Volume Control in Hemodialysis Patients

Bernard Charra, Charles Chazot, Jean-Marc Hurot, Guillaume Jean, Jean-Claude Terrat, Thierry Vanel, Guy Laurent

Centre de Rein Artificiel, Tassin, France

Cardiovascular disease is the main cause of the high mortality of dialysis patients and is largely due to poor control of blood pressure. Establishing and maintaining normal extracellular volume (ECV) is required to achieve normotension. The dry weight concept links ECV and blood pressure by a simple clinical relationship. Dry weight is the ideal postdialysis weight that allows a constantly normal blood pressure to be maintained without using antihypertensive medications.

*Maintenance of normal ECV requires control of salt intake to reduce interdialytic weight gain (*i.e.*, saline overload) combined with the diffusive and convective removal of salt and water from the body during dialysis sessions.*

Several problems are to be faced when using the dry weight method. Clinical evaluation must take into account the following confounding factors: weight varies with nutrition, clinical symptoms are unspecific and sometimes discordant, and there is a lag time between ECV and blood pressure changes. On the other hand, achievement of dry weight is hampered by dialysis times that are too short (and weight gains that are too high), by antihypertensive medications, and by poor heart conditions. A longer session time allows for a slower, easier, and more comfortable ultrafiltration.

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Key words

Extracellular volume, dry weight, blood pressure, ultrafiltration rate

Introduction

Cardiovascular (CV) disease is the primary cause of mortality in maintenance hemodialysis (HD) patients. Poor control of hypertension is, in great part, responsible for this situation. Several factors are involved in the pathogenesis of hypertension, but the main one is extracellular volume (ECV) overload. The achievement of an optimal fluid status, as expressed by "dry weight" (DW), should allow for controlling blood pressure (BP) in the large majority of HD patients.

Correspondence to:
Bernard Charra, MD, Centre de Rein Artificiel de Tassin, 42 Avenue du 8-Mai-1945, 69160 Tassin, France.
email: bcharra@aol.com

Sodium and water balance

Extracellular volume is about 15 L; sodium is the most prevalent cation in ECV. Physiologically, urine is the only exit route for sodium. When the kidney fails, no alternative route compensates for the lack of sodium output and it accumulates, thereby increasing body osmolality. Subsequent increased thirst and water ingestion results in the accumulation of isotonic saline in the ECV. In renal failure and HD, the patients who cannot restrict sodium in their diets develop a significant saline excess between dialyses. Conversely, when a dialysis patient loses too much ECV through vomiting or diarrhea, he develops saline depletion. The frequently used term, "dehydrated," to describe a patient with salt and water loss is inadequate. One should instead use the term "saline-depleted" because it accurately describes the disorder and implies the correct therapy.

In chronic renal failure (CRF), ECV increases [1] even if the overload is not such that edema is obvious. Patients with advanced CRF are particularly sensitive to sodium load [2]. Hypertension appears, even with a relatively low normal sodium intake. This peculiar sensitivity to sodium load increases as CRF progresses [2].

Dialysis professionals, as well as patients themselves, are often confused about the difference between the effects of restricting fluid versus restricting sodium intake on weight gain between dialyses. There is no reason to convince the patient to tolerate thirst and to restrict fluid intake to reduce the interdialytic weight gain, because excess dietary sodium, not fluid, is the real culprit [3]. For each 9 g sodium chloride, the patient's serum osmolality increases and stimulates thirst enough to drive a 1-L fluid intake.

