原 著

A Negligible Amount of Plasma Lactate Clearance by Large-pore Continuous Venovenous Hemodiafiltration in Septic Renal Failure.

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Abstract

The present study was carried out to determine if plasma lactate could be removed by large-pore continuous venovenous hemodiafiltration (LP-CVVHDF) in 10 patients with septic renal failure.

LP-CVVHDF was performed using a large-pore polyacrylonitrile hemofilter (cut off point: 55-65kD). The blood flow rate through the extracorporeal system was 80 ml/min with a bicarbonate dialysis fluid rate of 500ml/hr. The ultrafiltration rate was 500 ml/hr and a bicarbonate replacement solution was administered at a rate of 400-500 ml/hr in a postfilter fashion. Simultaneous samples of arterial, and filter inlet and outlet blood and ultradiafiltrate were collected before starting CVVHDF, and 4hr, 12hr and 24hr after starting CVVHDF.

Plasma lactate clearance (ml/min) with LP-CVVHDF was 15.9±0.4 at 4hr, 16.1±0.3 at 12hr and 16.5±0.4 at 24hr. There were no significant differences in the plasma lactate concentration among the time point. Lactate-sieving coefficient by LP-CVVHDF was 0.95±0.08 at 4hr, 0.98±0.09 at 12hr and 0.99±0.07 at 24hr.

The results show that plasma lactate clearance by LP-CVVHDF is much smaller than endogenous plasma lactate clearance in septic renal failure.

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Key words: lactate, tissue oxygenation, renal failure, hemodiafiltration, sepsis

Introduction

Plasma lactate concentration, a useful marker of general hypoperfusion, reflects the balance between lactate production and the ability of the liver and other organs to metabolize lactate[1]. Patients with critical illness can be considered to have normal lactate concentrations of <2mmol/L[2]. A mild hyperlactatemia (>2mmol/L) occurring in a stable septic patient is mainly due to a defect in lactate utilization, but not lactate overproduction[3]. This impaired lactate utilization may be caused by the altered liver function[4], which commonly occurs during sepsis.

Continuous venovenous hemodiafiltration (CVVHDF) using bicarbonate dialyzate was reported to be an effective therapy to treat severe lactic acidosis in critically ill patients complicated with renal failure or congestive heart failure[2]. However, plasma lactate is not removed by standard-membrane CVVHDF efficiently[5]. Large-pore CVVHDF (LP-CVVHDF) has a larger pore size than a standard membrane (cut off point: 30-50kD) to eliminate larger molecules[6], and is expected to be able to remove plasma lactate efficiently.

The present study was carried out to determine if plasma lactate could be removed by LP-CVVHDF using bicarbonate dialyzate in patients with septic renal failure.

Materials and Methods

Patients

This study was approved by the Ethics Committee of the Nagasaki University School of Medicine and conducted in the intensive care unit (ICU) of Nagasaki University Hospital from July 1999 to July 2000. Informed written consent was obtained from each patient or the relatives. The subjects were 10 patients with septic renal failure receiving CVVHDF. Sepsis was diagnosed according to the criteria of American College of Chest Physicians/ Society of Critical Care Medicine Consensus Conference[7]. The diagnosis of renal failure was based on the decreased renal function in need of dialysis[8]. The severity of the disease was assessed using APACHE II score[9]. The Glasgow Coma Scale was excluded from the calculation of the APACHE II score, as some patients were sedated and intubated.

Therapy

All patients received conventional intensive care therapy according to clinical requirements. The attending physician to maintain an adequate mean arterial blood pressure adjusted vasopressor agents (dopamine, dobutamine, norepinephrine, etc.). All intubated patients were sedated with a continuous infusion of buprenorphine and midazolam. The ventilator setting was adjusted by the attending physician to maintain clinically appropriate gas exchange. Hemodynamic monitoring consisted of continuous recordings of electrocardiograms, heart rate, arterial blood pressure and central venous pressure. We assessed the improvement by LP-CVVHDF of the respiratory, cardiovascular, coagulation and liver functions using the Sequential Organ Failure Assessment (SOFA) score[10].

