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Intermittent hemodialysis in critically ill patients with multiple organ dysfunction syndrome is associated with intestinal intramucosal acidosis

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Abstract *Objective*: Conventional intermittent hemodialysis in the critically ill patient can be associated with hemodynamic and respiratory instability. Intermittent hemodialysis induced arterial hypotension might be detrimental. We therefore studied the influence of intermittent hemodialysis on systemic and regional oxygen transport in critically ill patients.
Design: Prospective descriptive study.
Setting: Medical/surgical 24-bed intensive care unit in a university hospital.
Patients: Eleven critically ill patients admitted to the intensive care unit (APACHE III score: 82±12) and developing multiple organ dysfunction syndrome with acute renal failure. All patients were mechanically ventilated and hemodynamically stable with inotropic support. Systemic oxygen transport variables were calculated, and arterial blood lactate concentration was measured before, during, and after intermittent hemodialysis. Tonometer PCO_2 was measured using a tonometer, and arterial-tonometer CO_2 gap was used as an indicator of intestinal intramucosal acidosis.
Results: Intermittent hemodialysis induced an increase in calculated systemic oxygen consumption ($P<0.01$). During intermittent hemodialysis there was a significantly higher need of inotropic support ($P<0.05$) to maintain arterial blood pressure, cardiac index, and calculated systemic arterial oxygen delivery. The arterial-tonometer CO_2 gap increased significantly during and after the procedure.
Conclusion: In critically ill patients with multiple organ dysfunction syndrome intermittent hemodialysis induces an increase in oxygen consumption. Despite higher inotropic support to maintain systemic calculated oxygen delivery intestinal intramucosal acidosis occurs during intermittent hemodialysis and may even persist after the procedure is terminated.

Key words Oxygen transport · Tonometry · Multiple organ dysfunction syndrome · Acute renal failure · Hemodialysis

Introduction

In critically ill patients it has been hypothesized that intestinal ischemia may be an important cause of multiple organ dysfunction syndrome [1, 7]. Many of these patients are hemodynamically and respiratorilly unstable and need mechanical ventilation and inotropic support. The latter might provoke intestinal ischemia. They often develop renal failure, with a need for hemodialysis [2, 3]. This procedure, if performed in the conventional intermittent mode, may also induce hemodynamic and respi-

ratory instability with subsequent reduction in splanchnic blood flow.

This study evaluated the effect of conventional intermittent hemodialysis on hemodynamic parameters, systemic and regional oxygen transport in critically ill patients with multiple organ dysfunction syndrome and acute renal failure. Splanchnic perfusion was measured with a tonometer and arterial-tonometer CO_2 gap was used as an indicator of intestinal intramucosal acidosis [4, 5].

Methods

Patient selection and instrumentation

The study protocol was approved by the ethics committee of the University Hospital, University of Brussels (VUB). Eleven patients admitted to the intensive care unit and developing circulatory shock and multiple organ dysfunction syndrome with acute renal failure were studied. Mean age was 68±18 years, and APACHE III score was 82±12 (Table 1). Intermittent hemodialysis was chosen because of acute renal failure with hyperkaliemia (plasma $K^+ > 5$ mmol/l), fluid overload, metabolic acidosis, plasma areum concentration above 200 mg/dl, plasma creatinine concentration higher than 7 mg/dl, and creatinine clearance less than 15 ml/min.

Before hemodialysis was started all patients were hemodynamically stable, with mean arterial pressure (MAP) at 65 mmHg or higher, under inotropic support of dopamine (9.2±9.0 $\mu g\ kg^{-1}\ min^{-1}$), dobutamine (14.4±14.2 $\mu g\ kg^{-1}\ min^{-1}$), and/or norepinephrine (3.4±7.08 $\mu g\ kg^{-1}\ min^{-1}$). During hemodialysis inotropic and vasopressor support was further titrated to maintain MAP at this level. All patients were sedated with midazolam and fentanyl and mechanically ventilated with positive end expiratory pressure of 5–10 cmH_2O (Siemens Elema Servo 900C). The ventilatory conditions were not changed during the study protocol. The patients were instrumented with a thermodilution cardiac output catheter (Edwards Swan Ganz, Baxter, 7.5 F), inserted via a central jugular vein, and an 18-gauge arterial catheter inserted via a radial or a femoral artery. A nasogastric tonometer (Baxter) was inserted and the correct position of the catheter was determined by X-ray of the abdomen.