In the early days of dialysis, a low sodium diet was systematically prescribed to avoid fluid overload. This simple requirement has been widely forgotten [3]. A low salt diet is the most important tool to reduce interdialytic weight gain [4,5]. When end-stage renal disease makes it impossible for the kidney to adjust the ECV, the dialyzer must do this. Evaluation of ECV is the essential initial step for the treatment plan and requires the gathering of several pieces of data:

1. Clinical circumstances and symptoms are paramount. The absence of circumstances leading to salt depletion (diarrhea, vomiting, laxative or diuretic abuse) or excess (excessive salt intake) makes diagnosis of these conditions highly unlikely.
2. The main clues in assessing ECV are changes in BP and weight. An increase in predialysis BP is the main sign of

saline overload. Low BP postdialysis or an orthostatic hypotension persisting more than a few hours suggest saline depletion. Short-term weight variations allow for the quantitative estimation of changes in ECV.

3. Intravascular volume can be assessed by examining the jugular veins in the supine patient or by central venous pressure measurement. Edema can be present in advanced stages of saline overload, but a severe saline overload can also exist without any edema.
4. Cardiothoracic ratio on x ray, and changes in hematocrit, total protein, and serum albumin may be of great help in evaluating ECV changes.

Defining euvolemia from clinical criteria is a rather difficult task. Few groups have analyzed the clinical method of evaluating ECV [6,7]. Even frequently repeated evaluations may miss ECV changes. The mean change in dry body weight needed for hypovolemia correction is about +940 g, whereas a mean reduction in postdialysis weight of 2400 g is necessary in the case of saline overload [6]. This suggests a systematic bias of clinical evaluation to overestimate dry body weight.

Concept of dry weight

Although the term sounds simple, DW is a concept of relative complexity. That BP regulation in HD patients depends first on ECV, has been recognized since the early days of maintenance dialysis [8]. Nevertheless, it was 7 years before Thomson *et al*. coined the term "dry weight," stating, "It was presumed that the reduction of blood pressure to hypotensive levels during ultrafiltration and unassociated with other causes, represented the achievement of a 'dry weight' status." [9]. The term has been given many definitions since then. Our own is "that body weight at the end of dialysis at which the patient can remain normotensive until the next dialysis without antihypertensive medication" [7].

Dry weight is not the actual postdialysis weight. It is the ideal postdialysis weight allowing for a normal BP. The patterns of euvolemia are mandatory because normotension *per se* does not exclude saline overload, and hypotension during dialysis does not necessarily indicate that the patient has reached DW. It would, of course, be helpful to have a direct reading of ECV. Indeed, several nonclinical methods [inferior vena cava diameter, atrial natriuretic peptide (ANP) and guanosine monophosphate (GMP) serum levels, bioimpedance, blood volume monitoring] have been proposed to replace clinical assessment of DW, which is often reported to be unreliable, insensitive, or inaccurate. But the clinical method is cheap, immediate, and universally available at the patient's bedside. Furthermore, there is no necessity in the clinical day-to-day practice to know the absolute value of ECV. All we really need is to achieve the ECV value at which the patient is without signs of dehydration or fluid overload and remains normotensive without antihypertensive medications. A weight scale and a BP cuff are usually all we need for that.

Pathophysiology of dry weight

As opposed to the normal kidney that functions 24 hours per day, HD is discontinuous, a few hours every 2 or 3 days, leading to a peak-and-valley situation. The patient gains one to several liters of ECV during the interdialytic period. At the initiation of each HD session, the patient is saline overloaded, or "wet." He needs to lose the weight gained during the interdialytic period to return to the last postdialysis weight. If this weight has been found to be too high, the planned ultrafiltration (UF) must be increased. If it has been found to be too low, the planned UF must be decreased.

The water and salt subtraction from the plasma volume creates a disequilibrium situation between the plasma and interstitial spaces. At the end of the HD session, plasma volume reaches a nadir. Refilling from interstitial (and intracellular) spaces has started but is not yet completed (it takes about 4 hours). At disconnection the patient is hypovolemic, or "dry," and may have an orthostatic BP drop that will disappear within a few hours.

