ULTRAFILTRATION WITHOUT SIMULTANEOUS DIALYSIS FOR REMOVAL OF EXCESS FLUID

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Alwall [1] in 1947, described an artificial kidney, in which the principle of ultrafiltration could be applied for fluid removal. This made it possible to relieve the overhydrated uraemic patient from congestive heart failure and to control arterial blood pressure [2–5].

Ultrafiltration implies that water and solutes are pressed through a semi-permeable membrane, the driving force being a hydrostatic pressure gradient, which is achieved by applying a positive pressure on the blood side (a blood pump before the filter and a screw clip on the venous blood line), negative pressure on the dialysate side (achieved by a negative pressure pump or by gravity), or a combination of both [6]. In conventional haemodialysis, ultrafiltration is generally applied continuously or intermittently while the dialysis procedure (diffusion of substances across the dialysis membranes) is going on.

Ultrafiltration across artificial semipermeable membranes without simultaneous dialysis by applying a vacuum was used in rabbits [7] and in oedematous dogs [8]. In 1955, Alwall reported pure ultrafiltration for fluid removal in single oedematous patients [9,10]. More recently it was reported that excess fluid could be eliminated by negative pressure ultrafiltration performed either before a standard dialysis treatment or on alternative days [11]. The treatments were well tolerated without fall in blood pressure.

During the last few years, short-time dialysis (3–4 hr three times a week or every other day) has proved to be successful in the treatment of patients with chronic uraemia [12]. However, a limiting factor in reducing dialysis time is the inability to remove excess water and sodium comfortably 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 [13].

We observed earlier in single patients at our dialysis unit that rapid ultrafiltration was 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 readily 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 (Rhône-Poulenc) and a recirculating system with 75 litres of dialysis fluid (Rhodial) indicated that patients dialysed with this system could be more efficiently ultrafiltered without discomfort and arterial hypotension than when treated with conventional single-pass dialysis.

With these observations as a background, a study was performed in six dialysis patients with problems of overhydration and with vascular instability during standard dialysis. Blood pressure, pulse rate, and blood chemistries were followed during single-pass dialysis (Gambro Major 1.5 m²), ultrafiltration only, or recirculation dialysis (using the RP-6 dialyser and the 75 L Rhodial system), each treatment being performed for 3 hr [14].

Adequate ultrafiltration during single-pass dialysis was hampered by symptomatic hypotension and tachycardia with nausea and vomiting. To restore blood pressure, the negative pressure had to be reduced and albumin and/or sodium chloride had to be given i.v. The mean weight loss was 1.9 kg. However, during recirculation dialysis as well as during ultrafiltration without dialysis much more rapid ultrafiltration (3 kg in 3 hr) was tolerated without a fall in blood pressure and with essentially no symptoms, and none of the patients required i.v. fluid replacement. A considerable fall in plasma osmolality occurred with single-pass dialysis, whereas only a small decrease was found with recirculation dialysis and no change with ultrafiltration only. We concluded that a rapid fall in plasma osmolality interfered with blood pressure regulation and that ultrafiltration was far better tolerated provided that osmotic shifts were avoided or minimised. These results were recently fully confirmed [15–17].

We have successfully applied these findings to the treatment of selected uraemic patients with fluid overload who could not tolerate rapid ultrafiltration due to symptomatic hypotension. 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 L or more in 1 hr), whilst preserving the wellbeing 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.

Using a high-flux membrane dialyser (RP-6), Shaldon [18] managed to rid an overhydrated patient of 4.2 L in 1 hr by ultrafiltration only, followed by symptomless dialysis for 3 hr, with essentially no change in blood pressure during the two procedures — but with a fall in pulse rate during ultrafiltration.

Successful results with sequential ultrafiltration and dialysis or with ultrafiltration and dialysis on separate days have also been reported by other groups [11,15–17,19–23].

To be able to perform ultrafiltration without dialysis, and dialysis without ultrafiltration, a dialysate generator and control unit was modified [24,25]. During ultrafiltration no dialysate passes through the dialyser, as the inlet dialysate port is closed by a solenoid valve. Transmembrane pressure (TMP) up to 500 mmHg may be created with an effluent pump. Pure ultrafiltrate is
collected and measured. During dialysis, a positive pressure dialysate pump before the dialyser prevents ultrafiltration by eliminating the TMP due to the venous pressure, and dialysis without weight loss may be performed.

