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Solute mass balance during isovolaemic high volume haemofiltration

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Abstract *Objective:* To evaluate the effect of changing the amount of pre-dilution replacement fluid on the sieving coefficient (SC) and mass transfer of small solutes during isovolaemic high-volume haemofiltration (HVHF). *Design and setting:* Prospective interventional study in the intensive care unit of a tertiary university hospital. *Patients:* Eight patients with septic shock.

Interventions: Isovolaemic HVHF (6 l/h of replacement fluid) was performed. The proportion of replacement fluid delivered in pre-filter was altered to progressively decrease it from 6 to 0 l/h. Samples were simultaneously taken from the “pre-filter”, “post-filter” and ultrafiltrate (UF) sampling ports. *Measurements and results:* Sodium, potassium, chloride, total calcium, total magnesium, phosphate, total CO₂, urea, creatinine and glucose concentrations were measured in each sample. The sieving coefficients of chloride, total CO₂, phosphate, urea and glucose were higher

than 1 in most pre-dilution states. The sieving coefficients of sodium, potassium, calcium, magnesium, total CO₂ and urea decreased significantly with decreasing pre-dilution fluid rate. The sieving coefficients of chloride and glucose increased with decreasing pre-dilution fluid rate. There was a significant mass gain of sodium and glucose under all pre-dilution conditions. Mass chloride gains decreased with decreasing pre-dilution rates and changed into chloride loss during 6 l/h of post-dilution. Decreasing pre-dilution improved urea and creatinine mass removal. *Conclusions:* Small solute SC and mass transfer during isovolaemic HVHF are significantly affected by the proportion of replacement fluid administered pre-filter. Isovolaemic HVHF is neither isonatraemic nor isochloraemic.

Keywords Haemofiltration · Septic shock · Acute renal failure · Electrolyte · Sieving coefficient

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Introduction

The nomenclature workgroup of the Acute Dialysis Quality Initiative defined high-volume continuous venovenous haemofiltration (HVHF) as an ultrafiltration rate higher than 35 ml/kg per hour [1]. With such aggressive fluid exchange, inflammatory mediators such as cytokines can be removed from the circulation. Some investigators have recently applied this new technique to the treatment of critically ill patients. They have found that

HVHF can improve haemodynamics [2] and clinical outcomes [3, 4] in patients with septic shock and/or acute renal failure.

However, because of such aggressive fluid exchange rates (up to 100–150 ml/min of plasma water is lost and replaced with commercially available replacement fluids), there are some potential problems with HVHF. These problems might include hypothermia, the loss of useful substances such as vitamins and amino acids, difficulties in correct drug dosing and electrolyte abnormal-

Table 1 Patient's demographic characteristics (*APACHE II* Acute Physiology and Chronic Health Evaluation II score, *SAPS II* Simplified Acute Physiology Score II)

Patient no.	Age (years)	Gender	Diagnosis	APACHE II	SAPS II	Outcome
1	66	F	Aspiration pneumonia	44	89	Died
2	74	M	Nosocomial pneumonia	26	59	Died
3	67	F	Perforated bowel	20	48	Died
4	69	M	Nosocomial pneumonia	27	50	Died
5	41	M	Nosocomial pneumonia	28	55	Survived
6	67	M	Caecal abscess	15	27	Survived
7	64	M	Empyema	21	35	Died
8	58	F	Perforated ileum	25	42	Survived
Mean±	63.3±10.1	—	—	25.8±8.5	50.6±18.7	—

ities. Even when no ultrafiltrate (UF) is removed in excess of replacement fluid (so-called isovolaemic HVHF), significant amounts of solutes can be gained or lost. Furthermore, small solute clearance during HVHF is likely to be significantly affected by the proportion of replacement fluid administered pre-filter because replacement fluid infused pre-filter changes serum concentrations of such small solutes. Such small solute removal can be assessed in terms of sieving coefficient (the ratio between the UF and intra-filter plasma concentration for a given solute) which, multiplied by the UF rate, allows direct calculation of solute clearance and in terms of mass transfer (the difference between the mass administered and removed for a given solute over a unit of time during renal replacement therapy).