Plasma volume preservation during UF is linked to the initial interstitial volume status. The higher it is, the faster the refilling [10]. During the session, as the patient gets less and less volume overloaded, his refilling capacity decreases and the hazard of hypotension increases. Blood pressure usually remains stable during the first two thirds of the session. In some patients, hypotension, rather than being compensated by an adequate hemodynamic response, may be complicated by a vasovagal syncope [11]. In fact, several factors modulate cardiovascular compensation, including extracorporeal temperature, dialysate buffer, and calcium concentration.

More than anything else, the heart's compensation for an acute volume change is impaired by reduced left ventricular compliance, which is very common in HD patients. Ventricular wall stiffness leads to an amplified volume–pressure response. Hypotension occurs more easily when ECV decreases, and even a moderate volume overload can result in elevated pressure, including, eventually, backward failure, pulmonary congestion, and edema [12].

The most significant determinant of hypotension on dialysis remains UF. The incidence of hypotension has increased from less than 10% of the session in long HD to 20% – 50% of shortened sessions. Blood volume monitoring devices have been developed to detect rapid drops in plasma volume early and predict hypotensive episodes. They can be included in biofeedback loop systems adjusting the UF rate to the refilling capacity of the patient [13].

That hypertensive patients have a higher ECV than normotensive patients has been established using different techniques of ECV evaluation: dilution, inferior vena cava measurement, ANP, GMP, and bioimpedance [14–17]. Normotension can be achieved in 90% of patients by controlling ECV without antihypertensive medications by

using a long dialysis three times per week or by using daily dialysis [18,19]. A recent report [20] shows that it is also possible with a conventional 3 × 4-hour HD associated with a low salt diet and a strict UF policy.

What is the relationship between BP and ECV as measured by weight? A crucial point is that it is the average level of sodium in the body, that is, the *average* weight — which correlates with BP in HD patients — not the *change* in weight. The postdialysis weight is a fixed reference point of volume that can be tuned during the session, whereas predialysis weight varies according to the length of the interdialytic period and the ingestion of salt.

The lag phenomenon

Figure 1 shows the evolution of ECV as reflected by body weight and mean arterial pressure (MAP) in 712 patients during their first year of dialysis. Postdialysis weight drops sharply during the first month to achieve its lowest value, but average predialysis MAP decreases slowly and progressively, achieving its plateau only after 1 year or so.

The observed delay probably corresponds to the autoregulation response described by Guyton [21]. This lag time of some weeks has also been described at the start of dialysis [22] as when using diuretics to treat hypertension [23]. It is of particular importance that the medical team and patient be aware of the existence of this lag time. It is discouraging for the patient to be ultrafiltered down to a point where he gets cramps or hypotension without becoming immediately normotensive in return. The patient must understand that a delay between UF and reduction of ECV and BP "response" is usual and normal.

The probe for dry weight

The DW method of BP control includes two separate processes. We call the first one "the probe" for DW. It is used for all patients at the beginning of treatment, and for some patients during maintenance HD when the physician is confused and needs to plot the position to figure out where he stands. The second and simpler process is a daily prescription of postdialysis weight before each session to maintain normotension and patient comfort.

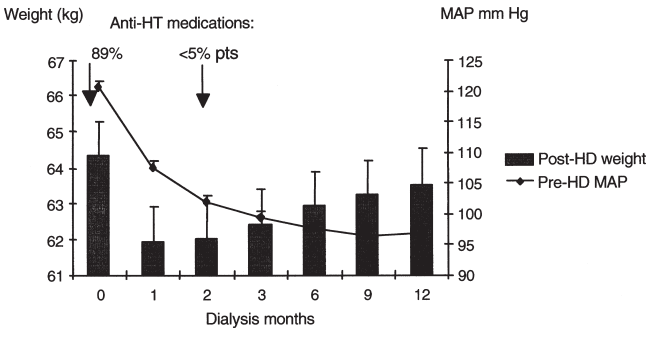

FIGURE 1 First hemodialysis (HD) year. Evolution of postdialysis weight (with SEM) and predialysis mean arterial pressure (MAP) (with SEM). HT = hypertension.

