Dialysis, Ultrafiltration, and Blood Pressure

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Summary

The effect of ultrafiltration on blood pressure was compared in six patients with problems of overhydration during single-pass dialysis, ultrafiltration only (the fluid bypassing the dialyser) and recirculation dialysis (using the RP 6 dialyser and the 75 l Rodal system). Adequate ultrafiltration during single-pass dialysis was hampered by symptomatic hypotension. However, during recirculation dialysis as well as during ultrafiltration without dialysis much more rapid ultrafiltration was tolerated without a fall in blood pressure. A considerable fall in plasma osmolality occurred with single-pass dialysis, whereas only a small decrease occurred with recirculation dialysis and no change with ultrafiltration only. We conclude that a rapid fall in plasma osmolality interferes with blood pressure regulation and that ultrafiltration is far better tolerated provided that osmotic shifts are avoided or minimised.

Introduction

In 1947, Alwall described the first artificial kidney in which the principle of ultrafiltration was applied for removal of water and sodium (extracellular fluid) from overhydrated patients. This made it possible to relieve the uraemic patient from congestive heart failure and to control arterial blood pressure. Ultrafiltration is generally applied continuously or intermittently, while the dialysis procedure (diffusion of substances across the dialysis membrane) is going on.

During the last few years, short-time dialysis (3–4 hr 3 times a week or every other day) has proved to be successful in the treatment of patients with chronic
uraemia (Cambi et al., 1974). However, a limiting factor in reducing dialysis time is the inability to comfortably remove excess water and sodium in a very short time. One reason for this is that rapid ultrafiltration during dialysis often leads to arterial hypotension assumed to be caused by hypovolaemia.

Earlier observations in single patients at our dialysis unit suggested that rapid ultrafiltration could be much better tolerated when performed without simultaneous dialysis than when dialysis was going on. This was seen for the first time in a woman who easily reacted with arterial hypotension when ultrafiltered during dialysis, but who could stand rapid ultrafiltration without any fall in blood pressure when the dialysis fluid (by mistake) bypassed the dialyser. More recent observations with the RP 6 dialyser and a recirculating system with 75 l of dialysis fluid (Rodial) indicated that patients dialysed with this system could be more efficiently ultrafiltrated without discomfort and arterial hypotension than when treated with conventional single-pass dialysis (Man et al., 1973; own observations).

These observations suggested that solute shifts brought about by diffusion across the dialysis membrane facilitate the development of arterial hypotension in patients rendered hypovolaemic by ultrafiltration.

The aim of the present study was to further elucidate the role of diffusion and ultrafiltration in the development of hypotension during dialysis treatment.

MATERIAL AND METHODS

Six patients with chronic uraemia treated with regular haemodialysis (3 x 4 hr/week) were studied. None of the patients was bilaterally nephrectomised. All the patients had great difficulties in keeping to the sodium and water restrictions and gained weight considerably during the interdialytic period.

Rapid ultrafiltration often resulted in episodes of hypotension, nausea, and vomiting, which required tilting of the patient head-down and intravenous supply of saline or albumin solution.

Each patient was studied three times with an interval of one or two weeks between the studies.

Experiment I

Single-pass dialysis was performed for 3 hr using the Nycotron ADPAC MK II-562 proportioning system and, in 5 cases, a Gambro Major dialyser, surface area 1.5 m², membrane thickness 13.5 µm, in one case a Cordis Dow 5 dialyser, surface area 2.25 m².

Ultrafiltration was kept as high as could be tolerated in order to dehydrate the patient as much as possible. The sodium concentration in the dialysis fluid was 139 mmol/l (SD ± 3.0 mmol/l), the potassium concentration 1.25 mmol/l, and the acetate concentration 40 mmol/l. The fluid contained no glucose.
Experiment II

Ultrafiltration only. The experiment was performed exactly as in experiment I, except that the fluid bypassed the dialyser through the shunt tubing in the proportioning system, negative pressure still acting on the membranes of the dialyser. Thus, diffusion of solutes across the dialysis membranes was minimised.

Experiment III

Dialysis was performed for 3 hr with the RP 6 dialyser, effective area 1.03 m² with ultrapermeable polyacrylonitrile membranes and the Rodial 75 1 recirculating dialysis fluid system. At the start of dialysis the sodium concentration in the dialysis fluid was 136 mmol/l (SD ± 3.4 mmol/l), the potassium concentration 1.25 mmol/l, and the acetate concentration 40 mmol/l. No glucose was added to the fluid. The blood flow was about 200 ml/min in all experiments.