Accordingly, we prospectively evaluated the sieving coefficient (SC) and mass transfer of small solutes during isovolaemic HVHF, while systematically altering the proportion of replacement fluid delivered in the pre-filter position.

Materials and methods

Institutional approval was granted by the hospital Ethics Committee. Informed consent was obtained from each patient's next of kin. This study was conducted as a component of a cross-over trial of isovolaemic HVHF in human septic shock [2]. In summary, patients were included in this study if they had established acute renal failure (requiring renal replacement therapy) and fulfilled Bone's [5] criteria for septic shock: tachypnoea (respiratory rate >20 breaths/min; if mechanically ventilated, >10 l/min), tachycardia (heart rate >90 beats/min), and hyperthermia or hypothermia (core or rectal temperature >38.3°C or <35.6°C). Patients were excluded if they had end-stage renal failure, acquired immunodeficiency syndrome, a life expectancy less than 6 months, or if withdrawal of therapy was a possibility. Eight patients were studied; their demographic characteristics are summarized in Table 1. Solute concentrations in patient serum and replacement fluid are presented in Table 2. Patients were randomized to receive an 8-h session of either isovolaemic continuous veno-venous haemofiltration (CVVH) or of isovolaemic HVHF. The order in which CVVH or HVHF was applied was random (sealed opaque envelopes). The first session was followed by an overnight wash out period. On the second day 8 h of the alternative therapy was applied (cross-over design). The current study was conducted during the HVHF period.

Table 2 Base line serum solute concentrations, mean±

	Patients	Replacement fluid
Sodium (mmol/l)	139.8±3.2	140
Potassium (mmol/l)	4.2±0.5	3.5
Total calcium (mmol/l)	2.23±0.18	1.6
Total magnesium (mmol/l)	0.97±0.13	0.8
Chloride (mmol/l)	94.4±3.1	100
Total CO ₂ (mmol/l)	21.7±3.8	0
Phosphate (mmol/l)	1.34±0.43	1.45
Urea (mmol/l)	13.1±5.6	0
Creatinine (µmol/l)	132.5±41.5	0
Glucose (mmol/l)	7.6±2.5	10.8

HVHF technique

Vascular access was obtained with 13.5-FG dual lumen catheters (Niagara, Bard, Ontario, Canada). A BM 11/14 machine (Edwards Lifescience, Sydney, Australia) was used for HVHF together with a 1.6 m² AN69 filter (Filtral 16, Hospal, Lyon, France). Blood flow was set at 300 ml/min and total replacement flow at 6 l/h (100 ml/min). Lactate-buffered replacement fluid (Haemofiltration Replacement Fluid, Baxter Healthcare, Sydney, Australia) was used. Additional potassium and phosphate ions were added to replacement fluid (KH₂PO₄, David Bull Laboratories, Sydney, Australia). Heparin sodium (David Bull Laboratories, Melbourne, Australia) was administered pre-filter at a rate of 1000 IU/h, while protamine sulfate (Fisons Pharmaceuticals, Sydney, Australia) was administered post-filter at a rate of 10 mg/h (regional anticoagulation). The circuit set-up is shown in Fig. 1.

Study protocol and measurements

With the assistance of an additional volumetric pump (Gemini PC-2, IMED Corporation, San Diego, Calif., USA), replacement fluid was infused both pre-filter and post filter simultaneously. Initially, all replacement fluid was infused pre-filter (6 l/h pre-dilution). Samples were taken from the pre-filter sampling port, post-filter sampling port and ultrafiltrate sampling port 5–10 min after commencing haemofiltration. Sampling was then repeated at 5 l/h pre-dilution with 1 l/h post-dilution, 4 l/h pre-dilution with 2 l/h post-dilution, 2 l/h pre-dilution with 4 l/h post-dilution, 1 l/h pre-dilution with 5 l/h post-dilution and no pre-dilution with 6 l/h post-dilution. At each time the sampling occurred after 5–10 min of steady-state of operation. Samples were drawn into plain tubes and sodium, potassium, chloride, total calcium, total magnesium, phosphate, urea, creatinine, total CO₂, and glucose concentrations