Key variables

Sodium intake must be reduced to the lowest level possible during the probe. The period of dialysis initiation needs the restriction to be especially tight. If the patient is followed in the clinics before HD start, the growing difficulty in controlling ECV and BP as CRF worsens is a good opportunity to show him the benefit of a low salt diet. When starting dialysis, the lower the weight gain, the easier it is to reduce the ECV to the level required to achieve normotension. It is easier to ask this effort of the patient at the start of dialysis when he is looking for a rapid improvement of his status. Usually, at this stage, a strict low salt diet excludes dry cheese, regular bread, and preserved or canned food. Typically, after some weeks, BP is back to normal and the low salt diet can be alleviated somewhat. Usually the patient has already lost in part his taste for salt, but this diet attenuation is usually quite appreciated.

Dialysate sodium activity, rather than concentration, governs its diffusion during HD. In practice, to achieve a neutral balance, due to the Donnan effect, dialysate sodium should be about 5 mmol/L lower than in plasma water [24]. Paradoxically, with shorter dialysis session duration, it has become usual to increase the dialysate sodium concentration in order to reduce intradialytic hypotensive episodes and cramps. In short-session HD, the simultaneous need to achieve a very high UF and to avoid intradialytic morbidity is one of the most evident limits of the method. Recent clinical papers [4,5] have pointed out the effectiveness of reducing dialysate sodium for BP control.

Ultrafiltration is quantitatively the most powerful tool at hand to control volume and BP. A few decades ago UF was difficult to achieve and monitor. Today the limiting factor is no longer the technique but patient tolerance. As long as refilling needs some hours, UF is necessarily time-limited and, therefore, dependent on session length and frequency.

The dry weight probe as carried out in Tassin

What typically happens during the first month of dialysis is shown in Fig. 2. Intense, carefully monitored UF and a strict low sodium diet permit a gradual reduction in predialysis weight of about 2 kg over the first month. The actual rate of decrease is strictly by trial and error, governed by the patient's tolerance. The occurrence of hypotension at the end of dialysis is the major proof that the patient has been brought to a low normal ECV. When this ECV low point has been achieved, the target postdialysis weight is re-evaluated by a few hundred grams. During this period antihypertensive medications are withdrawn. Failure to do so makes it almost impossible to achieve DW. The probe for DW represents a difficult transition for patients. This transition must be carefully explained to them and ongoing support from physicians and staff is essential.

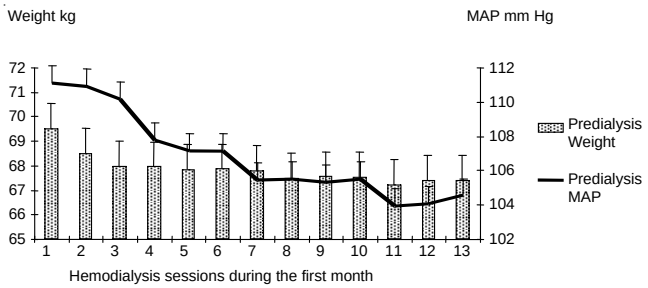

FIGURE 2 First hemodialysis month. Evolution of postdialysis weight (with SEM) and predialysis mean arterial pressure (MAP) (with SEM).

During this first month patients' appetites gradually improve. They become anabolic and begin to put on real body weight. This change complicates the problem of determining postdialysis weight. "In the initial period of dialysis the nephrologist like Janus is a double-faced gatekeeper; willing to decrease weight of ECV to normalize BP, yet prepared to increase weight to compensate for lean and fat body mass anabolic build-up" [25].

Remarkably, many patients maintained at DW have an even lower BP level than normal controls [26]. In this respect, they are similar to uncultured populations who habitually ingest a very low sodium diet [27]. To reduce cardiovascular morbidity, the target BP should be lower than usually recommended [28]. It should not exceed 120/70 mm Hg as suggested for the nonuremic population [29].