CVVHDF

The femoral vein was cannulated for vascular access with a 11-Fr, double-lumen catheter (UK-CATHETER KIT, Unitika, Japan). CVVHDF was performed using a polyacrylonitrile (PAN) hemofilter (APF-06S, Asahimedical, Japan). This membrane has the cut-off point of approximately 55-65kD, the mean pore size of 8.3nm and the effective surface area of $0.6m^2$. The study was carried out during the first 24 hr of treatment with the single hemofilter. Blood was pumped through the hemofilter at 80 mℓ/min (Q_B) by a CVVHDF peristaltic pump system (Jun-500, Ubemedical, Japan), and was then returned to the circulation. We used a bicarbonate dialyzate (Sublood-B, Fusoyakuhin, Japan). The bicarbonate dialyzate was simultaneously infused through the hemofilter, countercurrent to blood flow, at a constant rate of 500 mℓ/hr (Q_D). The ultrafiltration rate was 500 mℓ/hr (Q_F) and the same bicarbonate replacement solution was administered at a rate of 400-500 mℓ/hr (Q_R) in a postfilter fashion. The extracorporeal circuit was protected against coagulation with nafamostat mesilate (Futhan, Toriiyakuhin, Japan) or heparin in the afferent limb. The infusion of anticoagulants was adjusted to maintain the activated clotting time (ACT) about 150sec. Simultaneous samples of arterial, and filter inlet blood and ultradiafiltrate were collected before starting CVVHDF (0hr), and 4hr, 12hr and 24hr after starting CVVHDF. At each point, hemodynamic determinations, arterial blood gas analysis and hematological analysis were performed. Plasma lactate concentration was measured by ABL 620 (ABL radiometer, Denmark).

Calculations

The following formulas[5] were used:

Sieving coefficient = C_{uf} / C_{in}

Ultradiafiltrate lactate clearance (mL/min) = $(Q_F + Q_D) / 60 \times C_{uf} / C_{in}$

where C_{uf} is lactate concentration in ultradiafiltrate (mmℓ/L); and C_{in} is lactate concentration in inlet plasma.

Statistical Analysis

Results were presented as mean ± SD. Results were evaluated by Kruskal-Wallis and Wilcoxon test with $P < 0.05$ regarded as significant.

Results

Patients

The characteristics of the patients were summarized in Table 1. The mean APACHE II score was 16.1 ± 3.9. Three patients (30%) survived to leave the ICU. Seven patients (70%) died from irreversible multiple organ distress syndrome (MODS) following sepsis.

Table 1. Patient characteristics

Patient	Gender	Age (yr)	APACHE II Score	Pathology	Outcome
1	M	74	18	CABG, aortic-adbominal graft	Died
2	F	58	16	Bronchoesophageal fistula	Died
3	M	73	10	MNMS	Survived
4	M	86	17	Burn	Died
5	M	71	23	Interstitial pneumonia	Died
6	M	57	17	Crush syndrome	Died
7	F	60	11	CABG	Survived
8	M	80	14	CABG	Died
9	M	73	15	MVR	Died
10	M	76	20	Malignant lymphoma	Survived

APACHE Ⅱ, Acute Physiolosy and Chronic Health Evaluation Ⅱ; CABG, Coronary Artery Bypass Graft: MVR, Mitral Valve Replacement; MNMS, Myonephropathic metabolic synrome

Effects of LP-CVVHDF

Table 2 shows the data concerning the respiration score, the cardiovascular score, the coagulation score and the liver score abstracted from SOFA score. LP-CVVHDF did not improve either the respiration score (from 2.4±1.5 to 2.2±1.3) or the cardiovascular score (from 2.3±1.6 to 2.4±1.7). Moreover, LP-CVVHDF did not improve either the coagulation score (from 1.8±1.1 to 2.2±1.2) or the liver score (from 2.4±1.3 to 2.5±1.4).

Hemofilter data

The kinetic property of lactate under LP-CVVHDF was shown in table 3. There were no significant differences in the plasma lactate concentration among the time point. There was no significant change in the lactate clearance during the time course of LP-CVVHDF. There were no significant changes in lactate-sieving coefficient during the time course of LP-CVVHDF. Although not statistically different, plasma lactate concentration gradually increased in nonsurvivors (2.5±2.2 at 0hr, 2.5±1.9 at 4hr, 2.9±2.3 at 12hr and 3.5±3.3 mmol/ℓ at 24 hr). There was no significant change in the plasma lactate concentration in survivors (2.1±2.0 at 0hr, 2.1±2.1 at 4hr, 2.3±2.4 at 12hr and 2.6±2.6 mmol/ℓ at 24hr). Although not statistically different, plasma lactate concentration in nonsurvivors was higher than that in survivors at each time point.

Table 2. Effects of LP-CVVHDF

Function scores	Time after LP-CVVHDF(hr)	
	0	24
Respiratory score	2.4±1.5	2.2±1.3
Cardiovascular score	2.3±1.6	2.4±1.7
Coagulation score	1.8±1.1	2.2±1.2
Liver score	2.4±1.3	2.5±1.4

LP-CVVHDF, Large-pore Continuous Venovenous Hemodiafiltration; The respiratory, the cardiovascular, the coagulation and the liver score were abstracted from the Sequential Organ Failure Assessment (SOFA) score Results are expressed as mean±SD

Discussion

The present results show that plasma lactate clearance with LP-CVVHDF is nearly 16 mℓ/min throughout the time course and there were no significant changes in plasma lactate concentration during the time course. These results suggest that lactate elimination by LP-CVVHDF does not affect plasma lactate concentration.