In a more recent study [24], two patients (one bi-nephrectomised) with weight gains exceeding 3 kg between dialyses and marked intolerance to ultrafiltration were studied repeatedly during ultrafiltration and dialysis, either simultaneously or sequentially using the Gambro UDM apparatus and the RP-6 dialyser. Ultrafiltration during dialysis was associated with a marked drop in blood pressure and frequent symptoms, and thus was poorly tolerated. During 1 hr of ultrafiltration (55–69 ml/min), the blood pressure rose slightly but occasionally fell in the last 5 min, and there was always a slowing of the pulse rate. When dialysis preceded ultrafiltration, the blood pressure fell and the pulse rose in the same way as during dialysis after ultrafiltration. Ultrafiltration after the dialysis period caused a further fall in blood pressure but also a slowing of the pulse, and none of the patients could tolerate the same ultrafiltration rate as obtained when ultrafiltration preceded dialysis.

It is possible that the dialysis effect may persist during ultrafiltration and that the body cannot compensate for hypovolaemia by enough vasoconstriction. It was therefore suggested that in sequential treatment, the period of ultrafiltration should precede the period of dialysis to obtain an optimum effect [24]. However, we have later found that certain patients seem to tolerate ultrafiltration equally well in the middle of a dialysis or immediately after a dialysis as before dialysis (unpublished observations). Successful application of ultrafiltration after dialysis has recently been reported [20].

To study the haemodynamic mechanisms behind the aforementioned changes in blood pressure and pulse rate during ultrafiltration and dialysis, respectively, cardiac output measured by dye dilution using indocyanine green [26] was performed repeatedly on 7 uraemic patients with two different procedures, ultrafiltration alone to ‘dry’ weight for 1 hr followed by 3 hr dialysis without fluid loss, or 3 hr dialysis without fluid loss followed by 1 hr ultrafiltration [27–29]. Blood pressure was automatically recorded with an Arteriosonde Blood Pressure Manometer (Roche), heart rate (HR) with a cardioscope, and body weight was continuously followed with a Datex Metabolic Balance. The ultrafiltrate was collected in a measuring cylinder. Total peripheral vascular resistance index (TPVRI) was calculated from mean arterial pressure (MAP) and cardiac index (CI). The mean weight loss during ultrafiltration was 1.85 kg before dialysis and 1.73 kg after dialysis; the weight change during dialysis was negligible.

The most consistent changes occurred in TPVRI and CI (Figures 1 and 2). During ultrafiltration all patients showed an increase in TPVRI and a decrease in CI, whilst during dialysis the opposite changes took place, i.e. a decrease in TPVRI and an increase in CI. The decrease in CI during ultrafiltration occurred without marked change in HR whereas the increase in CI during dialysis was associated with an increase in HR. The blood pressure was variable (Figure 3). Hypotension occurred more frequently and was more marked during dialysis than during ultrafiltration.

The results show that ultrafiltration-induced hypovolaemia with decrease in
Figure 1. Changes in total peripheral vascular resistance index (Δ TPVRI) during sequential ultrafiltration/dialysis. ● ultrafiltration for 60 min followed by dialysis for 180 min, ○ dialysis for 180 min followed by ultrafiltration for 60 min

Figure 2. Changes in cardiac index (Δ CI) during sequential ultrafiltration/dialysis. Legends, see Figure 1
cardiac output is compensated for by vasoconstriction which prevents hypotension. The renin-angiotensin system appears not to be important for this reaction, since a comparable degree of vasoconstriction and stable blood pressure during ultrafiltration were also observed in bi-nephrectomised patients [24,29]. Dialysis per se apparently has a vasodilatory effect. Whether or not hypotension will occur during dialysis, depends on the extent to which an increase in cardiac output can compensate for this vasodilation. During conventional dialysis (i.e. simultaneous ultrafiltration and dialysis) the vasodilatory effect of dialysis may presumably interfere with the vasoconstriction response to ultrafiltration, thereby facilitating hypotension. Hence the rationale of separating ultrafiltration in time from dialysis to prevent hypotension, is obvious.

Rouby et al [30] who studied cardiac output by right heart catheterisation and thermodilution observed a decrease in CI and an increase in TPVRI during ultrafiltration. When the ultrafiltration rate was excessive, episodes of symptomatic hypotension occurred, associated with a fall in pulmonary wedge pressure. During subsequent dialysis with recirculating dialysate, CI rose again and TPVRI increased. Hampel [31] also reported haemodynamic changes during ultrafiltration and dialysis, similar to those found by us.

The reason why the peripheral resistance, which increases during ultrafiltration, decreases during dialysis is far from clear. We concluded that osmolar shifts may play a role in the development of dialysis-associated hypotension [14], but the effects of other specific solute shifts cannot be ruled out. Bauer and co-workers [32] noted as early as 1928, that sodium acetate had a vaso-
dilatory effect on the hind limb of the cat. It was recently found in selected patients, that a high dialysate acetate concentration was associated with several side effects during dialysis [33,34], which could be eliminated by replacing acetate by bicarbonate [33] but appeared not to be related to changes in plasma osmolality [35]. It was therefore suggested that acetate-bicarbonate transfer might play a more important part in the dialysis-induced vascular instability during dialysis than osmotic shifts. In the studies by Graefe and co-workers [33,35], a 2.5 m² hollow fibre dialyser (Dow HK-5) was used, which facilitates a rapid shift of acetate into the patient.