During experiments II and III ultrafiltration was kept as high as, or higher, than in experiment I.

Blood pressure, pulse rate, and weight loss were recorded every 15 min. Heparinised blood samples were taken from the arterial blood line for determination of plasma osmolality, and plasma sodium, potassium, urea, and total protein concentration before the start and after 1, 2, and 3 hr.

Blood pressure was measured with a sphygmomanometer, changes in body weight were recorded with a DATEX VM 104 metabolic balance scale, osmolality was measured with a Knauer osmometer, sodium and potassium by flame photometry, urea by the method of Chaney and Marbach (1962), and total protein by a Biuret method.

Statistical significances were evaluated by the paired t-test.

RESULTS

I. ‘Conventional’ Dialysis with Maximum Ultrafiltration (Figure 1:1)

A considerable fall in blood pressure occurred in all patients after 90–150 min of dialysis. During the episode of hypotension all patients developed nausea, one patient vomited, and another patient had an attack of angina pectoris. The lowest systolic and diastolic blood pressure recorded were ≤ 90 mmHg and ≤ 60 mmHg respectively in all patients. In 3 patients the diastolic pressure was too low to be measurable, when the fall in blood pressure was at its maximum. The pulse rate increased by a maximum of 15.8 ± 4.5 beats/min (mean ± SE). To restore blood pressure the negative pressure had to be reduced and albumin and/or sodium chloride solution (in total 150–300 ml) had to be given intravenously to all patients.

A weight loss of 1.92 ± 0.28 kg and a decrease in plasma volume (calculated from the change in total plasma protein concentration) of 5.4 ± 2.7% were observed. The plasma osmolality fell by 24.2 ± 2.4 mOsm/kg water, the plasma
Figure 1. Pulse rate, blood pressure, changes in body weight and plasma volume, plasma osmolality and urea concentration during I. single-pass dialysis. II. ultrafiltration only; and III. recirculation dialysis. During I, ultrafiltration was kept as high as could be tolerated, during II and III ultrafiltration was as high as or higher than during I. † = mean value ± SE
urea concentration by 12.5 ± 2.0 mmol/l, the plasma sodium concentration by
2.2 ± 0.48 mmol/l, and the plasma potassium concentration by 2.1 ± 0.5 mmol/l.
All these changes were significant (p < 0.01).

II. Ultrafiltration Only (Figure 1:II)

The blood pressure and pulse rate were essentially unchanged during the whole
procedure, except for a small, insignificant, fall in systolic blood pressure during
the first 30 min of dialysis. Two patients had an episode of vomiting each; the
other patients experienced no discomfort. None of the patients required intra-
venous fluid replacement.

The weight loss was 3.13 ± 0.37 kg and the decrease in plasma volume was
21.6 ± 5.2%. Plasma osmolality and plasma urea, sodium, and potassium concen-
trations were not significantly changed.

III. Recirculation Dialysis with RP 6 (Figure 1:III)

There was no significant reduction in blood pressure. The pulse rate increased in
4 patients by 12–48 beats/min and remained unchanged in 2 patients. The aver-
age maximum increase in pulse rate was 17.0 ± 7.1 beats/min (p < 0.01). No
symptoms of discomfort were observed and no intravenous fluid replacement
was required.

The weight loss was 2.98 ± 0.33 kg and the decrease in plasma volume was
20.1 ± 3.4%. Plasma osmolality fell by 7.3 ± 4.5 mOsm/kg (p > 0.1), plasma
urea concentration by 10.6 ± 0.7 mmol/l, and plasma potassium concentration
by 1.2 ± 0.2 (p < 0.01). The plasma sodium concentration increased by 2.5 ± 1.65 mmol/l (p > 0.1). The decrease in plasma osmolality was significantly higher
(p < 0.01) during single-pass dialysis (I) than during recirculation dialysis (III).

The patients felt much better and were much less fatigued immediately after
experiments II and III than after experiment I.

DISCUSSION

In all patients in the present study efficient ultrafiltration during single-pass
dialysis was hampered by symptomatic hypotension, which necessitated fluid
replacement to counteract the blood pressure reduction. On the other hand,
when the patients were subjected to ultrafiltration only, without any dialysis
fluid flowing through the dialyser, a far greater reduction in total water and
plasma volume could be tolerated without any change in blood pressure and
pulse rate. This indicates that the hypovolaemia was fully compensated for by
adaptive vasoconstriction.