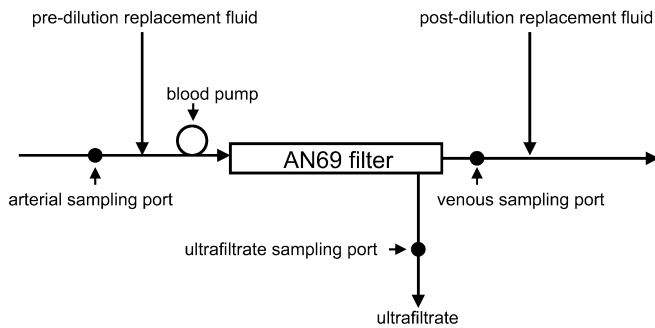


Fig. 1 Circuit set-up for high-volume haemofiltration

were measured (Hitachi 747 Analyser, Hitachi). Haematocrit and albumin concentrations were also measured on the morning of the study prior to HVHF (Hitachi 747 Analyser or Sysmex SE 9000 Analyser, Roche).

Calculations

Pre-dilution fluid in the BM11/14 machine is infused pre-blood pump. Therefore plasma flow (Q_p , ml/min) can be calculated as:

$$Q_p = (Q_b - Q_{pre}) \times (1 - Ht / 100)$$

Where Q_b is blood pump flow (300 ml/min), Q_{pre} is pre-dilution fluid rate (0–100 ml/min), and Ht is haematocrit in the venous blood (%). The pre-filter solute concentration (C_{pre} , mmol/l) is calculated as:

$$C_{pre} = (C_a \times Q_p + C_r \times Q_{pre}) / (Q_p / Q_{pre})$$

Where C_a is solute concentration in the blood from the pre-filter ("arterial") sampling port (mmol/l), and C_r is that in the replacement fluid. Pre- and post-filter albumin concentration (A_{pre} and A_{post} , g/l) were calculated as:

$$A_{pre} = A \times Q_p / (Q_p + Q_{pre})$$

$$A_{post} = A \times Q_p / (Q_p + Q_{pre} - Q_{uf})$$

Where A is the venous albumin concentration (g/l) and Q_{uf} is the ultrafiltrate rate (100 ml/min). The SC of a solute was calculated as:

$$SC = 2 \times C_{uf} / \{ C_{pre} / [1 - 0.00107 \times A_{pre} / 0.6] + [C_{post} / 1 - 0.00107 \times A_{post} / 0.6] \}$$

Where C_{uf} is solute concentration in ultrafiltrate (mmol/l) and C_{post} is post-filter solute concentration (mmol/l). The term "0.00107" is the constant to convert total plasma concentration to plasma water concentration [6]. Because we did not measure total protein concentration, this value was estimated (albumin divided by 0.6) [7]. Mass transfer (M_t , mmol/day) was calculated as:

$$M_t = (C_r \times Q_r - C_{uf} \times Q_{uf}) \times 60 \times 24 / 1000$$

Where C_r is solute concentration in the replacement fluid (mmol/l), Q_r is total replacement fluid rate (pre-dilution and post-dilution), and Q_{uf} is ultrafiltrate rate. Because of isovolaemic fashion both Q_r and Q_{uf} were 100 ml/min. The 60 refers to minutes, 24 to hours, and 1000 is correction factor for concentration in liters. A positive value of M_t suggests that a solute excess is infused into the patient.

Statistical analysis

A commercially available statistical package was used for data analysis (Staview, Abacus, Berkeley, Calif., USA). Data are pre-

