) previously proposed by Pollack et al. [8]. The use of high oxygen concentrations upon admission may have precluded accurate measurements of VO_2 by indirect calorimetry. Overall, the large variations noted in oxygenation parameters among this group of survivors question the rationale of aiming for a specific target level of VO_2 and DO_2 during pediatric sepsis.

Significant variability within serial measurements was also noted for pHa, pHi, and $\Delta PtCO_2$-$PaCO_2$. We suspect that these measurements may not have been really independent of changes in PCO_2 induced by mechanical ventilation. Although gastric tonometry has been repeatedly reported to predict the development of MODS and death in critically ill adult patients [12, 13], the experience in children has been less encouraging [14, 15]. First, Krafte-Jacobs reported that 20 % of pHi measurements in eight children with septic shock seemed to lack any physiologic basis [15]. Moreover, Duke et al. also showed that neither the absolute level nor changes in pHi predicted outcome in children with sepsis [14]. Conversely, Calvo et al. reported that gastric pHi was predictive of major hemodynamic complications occurring after congenital heart surgery [16]. Casado-Flores et al. recently reported that a pHi value of < 7.30 was an independent predictor of ICU mortality (47 %, 95 % confidence interval 26 to 69 %) [17]. We have been clearly unable to reproduce these findings as no death occurred, although 43 % of pHi measurements were < 7.30, 5 patients (45 %) presented a pHi < 7.30 on admission and 7 children (63 %) were noted to show a pHi < 7.30 on two or more occasions. Moreover, the long equilibration time used in this study should have been theoretically expected to reflect improvement in patient status. Based on our data, it is unclear how pHi or $\Delta PtCO_2$-$PaCO_2$ could be safely used to modify therapy.

Hyperlactatemia is often regarded as evidence of global anaerobic metabolism and oxygen supply dependency [6]. However, hyperlactatemia may also be due to factors unrelated to hypoxia and hypoperfusion, such as the inhibition of pyruvate dehydrogenase [31, 32]. We noted that the L/P ratio was inversely correlated with VO_2 upon admission. This may indicate the occurrence of an increased cytosolic redox potential when patients were highly hemodynamically unstable although these changes may not have been severe or lasted long enough to modify the proposed markers of mitochondrial function, e. g., BOH/AA and EC/FC. Unexpectedly, we observed an increasing L/P ratio at normal lactate levels in 1 child who survived sepsis. This may question the biological significance of the L/P ratio as being only a marker of the cytosolic redox potential in vivo. As reported among adults with sepsis [33] and children with extensive burns [34], this may rather reflect the occurrence of an increased rate of glycolysis and pyruvate utilization in order to meet increased metabolic needs as reflected by high VO_2 upon initial presentation.

We observed appropriate FFA, ketone bodies, and plasma carnitine levels. As 3-hydroxybutyrate and acetoacetate freely penetrate the cell membrane, it has been suggested that the arterial ketone body ratio may adequately reflect the redox potential within hepatic mitochondria during liver transplantation [35]. The value and the biological significance of this marker during pediatric septic shock remains unclear. Our data do not suggest an inhibition of carnitine palmitoyl transferase [36, 37, 38]. Indeed, although no carnitine deficiency was observed in this study, slightly increased plasma concentrations of EC may have been related to the net synthesis of ketone bodies, an increased production of toxic acyl-CoA esters [39], or an increased production of malonyl-CoA due to an increased rate of pyruvate oxidation. Circulating concentrations of these metabolic markers may simply not reflect intracellular conditions [27].

In this study, we showed that the normalization of serum bicarbonate and lactate has a timely association with patients recovery during pediatric septic shock. The unpredictable trends noted within the serial measurements of individual patients for VO_2, DO_2, pHi, or $\Delta PtCO_2$-$PaCO_2$ raise questions on how these markers may have been rationally used to modify therapy in this population.

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