Haemodialysis dose, extracellular volume control and arterial hypertension

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Abstract
Patients with chronic renal failure on periodical dialysis frequently are hypertensive. This frequency has increased in relation to the liberalization of diet and to short dialysis with a high sodium concentration in the dialysate. Although various factors influence the pathogenesis of this type of hypertension, volume overload is the most significant. The achievement of an optimal dry weight is still one of the most difficult and important tasks of a dialysis clinic. The reduction in extracellular volume in haemodialysis implies an improvement in dialysis tolerance. The time factor is one of the principal elements in this control, but it is possible, using other elements, to improve tolerance in 4–5 h sessions and to achieve the proper dry weight associated with normotension in most patients.

Keywords: extracellular volume control; haemodialysis; hypertension; long haemodialysis; short haemodialysis

Introduction
According to the data from the US Registry of haemodialysis patients, hypertensive patients on haemodialysis do not show higher mortality than those patients who are normotensive [1]. In this study, carried out on a random sample of 6585 patients, those with predialysis systolic blood pressure (BP) of <110 mmHg showed higher mortality than the rest of the patients, including the hypertensives. These patients have a risk of death between 1.8 and 2.3 times higher, from both cardiac and other causes. Other epidemiological studies which evaluated BP in haemodialysis patients as a factor independent of negative prognosis showed varying results [2]. On starting dialysis, between 80 and 90% of patients are hypertensive, and the majority already suffer from severe systemic repercussions: left ventricular hypertrophy, arteriosclerosis, and coronary, cerebral and peripheral vasculopathy. The control of BP in dialysis can, at least, help to stop the progression of accelerated vasculopathy in these patients. Adequate control of BP in dialysis offers positive results in long-term survival. In the short term, the only objective finding is a decrease in cerebrovascular events. Furthermore, BP is implicated in another series of cardiovascular risk factors as well as other mortality risk factors. We can conclude that it is essential to control BP in patients on haemodialysis, without adversely affecting other factors of prognostic value such as nutrition, or physical and psychological tolerance of the therapy.

Historical data on arterial hypertension in haemodialysis
During the 1960s, haemodialysis sessions were long, used a low sodium concentration in the dialysate (<138 mmol/l), membranes were less biocompatible and the dialysis machines were not as effective as they are today. Patients were recommended to take low-salt diets and the percentage of hypertensive patients was small. In the 1980s and 1990s, haemodialysis sessions were shortened. The sodium concentration in the dialysate was higher (≥140 mmol/l), great technical progress was made, but diet was liberalized and the percentage of patients with arterial hypertension (AHT) rose to >50%. However, this percentage of AHT in haemodialysis is not uniform in all units. In units using long haemodialysis sessions of 7–8 h or daily haemodialysis, the percentage of hypertensive patients is very low [3–5].

What clinical factors influence control of BP in patients on haemodialysis?
The clinical factors which have been shown to influence a better control of BP in haemodialysis
patients are: duration of the session, frequency of the sessions, haemodialysis tolerance, dialysis dose, low-salt diet, achievement of ‘optimal dry weight’, level of sodium in the dialysate, interdialysis weight gain, haemodiafiltration techniques, high-flux membranes and even the administration of antihypertensive drugs. Many of these factors are interrelated. With the exception of the use of antihypertensives, all others have an aim in common, i.e. the achievement of normal to low extracellular volume (ECV) between sessions, partially reflected by a lower dry weight [6].

**Dry weight**

The sodium balance is the result of the difference between sodium ingestion and elimination through dialysis, basically through ultrafiltration (UF). When ingestion is higher than elimination in dialysis, there is an expansion of ECV, which plays a key role in the development of AHT. Therefore, the concept of ‘dry weight’ emerges, defined as the lowest weight tolerated by the patient without symptomatology nor hypotension on dialysis, in the absence of a fluid overload. However, it is a well known fact that the maximum UF in haemodialysis depends on the rate of plasma refill, which reflects the transfer of fluid from the interstitial to the intravascular compartment and which may vary with the type of haemodialysis session. Therefore, the Tassin group defines dry weight as the post-dialysis weight obtained allowing pre-dialysis BP to remain normal (<130/80 mmHg) independently of interdialytic weight gain and without the use of antihypertensive medication [7]. It is true that the majority of patients on dialysis at present show a chronic fluid overload, which implies a high prevalence of AHT, as well as of the associated pathologies listed in Table 1. Today, more than two-thirds of the population on dialysis are hypertensive, reflecting a high degree of error in the estimation of the patient’s dry weight.