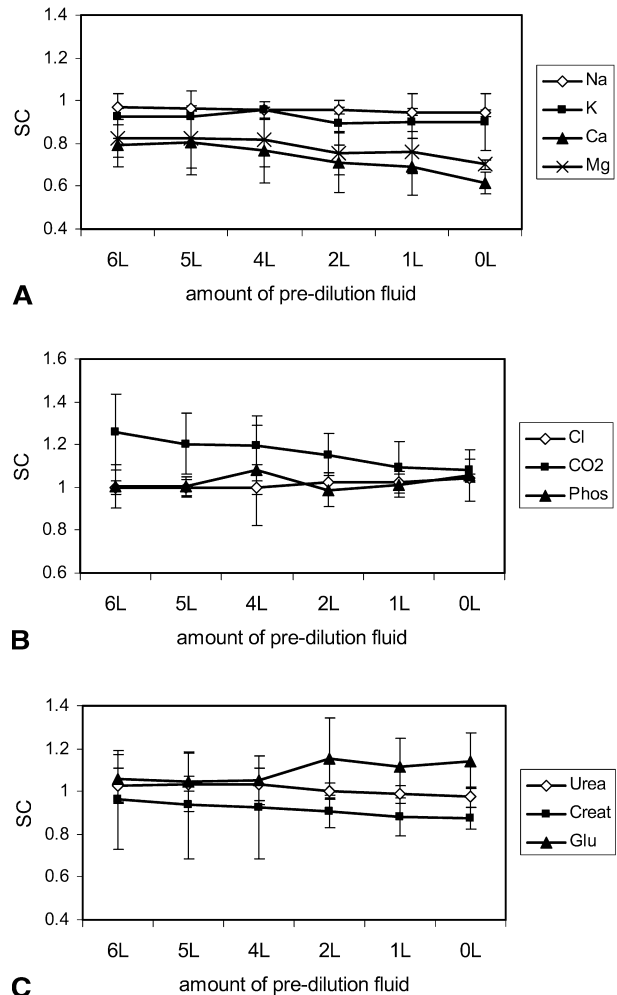


Fig. 2 A Means and standard deviations of sieving coefficients (SC) in sodium (Friedman's test, $p=0.0004$), potassium ($p=0.02$), total calcium ($p<0.0001$) and total magnesium ($p<0.0001$). B Means and standard deviations of SC in chloride ($p=0.001$), total CO₂ ($p=0.02$) and phosphate ($p=0.72$). C Means and standard deviations of SC in urea ($p=0.033$), creatinine ($p=0.47$) and glucose ($p=0.0015$)

sented as means \pm standard deviation. The changes in SC and mass transfer with different proportion of pre-dilution were compared using non-parametric analysis of variance (Friedman's Test). A p value less than 0.05 was considered significant.

Results

The SCs of cations, anions and other solutes, were calculated at variable pre-dilution fluid rates (Fig. 2). These calculations showed that the SCs of chloride, total CO₂, phosphate, urea and glucose were higher than 1 in most pre-dilution states. The SCs of sodium, potassium, calcium, magnesium, total CO₂ and urea decreased significantly with decreasing pre-dilution fluid rate (sodium: $p=0.0004$, potassium: $p=0.02$, calcium: $p<0.0001$, magne-

Table 3 Mass transfer of electrolytes, urea, creatinine and glucose with different amounts of pre-dilution, mean±SD (mmol/l per day)

	6 l	5 l	4 l	2 l	1 l	0 l	<i>p</i> ^a
Sodium	97.2±375.3	188.7±409.9	188.7±378.8	133.8±440.9	225.3±435.3	243.6±435.7	0.031
Potassium	-30.6±42.5	-36±54.4	-61.2±39.1	-32.4±53.7	-45±54.7	-50.4±56.6	0.058
Total calcium	-16.4±32	-15.3±32.6	-13.9±33.3	-12.1±35.6	-10.1±37	8.8±23.6	0.001
Total magnesium	1.6±19.3	2.7±19.7	2±20.4	1.6±21.5	-0.9±26	6.8±13.5	0.23
Chloride	577.5±438.8	540.9±402.4	486±358.6	174.9±500.7	156.6±540.7	-209.4±467.9	<0.0001
Total CO ₂	-2448±32	-2592±32.6	-2797.7±33.3	-3126.9±35.6	-3250.3±37	-3558.9±23.6	<0.0001
Phosphate	3.4±45.1	8.1±36.8	-2.7±59.5	20.3±57.8	16.4±58.3	5.9±67.1	0.70
Urea	-1376.2±45.1	-1446.2±36.8	-1524.3±59.5	-1968.7±57.8	-2018.1±58.3	-2046.9±67.1	0.0001
Creatinine	-12.2±220.7	-12.5±220.5	-13.3±200.8	-17±199.1	-17.6±220.1	-17.6±169.3	0.0003
Glucose	135.8±220.7	148.1±220.5	160.5±200.8	211.9±199.1	195.4±220.1	181±169.3	0.27

