Kinetics of intradialytic disequilibria: the problem, the causes, and new methods for the alleviation of patient morbidity

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Overview

In the last 30 years there has been considerable evolution of dialysis technique. Innovations include the introduction of the hollow-fibre dialyser, the change of buffer from acetate to bicarbonate, ultrafiltration control, and human recombinant erythropoietin. Despite these improvements there remains considerable intradialytic morbidity, including hypotension, cramp, nausea, vomiting, and headaches.

This communication documents the potential causative factors of intradialytic morbidity and includes a short discussion of the long-term complications that may result from such events and a review of some new areas of exploration that show the potential to alleviate some of the patient intradialytic morbidity. Technologies that show promise in the mitigation of these problems include new methods of continuous haematocrit and blood volume monitoring combined with individualized modulation of sodium, bicarbonate, and ultrafiltration during the course of treatment. The crux of this paper is that many of the intradialytic events are caused by rapid fluid removal without adequate vascular refilling. By understanding the effect of the dialysis treatment variables on vascular refilling, the care provider can monitor and prevent many of these problems.

The problem hypovolaemia

It has been estimated that 20–30% [1,2] of treatments have some intradialytic events requiring nursing intervention. While some doctors deny there are significant problems with intradialytic morbidity in their dialysis clinics, one only needs speak to the dialysis nurses to find the extent of these problems in the modern dialysis unit; they include hypotension, cramp, nausea, vomiting, and headaches.

These symptoms are multifactorial in origin and may be complicated by comorbid diseases. Two of the main causes are (1) the rapid removal of the plasma volume by ultrafiltration without adequate plasma refilling, and (2) impaired cardiovascular compensatory mechanisms in dialysis patients. These causes combine to produce dialysis-induced hypovolaemia. The cardiovascular compensatory mechanisms to overcome intradialytic hypovolaemia include decreased venous capacity, increased heart rate, increased cardiac contractility, and increased peripheral vascular resistance [3]. Plasma volume has a more significant impact on cardiac filling than would have been otherwise thought [4]. Figure 1 shows the interrelationships of the determinants of systemic blood pressure [4].

![Fig. 1. Determinants of systemic blood pressure.](image)

Relationship to dialysis therapy

Acetate/bicarbonate

Mion [5] introduced acetate as a substitute for bicarbonate in 1964. Acetate was chosen because it remained in solution in concentrate while providing the needed metabolic buffer for the dialysate. As treatment times were shortened due to the advent of efficient hollow-fibre dialysers in the early Seventies, it was found that many patients had problems when dialysed with acetate dialysate.

Acetate dialysate has been reported to cause hypotension and other problems during dialysis more often than bicarbonate dialysate [6,7]. Acetate dialysate also takes time to convert to bicarbonate in the human body, causing a temporary dialysis-induced metabolic acidosis. This causes nausea and instability in some patients. Because of the better patient stability with bicarbonate dialysate, acetate is used less frequently every year.

Graefe et al. [8] demonstrated that the maximum tolerable rate of ultrafiltration was higher with bicar-
bonate dialysate than acetate dialysate. Plasma volume refilling rates were lower in both high- and low-sodium dialysis when acetate was used as the buffer instead of bicarbonate [9]. The same study showed that this effect was more pronounced in patients with impaired cardiac function [9]. Hsu et al. [10] reported that 'improved hemodynamic stability utilizing bicarbonate dialysate may be due, in part, to greater plasma refilling and better preservation of plasma volume.' In addition it has been demonstrated that acetate has a vasodilatory effect [11].

![Fig. 2. Dysequilbria due to acetate.](https://academic.oup.com/ndt/article-abstract/11/supp8/3/1817137)

### Sodium

In the early days of dialysis patients were typically dialysed on hyponatraemic dialysate (sodium of 130–135 mEq/l). The concentration was low on the assumption that it would prevent sodium accumulation, helping to prevent or control hypertension. The patient could be ultrafiltered down to their dry weight without any significant dialysis morbidity, when treatment times were 8–10 h.