**Methods to determine the ‘dry weight’**

It is clear that proper estimation of dry weight in dialysis is of critical importance. However, up to now and despite the technological advances as applied to dialysis, there is no precise procedure for determination of dry weight. In the majority of dialysis units, the determination of dry weight is usually clinical, basically taking into account haemodialysis tolerance, interdialysis weight gain, diet, BP, heart rate, oedemas, cephalas and dyspnea [7,8]. However, in recent years, different procedures for dry weight determination have been described, which can greatly help in the evaluation of the patient’s hydration on dialysis (Table 2). Two of these useful methods for determining dry weight are described below.

**Table 1. Problems associated with the increase in extracellular volume**

<table>
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<tr>
<th>Problem</th>
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<tr>
<td>Arterial hypertension</td>
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<tr>
<td>Acute cerebrovascular event</td>
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<tr>
<td>Left ventricular hypertrophy</td>
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<tr>
<td>Ischaemic cardiopathy</td>
</tr>
<tr>
<td>Congestive cardiac failure</td>
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<tr>
<td>Diastolic dysfunction</td>
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<tr>
<td>Arrhythmias</td>
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<tr>
<td>Sudden death</td>
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<td>Ultrafiltration intolerance</td>
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<td>Higher mortality</td>
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**Table 2. Technique to determine dry weight**

<table>
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<tr>
<th>Method</th>
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<tr>
<td>Clinical estimation</td>
</tr>
<tr>
<td>Invasive techniques: central venous pressure and pulmonary artery pressure</td>
</tr>
<tr>
<td>Biochemical: PNA, GMP, adrenomedulin, calcineurin</td>
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<tr>
<td>Ultrasound of the lower vena cava</td>
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<tr>
<td>Electrical bioimpedance</td>
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<td>Isotopic techniques</td>
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<td>On-line evaluation of volaemia: Crit Line, Hemoscan</td>
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**Multifrequency electrical bioimpedance**

Multifrequency electrical bioimpedance (EBI) is a procedure based on the different resistance to an alternate electrical current offered by the various tissues in the human body [9]. Tissues with a high water content such as cerebrospinal fluid, blood or muscles are high conductors, while fat tissue, bone and lung tissues are highly resistant to the passage of electricity. The application of the formulae available today to multifrequency EBI determinations offers information on total body water and ECV, thereby allowing the indirect calculation of the intracellular volume. The use of this method, together with the variations in plasma volume during haemodialysis measured by sensors which determine the reduction in plasma volume as the haemoglobin, haematocrit or protein concentration increases, allows a fairly good estimation of the movements of fluids between the different compartments during a dialysis session.

**Isotopic methods**

The measurement of deuterium with isotopes is the most precise procedure for estimation of ECV [10]. However, the use of this method is limited due to the complexity of the technique. Nonetheless, studies exist which show a very high correlation between the isotopic and EBI findings and, therefore, the simultaneous use of multifrequency EBI and clinical evaluation has become the most adequate tool for the determination of dry weight.

**How to maintain the ‘dry weight’**

Various authors have shown that strict control of ECV with a severely salt-restricted diet together with
UF allows proper control of BP without antihypertensive medication in 4-h conventional dialysis sessions [11–13]. It is important to note that after having achieved adequate ECV, BP in some patients does not immediately normalize, but does so only after an adaptation period of the peripheral resistance, also known as the lag phenomenon [14]. The optimization of UF in haemodialysis should be directed towards the highest rate possible with good tolerance per session. Among the best strategies for improving UF, we cite the following.