During the measurements no enteral feeding was administered, and no aspiration of the gastric content was performed. All patients received H_2 receptor antagonists. Patients with a history of Billroth II procedure were excluded [1]. All patients were parenterally fed with a balanced diet of 30 kcal/kg.

Hemodialysis procedure

All patients were hemodialyzed for 4 h with a Gambro AK 100 or Hospal monitral dialysis proportioning and monitoring system. Nine dialysis sessions were performed with a cellulose acetate membrane (Altraflux, Altkin); two dialysis sessions were performed with a hemophan membrane (GFS 12, Gambro). The bicarbonate bath was prepared with Na^+ 140 mmol/l, K^+ 2–4 mmol/l (depending on plasma K^+ levels of the patient), Mg^{2+} 0.50 mmol/l, Ca^{2+} 1.75 mmol/l, HCO_3^- 38.5 mmol/l, acetate 5 mmol/l. The temperature of the bath was 37 °C. Blood flow was 200 ml/min; dialysate flow was 500 ml/min. Ultrafiltration rate was 2000 ml in all patients, with exception of one in whom ultrafiltration had to be limited to 1200 ml due to severe hemodynamic instability.

Measurement of hemodynamic variables and blood sampling

Before and at 90 and 180 min after the beginning of the hemodialysis session and 90 min after its end the following hemodynamic parameters were determined: heart rate, systolic arterial blood pressure (SAP), diastolic arterial blood pressure, cardiac index, central venous pressure, and pulmonary capillary wedge pressure. Cardiac output was measured with the thermodilution technique: ice chilled (<10 °C) 10 ml saline was injected at the end of expiration. Hemodialysis was ceased by stopping the running blood pump in order to avoid an effect of the blood flow in the dialysis system upon the cardiac output measurements. The cardiac output value was the mean of three consecutive measurements within a 10% variation. At the same times arterial samples were taken for hemoglobin concentration, PaO_2, $PaCO_2$, bicarbonate, lactate, SaO_2, and base excess. Mixed venous samples (aspirated from the distal port of the pulmonary artery catheter) were taken to determine PvO_2, $PvCO_2$, and SvO_2. All samples were maintained in anaerobic conditions. Oxygen delivery (DO_2) and oxygen consumption (VO_2) were calculated by the method of Fick.

Mucosal PCO_2 measurement

A physiological solution was used to measure carbon dioxide tensions [6]. After an equilibration period of 90 min PCO_2 in the saline (maintained in anaerobic conditions) was measured using a

Table 1 Overview of the patients (*A* alive, *D* deceased)

Patient	Age	Sex	Pathology	APACHE III score	Outcome
1	59	M	Diabetic ketoacidosis, sepsis	62	A
2	75	M	Aneurysm of the abdominal aorta	82	A
3	80	M	Aneurysm of the abdominal aorta	71	A
4	60	M	Aneurysm of the abdominal aorta	64	A
5	56	M	Cardiogenic shock	112	D
6	79	M	Cardiogenic shock	127	D
7	27	M	Trauma	57	D
8	78	F	Cardiac tamponade	61	D
9	66	F	Cardiogenic shock, ventricular septum defect[a]	98	D
10	73	M	Pneumonia	79	A
11	85	F	Abdominal sepsis	101	D

[a] All blood samples were obtained after closure of the septum defect

blood gas analyzer (ABL 520, Radiometer, Copenhagen, Denmark). Steady-state PCO_2 (PCO_2 ss) was calculated with the pHi slide calculator (Tonometrics, Worcester, Mass., USA).

Statistical analysis

Values obtained before, during, and after hemodialysis were compared using the Wilcoxon matched-pairs signed rank test. Results were expressed as mean ± standard deviation. Significance was defined as the *P*-value being less than 0.05.