In the ultrafiltration experiments no change in plasma solute concentrations
or osmolality were observed. In single-pass dialysis, on the other hand, there was
a rapid fall in plasma osmolality and urea concentration. This rapid solute shift seems to interfere with the ability of vasomotor adaptation to hypovolaemia.

When using the RP 6 dialyser and the recirculating dialysate system, the decrease in osmolality during dialysis was much smaller than with single-pass dialysis. The reason for this is probably that a rapid build-up of dialysable solutes (mainly urea) occurs in the small volume of recirculating dialysis fluid, tending to minimise the osmotic changes during dialysis. The same amount of weight loss and decrease in plasma volume was tolerated as in the ultrafiltration experiments without any blood pressure reduction, supposingly because the shift in osmolality was too small to interfere with the vasomotor adaptation to hypovolaemia. The increase in pulse rate, however, suggests that the adaptation was less complete than in the ultrafiltration experiment.

It is not apparent from the present study which osmolar shifts are of most importance to the development of hypotension. It is known that sodium is involved in blood pressure regulation. An increase in the sodium concentration of the dialysis fluid appears to facilitate efficient ultrafiltration (Stewart et al., 1972); the blood pressure response during dialysis was, however, not reported. A role of sodium is suggested in the present study by the observation that a small mean decrease in plasma sodium concentration occurred in the single-pass experiments during which the patients became hypotensive, whereas the concentration was unchanged or increased in the ultrafiltration and recirculation experiments during which the blood pressure remained stable.

A factor of possible importance for the development of hypotension might be the rapid fall in extracellular potassium concentration during dialysis. As expected, the average change in plasma potassium was greater with single-pass dialysis than with RP 6 recirculation dialysis. But with recirculation, a considerable fall in plasma potassium occurred in some of the patients (in 2 subjects by 1.7 mmol/l) without any reduction in blood pressure. More recent studies with RP 6 recirculation dialysis using a potassium-free dialysis fluid seem to rule out depletion of extracellular potassium as a factor of major importance for the development of hypotension (unpublished observations).

It should be pointed out that decreases in plasma potassium or magnesium concentrations or osmolality, alone or in combination, are vasoconstrictors in most regions of the vascular bed (Haddy & Overbeck, 1962) and that hypokalaemia and hypomagnesaemia under certain conditions may increase the arterial blood pressure (Haddy et al., 1969; Emerson et al., 1970). In dogs subjected to haemodialysis, hypokalaemia and hypomagnesaemia did not produce changes in blood pressure different from those observed under conditions of normal plasma potassium and magnesium concentrations (Hoppe & Emerson, 1974).

How the decrease in osmolality during dialysis interferes with blood pressure regulation is far from clear. None of the patients in this study was bilaterally nephrectomised; thus, interference with the renin-angiotensin system may have occurred. On the other hand, we have observed that a bilaterally nephrectomised
patient behaved similarly with regard to ultrafiltration and blood pressure as the patients in the present experiments. Several other possibilities may be considered. One would be that the blood pressure receptors in the carotid bodies or other pressure receptors are rendered less sensitive by a decrease in osmolality, possibly as a consequence of a minor osmotic disequilibrium between extra- and intra-cellular fluids. Alternatively the vasomotor centre or the efferent sympathetic pathways or receptors may be influenced by shifts in osmolality.

The findings of the present study may have important clinical implications. By introducing in the dialysis schedule a period of ultrafiltration without dialysis, it is possible to remove considerable amounts of fluid (in our experience up to 3 litres in 1 hour) whilst preserving the well-being of the patient, and a stable blood pressure. The rest of the dialysis can be performed without concomitant ultrafiltration thereby avoiding hypotension and other side-effects. We have recently started to dialyse selected patients according to these principles with considerable success.