Levraut et al evaluated total plasma lactate clearance by infusing 1 mmol/kg of sodium L-lactate in critically ill patients including septic patients[5]. They demonstrated that median plasma lactate clearance was 1379 mℓ/min (range 753.7 to 1880.7). Lactate clearance with LP-CVVHDF is estimated as<2% of endogenous plasma lactate clearance in critically ill patients. With regard to drug removal, it is generally accepted that extracorporeal clearance is clinically

Table 3. Parameters of lactate clearance

Parameters	Time after LP-CVVHDF(hr)			
	0	4	12	24
Plasma lactate (mmol/L)	2.4±2.0	2.4±1.9	2.7±2.2	3.2±3.0
PLC of LP-CVVHDF (ml/min)		15.9±1.2	16.1±1.1	16.5±1.1
LSC of LP-CVVHDF		0.95±0.08	0.98±0.09	0.99±0.07

LP-CVVHDF, Large-pore Continuous Venovenous Hemodiafiltration; PLC, Plasma Lactate Clearance; LSC, Lactate Sieving Coefficient Results are expressed as mean±SD

significant if its contribution to total body clearance exceeds 25-30%[11]. The present results show lactate sieving coefficient is close to one throughout the time course, which means that lactate (MW=90.08) clearance with LP-CVVHDF was compatible with the combined ultrafiltration/ dialyzate flow rates[5,12,13]. Accordingly, as we used a dialyzate flow rate of 500mL/hr with a ultrafiltration rate of 500 mℓ/hr, the lactate clearance with LP-CVVHDF was 1000 mℓ/hr, or 16.7 mℓ/min. Because this sieving coefficient of LP-hemofilter is equal to that of standard membrane[5], lactate clearance cannot be affected by membrane pore size due to small molecule.

Levraut et al divided stable septic patients to two groups depending on their blood lactate: ≦1.5mmol/ℓ (n=20, lactate=1.2±0.2mmol/ℓ) or ≧2mmol/ℓ (n=10, lactate=2.6±0.6mmol/ℓ)[3]. When they administrated 1mmol/kg L-lactate, the hyperlactatemic patients had a lower lactate clearance (473±102 mℓ/kg/hr) than those with normal blood lactate (1,002±284 mℓ/kg/hr). Lactate production in the two groups was similar (1,194±230 and 1,181±325 μmol/kg/hr). They concluded that a mild hyperlactatemia occurring in a stable septic patient was mainly due to a defect in lactate utilization. Even under lower lactate clearance in septic patients, plasma lactate clearance with LP-CVVHDF was<4% of endogenous lactate clearance in septic patients.

Plasma lactate concentration would indicate the prognosis in septic patients. Bakker et al compared the plasma lactate concentrations between the survived and the nonsurvived septic patients[14]. The period of increased blood lactate (>2mmol/ℓ) was significantly shorter in the survivors, compared with the non-survivors, indicating that the duration of lactic acidosis was the best predictor of survival from organ failure. Levy et al showed that hemodynamically unstable patients with sepsis needing catecholamine therapy had a lactic acidosis with an elevated L/P ratio and a decreased arterial ketone body ratio (AKBR)[15]. They concluded that the longer duration of lactic acidosis would be associated with the development of multiple organ failure and death. Thus, the duration of lactic acidosis can be the good predictor of survival and organ failure even under LP-CVVHDF.

Rogiers et al administrated 2mg/kg of Escherichia coli endotoxin into the dogs[16]. Endotoxin administration resulted in a sharp decrease in mean arterial pressure (MAP) and cardiac output (CO) and in a significant increase in plasma lactate. Continuous venovenous hemofiltration (CVVHF) with 3L/hr of ultrafiltrate improved CO but not MAP or plasma lactate, whereas CVVHF with 6L/hr of ultrafiltrate improved CO, MAP and plasma lactate. The lactate clearance with 6L/hr CVVHF was estimated about 100mL/min, estimated as >20% of the endogenous lactate clearance in the septic patients, which could influence the plasma lactate concentration. It was controversial whether low-flow (<1ℓ/hr) hemodiafiltration could improve hemodynamics in septic condition[17,18]. The present results show that low-flow LP-CVVHDF does not improve either the respiratory or the cardiovascular function. Kline et al administrated Escherichia coli endotoxin into dogs, resulting in endotoxin shock, and treated them with low-flow LP-CVVHDF (cut off point: 100kD)[6]. The treatment improved left ventricular maximum elastance representing left ventricular contractility but did not im-

prove MAP or CO. They concluded that low-flow LP-CVVHDF improved the cardiac function during acute endotoxin shock and appeared to successfully remove soluble negative inotropic mediators.

In conclusion, plasma lactate clearance by LP-CVVHDF is much smaller than endogenous plasma lactate clearance in septic renal failure.

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