With the advent of hollow-fibre dialysers, treatment times decreased to 4–6 h. When time was decreased, patients began to have problems during the dialysis treatment. It was suggested that these symptoms were related to a rapid decrease in plasma osmolality [12]. Osmolality changes during dialysis are primarily due to the removal of urea and the low sodium of the dialysate [13]. As early as 1973 it was shown that high sodium dialysate would help prevent dialysis dysequilibrium [14]. Other studies confirmed that with high-sodium dialysate there was a reduction of hypotension and increased vascular stability [15,16].

The drawback to increasing dialysate sodium is increased thirst [17] and weight gain [18] during the interdialytic period. This leads to the potential of hypertension if the patient is not ultrafiltered to dry weight during the subsequent dialysis treatment.

What are the mechanisms of the fluid shift in reaction to dialysate sodium? Water flows freely across the cell membranes. Sodium moves freely between the dialysate membrane and vascular space. It also moves freely between the capillary membrane dividing the vascular and interstitial fluid. Sodium is not transferred into the intracellular space because the cell membrane is a barrier to the diffusion of sodium [19].

Van Stone et al. [20] noted the changes in fluid distribution due to sodium, shown in Figure 3. In the same study they noted that higher dialysate sodium was associated with less symptomatic hypotension and that there was less extracellular volume loss with higher sodium.

The result of the low dialysate sodium is to move water out of the vascular space by ultrafiltration and into the tissue by the decrease in extracellular osmolality. This situation can cause a rapid volume depletion of the vascular space, resulting in hypovolaemic symptoms (Figure 4).

The result of the high dialysate sodium is to move water out of the vascular space by ultrafiltration and out of the interstitial and intracellular spaces by the increase in extracellular osmolality. This situation causes a relatively rapid filling of the vascular space, preventing most hypovolaemic symptoms (Figure 5).

Taking into account most of the available literature on the subject, Thews developed a theoretical model of the influence of sodium concentration on the patient’s status [19,21]. He concluded that with a valid model illustrating the reaction of the patient to dialysate parameters, problematic situations causing cramp and hypotension could be recognized and controlled (Figure 6).

It can be summarized that sodium has a major impact on the distribution of the fluid between the intracellular and extracellular fluid spaces. It can be reasonably stated that sodium controls the water move-

![Fig. 3. Physiological responses caused by dialysate sodium change.](https://academic.oup.com/ndt/article-abstract/11/supp8/3/1817137)
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Fig. 4. Result of low dialysate sodium.

Fig. 5. Result of high dialysate sodium.

Fig. 6. Thews' model of the influence of sodium on the internal milieu.

Ultrafiltration plays a key role in the change in the blood volume during dialysis. 'Clinically, ultrafiltration has quite a variable effect on vascular volume' [22]. The refilling of the vascular space from the interstitial space is often less than the ultrafiltrate volume. In addition to the effect of acetate, sodium, and impaired cardiac compensatory mechanisms detailed previously; excessive fluid gains and short treatment times have the potential to induce large changes in blood volume during dialysis. The volume removed is an important determinant of the likelihood of hypovolaemia during dialysis. Limiting patient fluid and sodium intake can decrease the volume to be removed, but patient compliance to dietary restrictions is not universal. No matter what volume is to be removed, optimizing plasma refilling rate and matching it to fluid removal rate should result in a more physiological treatment.

A model of the impact of ultrafiltration rate on the physiological mechanisms of the patient undergoing dialysis was developed by Thews and is shown in Figure 7 [21].

Haematocrit and blood volume monitoring

It was suggested as early as 1970 that patients may develop hypotension at a specific absolute blood volume (BV) [23]. Recent data using an on-line absolute haematocrit/BV monitor (Crit-Line, In-Line Diagnostics, Ogden, Utah) suggest that symptomatic hypotension occurs at a patient-specific absolute haematocrit [24–26]. At EDTA 1996 data was presented that suggest that absolute haematocrit is a repeatable measure of intradialytic events when there is not signi-
ificant access recirculation or red blood cell mass change [27]. Also the change in blood volume and slope of blood volume has been suggested as a useful predictor of a 'maximally tolerated blood volume change which may reflect dry weight' [25].