Acknowledgments

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References

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Open Discussion

CHAIRMAN (SHALDON, Montpellier) Dr Bergström, I would like to congratulate you on the most important paper I have heard in the dialysis field in the last
decade. We had the privilege of prior communication and we took it to the point of clinical application. I would like to add a personal experience using the RP 6 to ultrafilterate alone and then to dialyse without ultrafiltration, which was based on your work. The method is illustrated in Figure 1. The ultrafiltration was achieved by clamping the dialysate inlet port and leaving the dialysate outlet port open to atmosphere. The hydrostatic pressure was kept at 400 mmHg using a screw clamp on the venous line and a venous pressure manometer. After 1 hour the RP 6 was connected to the dialysis machine, and weight loss prevented by

\[ Q_B = 300 \text{ ml/min} \quad \text{U.F.} \quad 13.3 \text{ ml/mmHg/h} \quad \& \quad 80 \text{ ml/min at 360 mmHg} \]

\[ Q_D = 500 \text{ ml/min} \]
\[ Q_B = 250 \text{ ml/min} \]
\[ \text{TMP} = 0 \]
\[ \text{UF} = 0 \]

**DIALYSIS**

Figure 1. Method of using RP 6 dialyser in open circuit for ultrafiltration followed by dialysis without ultrafiltration
Figure 2. Results in male patient, PM, of one hour of pure ultrafiltration followed by 3 hours of single pass pure dialysis.
balancing the venous pressure of 70 mmHg with positive dialysate pressure of 70 mmHg. Weight changes were measured by a continuous recorder. Over a 3 hour single-pass dialysis with a dialysate flow of 500 ml/min, weight did not vary by more than ± 50 g.

Figure 2 shows the results. The ultrafiltration rate was 70 ml/min with a total volume of 4.21 in 1 hour. Plasma sodium was 136 mmol/l, potassium 6.0 mmol/l, creatinine, 16.0 mg/100 ml and serum osmolality 320 mOsm/kg. They were all unchanged over the period of ultrafiltration and the values were identical in plasma and ultrafiltrate.

The haematocrit rose from 27 to 35% and the total protein from 7.1 to 8.1 g%. The pulse rate slowed from 82 to 64 and the blood pressure was constant at 180/110.

The patient was asymptomatic. At the end of 3 hours dialysis the serum osmolality was 304 mOsm/kg, the urea 74 mg/100 ml, the creatinine 10 mg/100 ml, the sodium was 138 and the potassium 4.4 mmol/l.

The haematocrit stayed constant at 35% and the total protein dropped to 7.9 g%. The weight loss was 4.0 kg after washing in the blood. The pulse did not change and the blood pressure rose slightly to 180/120.

The patient had no cramp, fatigue or headache at any time and felt very active at the end of the 4 hours.

I believe you have discovered a mechanism for control of the peripheral resistance independent of the renin-angiotensin system which depends on a constant serum osmolality and an intact sympathetic nervous system to protect the body during plasma volume contraction.

Then after plasma volume contraction you may induce a serum osmolality drop without symptoms. But you must vary these parameters independently.

Congratulations! I think you may have revolutionised the future of end-stage renal failure treatment.

BROD (Hanover) If the plasma volume drops by 20%, as you have shown, and if blood pressure does not change and if pulse rate does not change, what happens haemodynamically? There must either be a rise of the cardiac output, and there is no rise of pulse rate to suggest this, or there must be a fair degree of vasoconstriction or venoconstriction.

BERGSTROM We do not know yet. I would think there is vasoconstriction.

KERR (Newcastle) A fascinating paper! How do you explain the lower fall in osmolality in RP 6 recirculation dialysis? It does not appear to be explained by the changes in sodium and urea you described. Is it due to dextrose in your dialysate or have you any other explanation?

BERGSTROM In the single-pass experiments sodium decreased by 2 mmol/l and potassium by 2 mmol/l. Since these changes should occur together with anion equivalents it means together 8 mmol/l. Adding this to 13 mmol of urea gives 21 mmol/l; thus only 3 mmol are not accounted for.

In the recirculation experiments sodium increased by 2.5 mmol/l and potassium decreased by only 1 mmol/l. Together with the anions this makes a net increase of 3 mmol/l. Subtracting this from 11 mmol of urea gives 8 mmol/l. The measured change in osmolality was 7 mOsm/kg.

The reason why the mean sodium concentration increased, though insignifi-
cantly, is not clear. One explanation could be that water is more rapidly equili-
ibrated across the polyacrylonitrile membrane than solutes, resulting in a relative 
increase in sodium when the concentration of dialysable solutes increases in the 
dialysis fluid. Another explanation could be that the polyacrylonitrile membrane 
is negatively charged resulting in a polarisation phenomenon. The average changes 
are based on a relatively small number of observations and technical errors can-
not be excluded.