Results

Hemodynamic variables and blood values

During hemodialysis there was a non significant decrease in the systolic and diastolic arterial blood pressure and in the cardiac index in all patients. A significantly higher dose of inotropic agents (dobutamine) was needed to maintain blood pressure and cardiac index. Dobutamine infusion before hemodialysis was 14.4 ± 14.2 µg kg^{-1} min^{-1} during hemodialysis 18.2 ± 13.6 µg kg^{-1} min^{-1} (after 90 min; $P<0.05$), 18.2 ± 13.6 µg kg^{-1} $min^{-1}1$ (after 180 min; $P<0.05$), and after hemodialysis 16.8 ± 14.2 µg kg^{-1} min^{-1} ($P<0.05$). Central venous pressure and pulmonary capillary wedge pressure remained stable during the study protocol (Table 2).

Hemoglobin concentration, PaO_2, and SaO_2 were not affected by the intermittent hemodialysis. Bicarbonate concentration increased during intermittent hemodialysis (90 min and 180 min after the start of hemodialysis: $P<0.05$). After hemodialysis the bicarbonate concentrations were comparable to these obtained before the procedure. $PaCO_2$ increased during the first 90 min after the start of hemodialysis ($P<0.05$). After 180 min and after the hemodialysis $PaCO_2$, however, decreased significantly ($P<0.05$). Mixed venous oxygenation decreased during the procedure (90 min and 180 min after the start of hemodialysis: $P<0.02$). A sustained fall in SvO_2 was noted after the end of dialysis ($P<0.02$). Calculated systemic oxygen delivery, which in this situation is most dependent on cardiac index, was not altered during the procedure. Calculated oxygen consumption was increased during (90 min after the start of hemodialysis: $P<0.01$) and after (90 min after the end of hemodialysis: $P<0.02$) the hemodialysis session (Table 3). Lactate concentrations did not change during nor after the procedure.

Mucosal PCO_2

Mucosal steady-state carbon dioxide concentrations increased 90 min after the start of hemodialysis ($P<0.005$). Compared with the values obtained before hemodialysis, steady-state carbon dioxide tensions 180 min after the

Table 2 Hemodynamic values[a] (*PCWP* pulmonary capillary wedge pressure, *CVD* central venous pressure, *CI* cardiac index, *SAP* systolic arterial blood pressure, *DAP* diastolic arterial blood pressure, *Hb* hemoglobin)

[a] None of the changes was significant

	Before hemodialysis	During hemodialysis		After hemodialysis
		At 90 min	At 180 min	
PCWP (mmHg)	17.0 ± 4.0	15.6 ± 4.2	15.2 ± 3.5	16.3 ± 3.4
CVD (mmHg)	15.3 ± 5	12.4 ± 6.6	11.9 ± 4.9	14.2 ± 5.0
CI ($l\,min^{-1}\,m^{-2}$)	3.66 ± 1.47	3.49 ± 1.36	3.12 ± 1.20	3.70 ± 1.49
SAP (mmHg)	120.5 ± 27.3	114 ± 27.5	120 ± 25.3	119.7 ± 23.8
DAP (mmHg)	56.3 ± 10.1	61.2 ± 16.5	61.7 ± 15.6	60.7 ± 13.2
Hb ($g\,dl^{-1}$)	10.33 ± 0.83	10.35 ± 0.84	10.75 ± 0.65	10.38 ± 0.48