^aFriedman's test among different pre-dilution rates

sium: $p < 0.0001$, total CO₂: $p = 0.02$, urea: $p = 0.033$). On the other hand, the SCs of chloride and glucose increased with decreasing pre-dilution fluid rate (chloride: $p = 0.001$, glucose: $p = 0.0015$).

Mass transfer calculations showed significant mass gains or losses of some small solutes despite isovolaemic therapy. The mass transfer values for electrolytes and glucose are shown in Table 3. They demonstrate a significant gain of sodium and glucose under all pre-dilution conditions. Mass chloride gains decreased with decreasing pre-dilution rates and changed into chloride loss during 6 l/h of post-dilution ($p < 0.0001$). Decreasing pre-dilution improved urea and creatinine mass removal (urea: $p < 0.0001$, creatinine: $p = 0.0003$). However, it also increased total CO₂ loss ($p < 0.0001$).

Discussion

This investigation of the effect of changing the proportion of replacement fluid administered pre-filter on SC and mass transfer for small solutes during HVHF revealed several important findings.

First, the SC of sodium, potassium, calcium, magnesium, total CO₂ and urea decreased as the proportion of replacement fluid administered pre-filter decreased. This phenomenon has several possible explanations. One may be related to the effect of the phenomenon called "concentration polarization" [8] on SC. With increasing blood viscosity the thickness of the protein layer at the blood-membrane interface can be expected to increase. This increase should reduce effective membrane permeability and thereby SC. For cations, such as sodium, potassium, calcium and magnesium, decreased SC might also be explained by changes in the Gibbs-Donnan effect. Pre-dilution replacement fluid in fact should decrease the concentration of negatively charged proteins in blood thus decreasing their capacity to electrically hinder cation convection. This Gibbs-Donnan effect might also explain the increase in the SC of chloride with decreasing pre-dilution.

Mass transfer for sodium and calcium increased, that of potassium and chloride decreased, and that of magne-

sium, phosphate and glucose did not change with decreasing pre-dilution. The combined effect of pre-filter concentration and SC determines the mass transfer of a given solute. For example, because replacement fluid contains electrolytes and glucose, pre-filter fluid administration changes the pre-filter concentration of these molecules. Such changes, in addition to changes in SC, make the prediction of the final mass transfer balance difficult. Clinicians need to be aware of how changing the site of administration of the replacement fluid can powerfully affect solute mass balance even during isovolaemic therapy.

Sodium and potassium

During isovolaemic HVHF patients gained a significant amount of sodium. For example, 243 mmol sodium (equivalent to 14 g salt and to 1.6 l of normal saline) would be gained if HVHF were conducted for 24 h in pure post-dilution mode. This is despite a mean serum concentration of sodium (139.8 mmol/l), which was almost identical to the replacement fluid concentration (140 mmol/l). This gain occurs because the SC of sodium is less than 1, and because of the high volume of replacement fluid infused. The clinical effects of such positive sodium balance may be important (organ oedema).

Although the mean serum potassium concentration was in the normal range, more than 30 mmol/day potassium could be removed during HVHF. Replacement fluid often contains a low concentration of potassium to facilitate the treatment of hyperkalaemia. We added potassium to the replacement fluid to increase the potassium concentration from 1 to 3.5 mmol/l. If such additional potassium were not given, HVHF would of course cause severe hypokalaemia.