To elucidate the relative role of osmolar (sodium) and acetate shifts during dialysis, an investigation was made on 6 patients with problems of overhydration [29,36]. Each patient underwent rapid ultrafiltration for 1 hr (mean weight reduction 2.0 kg), using the 1 m² RP-6 dialyser, at the beginning of 5 dialysis treatments with weekly intervals. Ultrafiltration was undertaken without dialysis (controls) and with simultaneous dialysis using acetate (40 mmol/L) or bicarbonate (25 mmol/L) in the dialysis fluid at a dialysate sodium concentration of 133 or 145 mmol/L, respectively.

The systolic blood pressure and mean arterial pressure, which were stable with ultrafiltration only and fell slightly when using a high dialysate sodium concentration, was much more reduced when the dialysate sodium concentration was kept low. These changes were apparently related to the changes in plasma osmolality. Acetate had no effect on blood pressure at the higher sodium concentration, but a slight (not significant) additive effect when used in the low-sodium dialysate, but shifts in osmolality (sodium concentration) seem to be more important than the effect of acetate. It is possible that the role of acetate becomes relatively more important when using a large surface dialyser, as the shifts of acetate and bicarbonate will be more rapid than when using a 1 m² dialyser.

One hypothesis for the development of vasodilatation during dialysis would be that the baroreceptors, cardiopulmonary receptors, or the autonomic nerves are affected by the rapid change in osmolality (or concentration of specific solutes) and that the sensitivity to solute shifts varies from patient to patient. Severe hypotension during dialysis has been related to autonomic neuropathy [37,38], which appears to affect the afferent limb of the baroreceptor reflex arc [39].

It was recently reported that plasma noradrenaline increases during ultrafiltration alone but falls or is unchanged during dialysis with or without fluid loss [23,40]. It was therefore suggested that relative depletion of circulating noradrenaline by dialysis might cause or contribute to the vascular instability during dialysis.

However, the aforementioned results by our group [29,36], demonstrating that blood pressure during simultaneous rapid ultrafiltration and dialysis is better maintained by using a high-sodium dialysate than a low-sodium dialysate, more recently confirmed by Locatelli et al [41], underline the pathophysiological role of osmotic (sodium) changes in dialysis-associated hypotension, and would tend to minimise the role of dialysis of hypertensive substances.

The role of the renin-angiotensin system is still unsettled. The haemodyna-
mic reactions described during ultrafiltration and dialysis, when separated from each other, are also observed in bi-nephrectomised patients [24,29].

Lastly there is the possibility that solute shifts during dialysis might have a direct vasodilatory effect not mediated by the autonomic nervous system. There is a striking similarity between the haemodynamic response to dialysis (vasodilatation, increase in cardiac output, and heart rate) and the action of vasodilatory antihypertensive agents, such as hydralazine. One important difference is, however, that the plasma renin activity, which is known to be stimulated by vasodilator agents, decreases during dialysis [29]. As mentioned before, acetate, is a vasodilator agent and may exert an effect directly on peripheral vascular tone [32].

Practical Considerations

It should be strongly emphasised that sequential ultrafiltration and dialysis is a method which should only be used on selected patients or in special situations. In patients with acute renal failure with severe overhydration and cardiovascular instability, sequential treatment or ultrafiltration and dialysis on alternate days may be life-saving. In chronic uraemia it should be reserved for patients who develop symptomatic hypotension when ultrafiltered during standard dialysis, or, on special occasions, even in other patients, when weight gain in the interdialytic period is excessive. Old patients with cardiovascular disease and myocardial insufficiency who are intolerant to standard dialysis seem to tolerate sequential treatment better; thus, it should be possible to widen the indications for haemodialysis in this group of patients.

During one year at one centre in Stockholm, sequential treatment was carried out in 898 out of 5,478 dialyses, i.e. 16%. Bent Nielsen from Copenhagen used sequential treatment in 7% of the treatments (personal communication).

To perform sequential ultrafiltration and dialysis no special equipment is required, provided that the negative pressure on the dialysate side is acting on the membrane, when the dialysate by-passes the dialyser (e.g. after provoking an alarm). If this is not the case, a vacuum pump may be applied on the dialysate outlet tubing while plugging the dialysate inlet. The transmembrane pressure can also be increased by applying a screw clamp on the venous blood line. This method is, however, less suitable, since it carries the risk of haemolysis with an increase in plasma potassium, especially if single-needle technique is used (unpublished communication).