Table 3 Respiratory and oxygen transport values

	Before hemodialysis	During hemodialysis		After hemodialysis
		At 90 min	At 180 min	
pH	7.316 ± 0.075	7.346 ± 0.064*	7.380 ± 0.066*	7.378 ± 0.054*
PCO_2 (mmHg)	41.54 ± 8.75	43.00 ± 8.80*	40.63 ± 8.07	38.09 ± 6.90*
PO_2 (mmHg)	85.18 ± 21.43	94.18 ± 19.44*	93.54 ± 26.87	100.90 ± 17.46
HCO_3 ($mmol\,l^{-1}$)	20.63 ± 5.04	22.45 ± 3.88*	23.27 ± 3.50**	22 ± 3.68
SaO_2 (%)	95.3 ± 1.8	95.2 ± 1.8	94.9 ± 2.5	95.5 ± 2.3
SvO_2 (%)	68.7 ± 6.5	62.6 ± 9.3**	61.2 ± 8.8**	63.1 ± 5.9**
DO_2 ($ml\,min^{-1}\,m^{-2}$)	491 ± 178	470 ± 170	441 ± 172	505 ± 197
VO_2 ($ml\,min^{-1}\,m^{-2}$)	128 ± 33	147 ± 44***	134 ± 58	166 ± 64**
Lactate ($mmol\,l^{-1}$)	1.60 ± 0.93	1.49 ± 0.80	1.50 ± 0.79	1.68 ± 1.07
PCO_2ss (mmHg)	50.13 ± 7.82	54.95 ± 10.08****	55.8 ± 11.10***	53.1 ± 8.20*

*$P<0.05$, **$P<0.02$, ***$P<0.01$, ****$P<0.005$

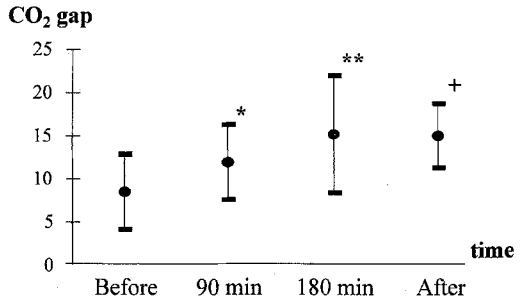

Fig. 1 Arterial-tonometer CO_2 gap (mmHg) time-related to hemodialysis. The values are compared with the values before hemodialysis using the Wilcoxon matched-pairs signed rank test. $^*P<0.05$; $^{**}P<0.02$; $^+P<0.01$

start of hemodialysis were also higher ($P<0.01$). After the end of hemodialysis steady-state mucosal carbon dioxide tensions remained higher than before hemodialysis ($P<0.05$). The mean arterial-tonometer CO_2 gap before hemodialysis was 8.59 ± 4.36 mmHg; 90 min and 180 min after the start of hemodialysis it was, respectively, 11.95 ± 4.31 mmHg ($P<0.05$) and 15.18 ± 6.82 mmHg ($P<0.02$); 90 min after the end of the hemodialysis session it was 15.00 ± 3.79 mmHg ($P<0.01$; Fig. 1).

Discussion

Intermittent hemodialysis in critically ill patients may be associated with hemodynamic and respiratory instability. The hemodynamic instability might compromise systemic oxygen delivery and even more regional oxygen delivery to the gastrointestinal tract [1]. It has been hypothesized that this ischemic distress leads to intracellular CO_2 accumulation and intramucosal acidosis, which might further deteriorate the condition of the critically ill [7]. We therefore studied the effect of conventional hemodialysis on hemodynamic variables, systemic oxygen transport, and regional oxygen transport to the splanchnic region in critically ill patients with multiple organ dysfunction syndrome and acute renal failure. In all patients intermittent hemodialysis was chosen because of acute renal failure due to acute tubular necrosis [8]. All patients were sedated and mechanically ventilated. Hemodynamic stability was provided by inotropic support with exogenous catecholamines.

Regional oxygen transport was evaluated by means of a gastric tonometer. This tonometer was developed by Fiddian-Green [4, 5] to measure intestinal pH. In postoperative patients intestinal pH measured with the tonometer device is correlated well with the intramucosal acid-base status [4, 5]. In patients with renal failure, especially during hemodialysis, intestinal pH measured with the tonometer is not a good indicator of intestinal acidosis [1]. Indeed, the two variables of the Henderson-Hesselbach equation, bicarbonate concentration and the steady-state PCO_2, are affected by the presence of renal failure and by the hemodialysis procedure. In critically ill patients decreased bicarbonate concentrations are due to an excess of proton production secondary to lactate production as a result of anaerobic glycosis. In critically ill patients with acute renal failure the acidosis is also the result of decreased acid excretion by the kidney [2]. Moreover, during intermittent hemodialysis bicarbonate is administered to the patient, and this may result in falsely elevated values of the intestinal pH as measured with the tonometer device.