Another recent study presented at the 1996 National Kidney Foundation Spring Clinicals [28] (using the Crit-Line hematocrit and blood volume monitoring technology) indicated that a significant number of patient events previously not attributed to hypovolaemia may be associated with blood volume decreases of more than 10%. In the study population 94% of the patients with cramping and 98% of the patients with nausea or vomiting had a blood volume decrease of greater than 10% during the dialysis treatment. In the same study 84% of the hypotensive episodes were accompanied by blood volume decrease of greater than 10%. The study concluded that cramping 'may be postulated as being hypovolemic producing hypoperfusion leading to tissue ischemia resulting in cramping.' [29]

The problem becomes magnified in patients with frequent intradialytic morbid events. To stabilize the patient after an hypovolaemic episode clinicians use various strategies that usually lower the total ultrafiltration volume possible to remove during dialysis. To overcome hypovolaemic/hypotensive problems the therapist lowers ultrafiltration, increases volume, or adds osmolytes by infusing normal or hypertonic saline or mannitol. These procedures allow for the stabilization of the patient and prevent uncontrolled hypovolaemic shock (Figure 8). However, they also complicate patient fluid management in that it may be difficult to achieve fluid management goals after an intradialytic event. It has been shown that repeated events have a correlation with long-term cardiovascular problems [30].

Further complicating this situation is the fact that hypovolaemic episodes may occur even though the patient has severe oedema. Since the patient does not achieve dry weight and is fluid overloaded, this often leads to hypertension. Antihypertensive medications taken to lower the blood pressure then make it more difficult to remove the fluid in successive dialysis sessions [31].

A study to determine why patients did not stay on dialysis for the prescribed time found that in 6.8% of the treatments, patients signed off treatment early [32]. In this study cramping was the cause of 17.9% of early removal from treatment. ‘Feels bad or sick’ was the cause of 14.2% of the early withdrawals. The significance of this data indicates that dialysis morbidity not only has an effect on the patient’s fluid management but can also affect the efficiency of the waste removal during treatment by shortening treatment time.

Even though hypertension is multifactorial it has been shown that at least 50% of hypertension in dialysis patients is due in part to fluid overload [33]. There is a correlation between hydration and cardiovascular health. Patients who are always oedematous are more prone to cardiovascular problems such as hypertension, congestive heart failure, and left ventricular hypertrophy [31,34]. It is imperative that we understand at least those variables within the control of the physician to manage patient fluid status. Understanding those fluid management variables will help to indicate methods to manage the dialysis patient’s fluid balance more effectively, preventing the

Fig. 8. Relationship of fluid overload to hypotension and hypertension. Adapted from Charra (1996) ASIAO presentation.
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It is well known that determination of dry weight is often arbitrary, usually based on the Watson tables and fat measurements. It has been defined in clinical practice as 'the level below which further fluid removal would produce hypotension' [31]. That the patient can be made hypotensive even when oedematous illustrates the inadequacy of this concept of dry weight determination. Haematocrit and blood volume monitoring can help to determine if the patient is at the proper dry weight or if more fluid should be removed during dialysis.

Guyton showed the relationship between blood volume and extracellular fluid volume [35] (Figure 9). If one examines this relationship, the dialysis patient located along the 'A' portion of the graph would be expected to show little or no reduction in blood volume during the removal of extracellular fluid during dialysis. This flat type of BV profile during dialysis is indicative of oedema and fluid overload.

The patient along the 'B' portion of the line should show some change in blood volume as extracellular fluid contracts, but the slope of the line of contraction should be shallow. Profile B is equivalent to a profile of a patient who has a reasonable reduction of blood volume during dialysis but did not go into hypovolaemic shock. The normal patient along the 'C' portion of the line should show a steep slope as EC volume is contracted, associated with a large contraction of blood volume. Profiles with excessive slope such as C are indicative of hypovolaemic shock.