Some authors question the clinical practice of deliberately bringing the patient to the edge of hypovolemia and hypotension. Indeed, hypotension on dialysis, *per se*, is not sufficient to allow the conclusion that a patient has achieved DW, but orthostatic hypotension at the end of the session is a necessary condition to assert that a patient has achieved DW using the probe. In practice, one must reduce the weight very progressively over several sessions in order to distinguish DW achievement from a hypotensive episode resulting from a too rapid UF rate.

Maintaining dry weight on a day-to-day basis

Starting from clinical information collected at the bedside, one can guess where the patient stands in terms of ECV and prescribe a target postdialysis weight. When BP is normal both before and after dialysis, and no disturbing orthostatic symptoms occur after a few hours, the patient is probably at DW. If BP is elevated even slightly, DW is reduced by a few hundred grams. If, on the other hand, the patient experiences an orthostatic hypotension that persists more than a few hours after disconnection, then postdialysis weight is increased. The trial-and-error process can be alleviated by ambulatory BP measurement, which gives a more objective view of the real BP than intermittent measurements.

The use of weight as the practically quantifiable surrogate of ECV is rendered more difficult by the lean and fat body-mass fluctuations. During or after catabolic events (surgical procedure, hospitalization, *etc*.) the patient loses lean and fat body mass; therefore, prescribed DW must be lowered to maintain a steady ECV. The opposite situation of anabolism is usually less apparent. When a patient's food intake improves and lean and fat mass increase, he often fails to notice or mention it. Appetite and food intake must be regularly and systematically assessed.

Causes of failure of the dry weight method

In many reports, a large proportion of patients are reported to be hypertensive in spite of being at their "dry weight." This is, in almost all cases, due to the fact that either the DW has been overestimated, or that the correctly estimated DW could not be achieved.

Problems may occur in clinical evaluation of DW. Four main points must be kept in mind when using weight as the mirror of ECV:

1. Dry weight is a mobile target. Because weight is used as the surrogate of ECV, any factor of weight variation must be identified and measured when evaluating DW. Dry weight must be readjusted on a regular systematic basis because appetite and nutrition keep changing all the time and food intake is difficult to appreciate.
2. Clinical symptoms are unspecific and sometimes discordant. For instance, a grossly volume-overloaded patient may get hypotension and cramps during HD, especially if the session time is short and the UF rate is high. Dry weight must not be modified on the basis of a single symptom or data point, but on a cluster of information.
3. The lag time of some weeks between change in ECV and change in BP must be accounted for in the probe for DW. One should not expect an immediate BP response to changes in ECV. This is true when DW increases as well as when it decreases.
4. An important difficulty in clinical evaluation of DW comes from the common confusion between DW and interdialytic weight change. Interdialytic weight changes are first-order oscillations of weight due to the intermittent nature of HD, but DW is the short-term stable value that allows the BP to be normal.

Blood pressure is the target of ECV control, but in the meantime it is an essential factor in assessing ECV. One must therefore insist on the importance of ECV evaluation criteria, which must also be met. If a normotensive patient has edema, he is saline overloaded. If a normotensive patient has shortness of breath or a high venous pressure (or full jugular veins), or an enlarged heart on chest x ray, he must be strongly suspected of being saline overloaded. This capacity for developing saline overload without hypertension is illustrated in a recent study [16] showing that a proportion of normotensive Tassin patients have an increased ECV according to bioimpedance. It may

be due to the reduced salt (or volume) sensitivity with increasing HD treatment duration [30].

As already mentioned, antihypertensive treatment is a major source of failure to achieve DW because low BP is artificially maintained by the medication, even if the patient is not really "dry," and because it is a strong impediment to UF [31].