Calcium and magnesium

We found that calcium and magnesium had low SCs (from 0.6 to 0.8), and that these SCs decreased with de-

creasing pre-dilution more significantly than for other solutes. This can be explained by the measurement of total instead of ionized serum calcium and magnesium concentration. Protein-bound calcium and magnesium cannot move across the membrane. Pre-dilution replacement fluid dilutes serum protein concentration and should increase free calcium and magnesium concentration, facilitating their movement across the membrane. An important finding is that more than 10 mmol/day of calcium can be removed from a patient during isovolaemic HVHF, even though the replacement fluid contains 1.6 mmol/l of calcium. In support of our observation, Tan et al. [9] reported that hypocalcaemia was common during conventional continuous veno-venous haemodiafiltration (1 l/h dialysate and 700 ml/h replacement). HVHF might contribute to hypocalcaemia if used for more than 24 h.

Chloride and total CO₂

The SCs of chloride and total CO₂ were greater than 1 in this study, a finding consistent with previous investigations [10, 11]. This phenomenon is possibly due to a Gibbs-Donnan effect. An interesting finding is that despite a lower mean serum chloride concentration in our patients (94.4 mmol/l) than in the replacement fluid (100 mmol/l), more than 200 mmol/day of chloride could be removed from a patient during HVHF with pure post-dilution. Such chloride loss would likely increase the patient's strong ion difference and attenuate any metabolic acidosis [12], which is often seen in acute renal failure patients.

Phosphate

Tan et al. [13] reported that hypophosphataemia was common during continuous veno-venous haemodiafiltration. We added phosphate to the replacement fluid to prevent such hypophosphataemia. More than 200 mmol/day of phosphate would have been added to replacement fluid for HVHF. This would lead to a phosphate mass gain of only approximately 10 mmol/day. These observations suggest that serum phosphate concentration should be closely monitored during isovolaemic HVHF, and that phosphate administration is mandatory if one wishes to avoid severe hypophosphataemia and its consequences on organ function [14].

Urea and creatinine

The SC of urea was slightly greater than 1 with high pre-dilution fluid rates (from 6 to 4 l). This phenomenon can be explained by urea movement out of the erythrocyte in

response to a dilution gradient. Cheung et al. [15] measured urea mass in plasma before and after replacement fluid infusion during pre-dilution haemofiltration. They found that there was approximately a 10% increase in urea mass in plasma after dilution. In our study, with 6 l/h of pre-dilution, plasma would have been diluted by almost 40%. Although we did not measure urea concentration after replacement fluid infusion, there could have been significant urea mass movement across the erythrocyte membrane, which would have then increased the urea concentration in plasma and thereby increased the calculated SC.

Glucose

The SC of glucose was always greater than 1. The cause of this phenomenon is unclear but the slight negative electric charge of glucose might have played a role. Mass transfer calculations showed that approximately 200 mmol/day glucose would have been infused into each patient, equal to 602 kJ energy intake. The average glucose concentration in our population was 7.5 mmol/l. If intensive insulin therapy were applied to keep blood glucose concentrations between 4.4 and 6.1 mmol/l [16], approximately 1000 kJ/day of additional energy would be administered during isovolaemic HVHF. This gain should be taken into account for the calculation of a correct caloric balance.

This study has some limitations. First, only eight patients were studied. Some of the findings could have been influenced by individual variation, as mass transfer is dependent on the serum concentration of each solute in each patient. Nonetheless, the concentrations of solute were not markedly abnormal and were representative of the likely values in a similar larger population of patients with septic shock and acute renal failure. Second, we conducted measurements soon after HVHF was started and not after several hours of application. "Protein fouling" of the membrane due to high transmembrane pressures over time might significantly reduce the SC of solutes and their mass transfer. However, the effect of such "fouling" on small solute movement should be relatively small.

In summary, we evaluated the effect of changing the proportion of replacement fluid delivered in the pre-filter position on the SC and mass transfer of small molecules during HVHF. Beyond the expected and often desirable losses of urea, creatinine and potassium, isovolaemic HVHF can cause significant gains of sodium and glucose and significant losses of calcium, phosphate and chloride. The proportion of replacement fluid administered pre-filter has a marked effect on overall solute balance and mass removal. Isovolaemic HVHF is in fact neither isonatraemic nor isochloroemic. Physicians who apply HVHF to critically ill patients should be aware of these previously unreported effects.

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