Recent data indicates that blood volume monitoring can reveal previously undetected oedema [36,37]. The patient may lose lean body mass and should have a lower dry weight. Such a patient is oedematous, but this fact is not detected by the clinician. Some have estimated that undetected fluid overload may be present in up to 20% of patients [37]. Using haematocrit and blood volume monitoring, oedema is detected by a relatively flat curve of BV and haematocrit.

The Crit-Line absolute haematocrit and blood volume sensor is a major technical step forward because it can detect and thus help to prevent haematocrit and blood volume changes which lead to intradialytic morbidity. Prevention of many of these episodes is possible if the technology could be integrated into the dialysis machine.

Integration of the absolute haematocrit and blood volume monitoring into the dialysis machine

The Althin Drake Willock® System 1000® is based on standard microcomputer architecture and a touch screen. This machine is able to individually modulate sodium concentration, bicarbonate concentration, and ultrafiltration rate in 15-min increments. An individualized patient profile may be saved and recalled for later use. Up to 18 profiles may be stored in the machine at once. Unique individual profiles may be set for any treatment. With a standard computer architecture and touch screen, the System 1000 can be upgraded to include new technologies as they are developed.

Absolute haematocrit and blood volume monitoring has been integrated into the System 1000. This provides a window into the patient's blood volume, showing the physiological response to the fluid and sodium model. This allows the detection of changes which would lead to intradialytic morbidity and can help prevent the occurrence of such problems.

Initially the machine will alert the operator by audio and visual alarms when the haematocrit increases or blood volume decreases to an operator-set limit. The machine can be calibrated to reduce UF or slow blood flow upon detection of this alarm, as the physician might prescribe. As more clinical data is accumulated on the patient response to UF rate and sodium modulations during treatment, the machine/patient interface will be incorporated into a feedback loop, with the machine able to prevent most hypovolaemia-caused dialysis morbidity (Figure 10).

Being able to monitor and respond to intradialytic events prior to the event occurring should be able to reduce morbidity and improve the quality of life for the patient. In addition this should help the long-term fluid management of the patient, which can help to
reduce cardiovascular problems caused by fluid overload.

Over time as clinical data substantiates this technology, the System 1000 software will be modified to allow ultrafiltration to true dry weight based on the measured plasma refilling rate of the patient. This will help patients with fluid-overload-caused hypotension to become normotensive and help reduce use of antihypertensive medication. There is early anecdotal evidence supporting a significant reduction of antihypertensive medication required in one clinic's patient population by utilizing this technology [Unpublished comments of Dr S. Provost], but significant clinical research is still necessary to see if this conclusion can be drawn with different patient populations.

Integrating the Crit-Line technology into System 1000 also includes the ability to monitor the oxygen saturation level of the blood. There is evidence that dialysis patients have a higher incidence of sleep apnoea, with its attendant cardiac risks, than the normal population [38,39]. This will allow for easy determination of the patient's oxygen needs during dialysis.

In addition the System 1000 connects to a laptop computer or network to print out the profiles of UF, bicarbonate, and sodium overlaid with the haematocrit, blood volume, or oxygen saturation profiles from the patient. This will provide physicians with a method to determine whether the profiling prescription works, to evaluate patient hydration changes easily, and to determine patient oxygen requirements. Another important benefit of this technology is the ability to monitor access recirculation.

Conclusion

As ultrafiltration removes fluid from the vascular space, refilling the vascular space becomes one of the key tools to prevent dialysis morbidity events. As early as 1991 it was noted that 'Maximizing plasma refilling rate is the only means to minimize the fall in plasma volume' [40]. The conclusion of this paper is that many of the intradialytic events are caused by rapid fluid removal without adequate vascular refilling. By understanding the effect of the dialysis treatment variables on vascular refilling, the care provider can monitor and prevent many of these problems.

Modern dialysis machines such as the Althin Drake Willock System 1000 will utilize bicarbonate dialysate combined with profiled sodium and UF. These profiles will be controlled and monitored using patient physiological data from haematocrit and blood volume monitoring. This will help to prevent most of the potential hypovolaemic-caused events, increase treatment efficiency, improve patient fluid management, and reduce long-term treatment complications due to fluid overload, thereby improving the quality of life for the dialysis patient.

References


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