Dialysis cannot be completely separated from ultrafiltration when using standard equipment due to the fact that even with the dialysate negative pressure at zero (atmospheric pressure), there is a transmembrane pressure gradient and, thus, obligatory ultrafiltration. The ultrafiltration rate is, however, low, when using a standard dialyser. When using a dialyser with a high-flux membrane and/or large surface area (e.g. Rhône-Poulenc RP-6, the Gambro Ultra-diffuser, or other high-flux devices) special equipment is required which allows more precise control of transmembrane pressure during dialysis by counterbalancing the blood pressure using positive pressure in the dialysate, e.g. as in the aforementioned UDM device (Figure 4).
Ultrafiltration in Non-dialysis Patients

Ultrafiltration without dialysis has been advocated [42] and successfully applied in non-uraemic patients with severe, diuretic-resistant fluid overload [15,43–47]. In patients with congestive heart failure and pulmonary oedema, liver cirrhosis with ascites, and diabetic nephropathy with nephrotic syndrome 2–8 kg of fluid could be removed asymptptomatically in 1.5–2.5 hr with immediate clinical improvement [43,46]. Some cases regained responsiveness to diuretics after treatment. We now use a system with percutaneous cannulation of one or both femoral veins, a blood roller pump, a single-needle monitor (if only one vein is cannulated), an ultrafilter or dialyser (we used RP-6 or Gambro Ultradiffuser), and another roller pump for creating negative pressure (Figure 4). The technique is very simple and its application in severe cases of overhydration warrants further clinical trials. An even simpler system was devised by Kramer et al [45], who by cannulating the femoral artery and vein and using a hollow fibre ultrafilter with high internal resistance (Amicon XM 50) could avoid the use of a blood pump, negative pressure pump, or venous clamp.
References


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Open Discussion

DORHOUT MEES (Utrecht) I would like to suggest that EDTA accept some common definitions for the different terms used for this subject, to end confusion in this field.*

Secondly, you treated some patients with the nephrotic syndrome. In the nephrotic syndrome blood and plasma volumes may be low so that ultrafiltration might cause unpleasant complications. Did you measure blood and plasma volume in these patients and what were their reactions?

BERGSTROM We made only relative measurements by measuring the total protein concentration in the plasma of the patient. We are aware of the risk of hypovolaemic hypotension in nephrotic patients and now give albumin to these patients during ultrafiltration which increases vascular stability and mobilises fluid from the interstitial space.

DORHOUT MEES So you did not ultrafiltrate without simultaneous infusion of plasma or albumin?

BERGSTROM We sometimes gave albumin and sometimes not.

* See Preface. Editor
DORHOUT MEES So it was possible to perform ultrafiltration without albumin infusion in these nephrotic patients?

BERGSTROM Yes, we did in some cases and we had no severe problems with them.

DORHOUT MEES I think that indeed many of these patients do not have such low blood volumes — we have measured them and found that they were often not reduced so that would be in accord with our observations.

LEGRAIN (Chairman) I must say that we fully agree with what has just been said about the danger of using the technique in patients who are hypovolaemic. They can go very quickly to cardiac arrest and we have had problems with recovery. Could you comment a little more about that?

BERGSTROM We have also had this type of episode with hypotension but it is possible by giving concentrated sodium chloride or albumin very quickly to counteract the fall in blood pressure especially if one stops the ultrafiltration temporarily. You may be able to pick up imminent hypotension as an increase in pulse rate comes before the blood pressure drops.

THAYSEN (Copenhagen) I should like to ask you Dr Bergström how many patients have you treated? I mean non-uraemic patients with cardiac failure, nephrotic syndrome or hepatic failure with oedema, and in how many cases have you found that they became sensitive to normal diuretic treatment again?

BERGSTROM We have now treated 20 patients who did not require dialysis. Some of these patients had mild renal failure but were not treated primarily as dialysis patients and many of them had practically normal function. We saw in 4 cases a clear-cut return of sensitivity to Frusemide and in one patient this lasted for seven months before we had to make the next treatment of the patient.

PRECHT (Berlin) We saw in your slide an indication for sequential ultrafiltration in acute renal failure. Most of these patients are hyperkalaemic. Do you perform ultrafiltration in these patients? Or is it dangerous?

BERGSTROM Well, if the patient is severely hyperkalaemic I think you should dialyse the patients as soon as possible or give the patient resins. There are, however, situations where an overhydrated patient is so unstable with regard to blood pressure that you cannot dialyse the patient in the conventional way. If you take off excess fluid using pure ultrafiltration it may be possible to dialyse the patient the next day.
PART VI

TRANSPLANTATION 1

Chairmen: A Struyvenberg
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