One of the main potential problems in achieving DW is insufficient dialysis time, that is, insufficient time allocated for UF. That a shorter session leads to more hypertension, and at the same time hypotension, can be understood. When session time is shortened, UF rate is increased and hypotension and other intradialytic events become more common. This has several bad effects. The patient has a poor perception and acceptance of HD and asks for a shorter session. The nurse has to cut down the UF rate or give saline, so prescribed DW is not achieved. The physician wrongly re-evaluates DW. Often he prescribes a higher dialysate sodium. This, on one hand, reduces the diffusive sodium drag from the patient and, on the other hand, leads to increased osmolality, thirst, and interdialytic weight gain. Altogether the patient does not achieve DW; he is saline overloaded and more hypertensive. He therefore needs more UF and eventually antihypertensive drugs, which further potentiate hypotension. Interdialytic hypertension and intradialytic hypotension keep amplifying each other in a vicious cycle. Reducing dialysis time amplifies BP variations.

Another potential factor in achieving an adequate ECV is the existence of so-called hypotension-prone patients [32,33]. We have already mentioned risk factors such as left ventricular hypertrophy (LVH) and impaired diastolic relaxation [33,34]. But in most cases, intradialytic hypotension is multifactorial and the conditions of dialysis seem more important than patient characteristics.

Other causes of hypertension in dialysis patients

Other explanations for failure of the DW method to achieve normotension are the eventual existence of non volume-dependent causes of hypertension, and inaccurate estimation of the true BP value.

Some rare causes of hypertension in dialysis (renal artery disease, hypertension secondary to endocrine causes, hypercalcemia) can be unaffected or aggravated by the reduction of ECV.

Inaccurate estimation of the true BP value is a more usual explanation of the failure of the DW method to achieve normotension. There are several reasons for this:

1. The hemodialysis intermittent process superimposes on the natural time pattern a new rhythm of volume and BP fluctuations (48- or 72-hour pattern). The importance of these changes in rhythm and BP variation amplitude are only starting to be appreciated.
2. Blood pressure is measured before, after, or between dialysis sessions.
3. A white coat effect has been reported in HD patients [35].
4. Casual and ambulatory BP monitoring measurement correlation is widely variable. According to the literature, ambulatory BP monitoring

    i. correlates better with postdialysis BP [36], predialysis BP [37], or does not correlate at all [38];
    ii. is the most reliable BP measurement tool [39]; and
    iii. shows poorer BP control in HD patients than expected from casual measurement [40].

Are there forms of hypertension that are truly refractory to dialysis? The increased BP readings observed at session end have been attributed to stimulation of the renin–angiotensin system [41], but this has not been proven [42]. Several studies have demonstrated that so-called refractory hypertension is most often due to excessive postdialysis weight [15].

Other effects of controlling ECV

In addition to its effect on BP normalization, control of ECV is associated with several other outcomes. Extracellular volume excess is a direct cause of LVH. In fact, LVH may be more strongly linked to sodium intake than to hypertension itself [43]. Fluid overload is a major factor in the development of cardiac disease associated with renal failure, leading to increased venous pressure, dilatation of cardiac cavities [3], mitral and tricuspid regurgitation, and congestive heart failure.

A lower salt intake reduces the incidence of stroke in nonuremic patients [44]. The correlation between stroke prevalence/mortality and salt intake is tighter than with BP [45].

Control of ECV is an essential condition for achieving a normal BP on dialysis. This is, in turn, the first requirement to reduce cardiovascular morbidity and mortality. The long, slow, and daily dialysis cumulative experience shows that high cardiovascular mortality is not the fate of chronic HD patients, any more than hypertension is an inevitable consequence of dialysis [46].

Normotension in HD patients may be achieved independently of the time or dose of dialysis; a significant proportion of patients dialyzed using "conventional" short HD do achieve normotension. In units where low salt diet, reasonable dialysate sodium, and strict UF policy are implemented, normotension is also obtained in almost all patients, without antihypertensive drugs. This can be achieved even if the dialysis time is short [20], but it is then more difficult than with a long or daily dialysis. More than anything else, the success of the dry weight method of BP normalization requires the conviction and determination of the physicians in charge of dialysis patients.

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