Arterial carbon dioxide tension is also altered during intermittent hemodialysis, and most authors report a decrease. Altered $PaCO_2$ in turn influences steady-state mucosal CO_2 tension. Therefore to avoid the effect of $PaCO_2$ on mucosal steady-state PCO_2 we used arterial-tonometer CO_2 gap to evaluate intestinal intramucosal acidosis. This parameter is independent of the arterial bicarbonate concentration [1]. PaO_2 and SaO_2 measured during (at 90 min and at 180 min) and after dialysis did not change; changes between the measurements, however, cannot be excluded. During intermittent hemodialysis hemodynamical instability with arterial hypotension was observed in many patients. To maintain arterial blood pressure inotropic support was increased. This allowed the maintenance of cardiac index and calculated systemic oxygen delivery. Other authors have reported a significant decrease in cardiac index in critically ill patients during hemodialysis using a bicarbonate bath [8, 9].

The dialysate seems to play a very important role in the hemodynamic alterations reported during intermittent hemodialysis. Acetate hemodialysis has been described to provoke more myocardial depression and hemodynamic instability than bicarbonate hemodialysis [10, 11]. On the other hand, with bicarbonate baths, increased ionized calcium has been shown to improve left ventricular contractility [12].

Oxygen consumption increased during and immediately after the end of the intermittent hemodialysis. This observation has also been reported by Bouffard et al. [13]. These authors measured oxygen consumption by calorimetry during and 2 h after hemodialysis in patients without inotropic support, indicating that the increase in oxygen consumption occurs independently of the increase in inotropic support. Therefore our observations suggest that the increase in oxygen consumption during intermittent hemodialysis might be related to the procedure itself. This suggestion needs to be confirmed by further studies including a control group without catecholamines and/or extending the observation period before and after the hemodialysis procedure.

Mucosal steady-state carbon dioxide tension and arterial-tonometer CO_2 gap increased significantly during hemodialysis. This increase persisted after hemodialysis.

This observation may indicate that during intermittent hemodialysis intestinal intramucosal acidosis develops, and that this acidosis persists for some time after intermittent hemodialysis has been stopped. Because of the limited observation period after hemodialysis in our study it is not possible to document the exact duration of the intestinal intramucosal acidosis. The intramucosal acidosis may be related to the increased need for exogenous catecholamines, as administration of inotropic agents (e.g., dobutamine) may have deleterious effects upon splanchnic blood flow. It may also be a bioincompatibility phenomenon. Indeed, bioincompatible cellulose membranes have been shown to be at risk for cardiopulmonary complications. In our study both cellulose acetate and hemophan membranes, which have different biocompatibility, were used. The differences of numbers (nine cellulose membranes versus two hemophan membranes) are, however, too small to make any meaningful conclusion with regard to the membranes used.

Transient hypoxia has been reported associated with pulmonary vessel leukostasis and interstitial edema [14] and a release of interleukines from human monocytes during hemodialysis [15, 16]. Interleukines play a major role in the onset of the systemic inflammatory response syndrome and the infusion of interleukines in an animal model induced hemodynamic alterations similar to those observed in sepsis [17]. These alterations may play an important role in the genesis of intestinal ischemia and the subsequent development of intramucosal acidosis. They may also contribute to the observed increase in oxygen consumption. In this regard, Schiffl et al. [18] reported also a greater morbidity and mortality in critically ill patients who were dialyzed using a nonbiocompatible membrane.

An alternative for the intermittent hemodialysis is continuous renal replacement therapy. Ultrafiltration with this technique is thought to be less aggressive and hemodynamically better tolerated than in the intermittent mode. Therefore the continuous mode seems to be preferable [19]. This should be evaluated by further studies.

It can be concluded that intermittent hemodialysis in critically ill patients with multiple organ dysfunction syndrome and acute renal failure increases oxygen consumption. This is associated with intestinal intramucosal acidosis, which is not corrected by increasing doses of inotropic agents.

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