CHAIRMAN (SHALDON) I would like to add a remark, Dr Bergström. We are 
fairly certain there is a difference between individual patients in the tolerance 
of the change in osmolality that the patient can support at the same time as 
you are contracting the plasma volume. For instance we could not do this, 
particularly on bilaterally nephrectomised patients. If we combine ultrafiltration 
with dialysis, with Δ osmolality in some of these patients exceeding about 5, 
the mechanism protecting the blood pressure seems to be impeded. Do you 
think that what you have here is a phenomenon whereby an unknown mechan-
ism which prevents the drop in blood pressure in the presence of contraction of 
the plasma volume is impeded from working normally when you have a signifi-
cant change in osmolality?

BERGSTROM Did I get the question?

SHALDON Yes, in other words if you contract the plasma volume and create an 
osmotic disequilibrium at the same time there is going to be an individual variable 
as to how much disequilibrium you can create before the peripheral resistance 
mechanism can no longer compensate and keep the blood pressure up. But you 
can produce these two changes in the body separately as we have done, taking 
5 kilos off in one hour and then dialysing the patient for three hours without any 
change in body weight and with the blood pressure remaining stable at 180/110 
for 4 hours. There was no Δ osmolality, 14% contraction of the plasma volume, 
and then in 3 hours a Δ osmolality of 15 with no change in the plasma volume. 
The symptoms which you normally expect were completely absent at the end of 
the dialysis with the same post-dialysis urea and creatinine as he would have had 
on a conventional 4 hour dialysis.

CAMBI (Parma) At the end of the first hour with ultrafiltration only, you should 
have an increase in concentration of osmotically active solutes. Starting standard 
dialysis at this point, aren’t you afraid of a disequilibrium syndrome?

BERGSTROM I am not afraid of that because if you do all the ultrafiltration in 
the first hour, thereafter continuing with only dialysis you are not at risk if you 
are careful not to contract the plasma volume further. The risk may be that with 
the conventional systems used today you cannot abolish the transmembrane 
gradient completely.

BAHLMAN (Hanover) I would like to ask the Chairman and the previous speaker 
about the actual values of sodium concentrations used in the dialysate and there-
fore the resulting difference in osmolality between the serum and dialysate in a 
conventional dialysis. The reason for asking is that apparently similar results can 
be obtained by increasing dialysate sodium in patients previously dialysed with a 
low sodium concentration. We observed this by increasing the dialysate sodium
concentration from 138 to 145 mmol/l and neither hypotension nor cramps happened in these patients as mentioned by you as well.

BERGSTROM I can answer this question. Increase in the sodium concentration has been tried in order to avoid side effects during dialysis. It has been reported by — I think, Stewart — that you can remove fluid more easily that way; on the other hand they did not report any blood pressure values in their experiments, and they claimed that they could permanently reduce the patient’s weight on this basis. Our experience with increasing the sodium concentration was the same with regard to well-being during dialysis. However, in the long run all our patients became hypertensive and gained too much weight between dialyses. I would not advise using this as a routine.

KOPP (Munich) I would like to comment on Dr Bergström’s paper. I congratulate him and I can fully confirm his results on the basis of our own observations, without having had the privilege of prior communication. However, this experience was obtained from a different patient group — namely on acute patients with acute renal failure who were in either hypotension or even shock and had to be dialysed. Now these patients were heavily fluid overloaded, which was measurable particularly by the respiratory pressure on the ventilator. We had to ultrafilter first and we followed exactly the regime which you recommended, to ultrafilter them first, and then to continue dialysis. Now the observation which may shed some light on the proper physiology of where the fluid comes from in chronic patients is this; that during this hour of ultrafiltration, both by X-ray and by the fall in the respiratory pressure, it was apparent the fluid was removed from the lungs. The patient did not react very dramatically and in this way we were able to improve their respiratory distress, with no special problems of pulse rate or blood pressure.

BERGSTROM I can also confirm that we have used ultrafiltration only, followed by dialysis in acute renal failure when you have patients with low or unstable blood pressure. I think this may extend our possibilities for the use of haemodialysis in the very sick acute uraemic patients, who could not, for circulatory reasons, take dialysis before.

SHALDON I would just like to say you must not be obsessed with this hour; with this high flux membrane you can remove 5 kilos in one hour, or you can remove 1 kilo in 12 minutes.

DRUKKER (Amsterdam) Only one brief question to both Dr Bergström and Dr Shaldon. When you perform rapid ultrafiltration, people get muscle cramps rather frequently? Is there any difference in frequency of muscle cramps with your technique?

BERGSTROM You get no muscle cramps if you only ultrafiltrate.