**Convective transport**

Isolated or sequential UF is still useful in achieving proper dry weight in patients with poor tolerance or large weight gains. The modern haemodiafiltration techniques (AFB, on-line haemodiafiltration or PFD) show a lower incidence of hypotension, cramps, vomiting and cephalaeas, which makes reaching UF objectives easier than in conventional haemodialysis.

**Temperature**

The use of low temperature of the dialysate (35°C instead of the usual 37°C) allows better haemodynamic tolerance to UF. The increase in peripheral vascular resistance and the improvement in cardiac contraction are two of the factors implicated in better haemodynamic tolerance, seen principally as a lower number of hypertensive events.

**Frequency**

Daily dialysis for 2–3 h per session, 6 or 7 days per week is the most physiological form of haemodialysis known to date. Although its use began >15 years ago, in recent years there has been a resurgence in the use of this frequency, due to the Italian experience [15]. Among the advantages of this type of therapy is a higher weekly Kt/V than in conventional haemodialysis, together with greater elimination of phosphates and medium to large sized molecules, and, above all, it is associated with the normalization of BP in almost all cases, without the use of antihypertensive medication. This decrease in BP is closely related to the decrease in ECV. This procedure has also been associated with a decrease in left ventricular hypertrophy, a decrease in the need for erythropoietin to correct anaemia and an improvement in the patients’ quality of life.

**Profiles**

When adequate UF is not achieved using the procedures described above, modern haemodialysis monitors allow the modification of conductivity, sodium concentration or the UF rate in each session [16]. The increase in the sodium concentration in the dialysate favours the passage of sodium into the intravascular space, thereby increasing osmolarity and the movement of water from the intracellular space towards the interstitial space and the vascular bed.

The higher intravascular volume reached with hypertonic dialysis improves tolerance and allows greater UF. On the other hand, the risk of this procedure is an accumulated net positive sodium balance, giving rise to greater thirst, higher fluid ingestion, higher ECV and, therefore, higher incidence of AHT. Therefore, the high sodium concentration in the dialysate must be followed by a decrease in the same session, allowing a sodium loss by diffusion towards the dialysate. However, a low sodium concentration gives rise to a decrease in the ECV osmolarity, producing movement of water towards the intracellular compartment, thereby increasing the tendency to hypotension. Therefore, the variable sodium profiles must be synchronized with the UF profiles, so that the latter are higher with high sodium concentrations in the dialysate and decrease to a minimum when the sodium concentration in the dialysate falls at the end of the session.

**Long haemodialysis and control of BP**

Long haemodialysis can achieve adequate BP control in the majority of patients. Charra et al. [3] mention two possible explanations for this: (i) the ease with which long haemodialysis maintains ‘optimal dry weight’; and (ii) the possibility of greater elimination of vasoactive substances in long haemodialysis. Some of these substances, such as asymmetric dimethyl arginine, which is a potent nitric oxide synthetase inhibitor, are more easily eliminated with higher dialysis doses. In Tassin [3], long haemodialysis is coupled with high dialysis dose (Kt/V 1.71) at least of small molecules, but in the case of New Zealand, in 7 h dialysis, Kt/V is 1.2 [4]. Furthermore, short, high-flux dialysis should include higher clearance of these vasoactive substances. Only the presence of compartments with a low substance transfer rate can explain greater elimination in long dialysis. In a study comparing Swedish patients on 5-h dialysis with patients in Tassin on 8-h dialysis, the hypertensive Swedish patients showed a corrected ECV for post-haemodialysis weight which was significantly greater than that of the normotensive patients, both Swedish and French [17]. This study concludes that normotension can be achieved independently of haemodialysis duration (between 5 and 8 h) and dose (mean Kt/V 1.5–1.9) if the post-dialysis control of ECV is adequate, but the shorter the haemodialysis, the more difficult it is to achieve this control.

**Why is it more difficult to achieve correct ECV with short haemodialysis?**

Three factors can explain this. The first is haemodialysis tolerance: the volume of ultrafiltrate per time unit is the principal cause of hypotension and its
appearance impedes weight reduction. The mean UF rate of the Tassin patients was 5.4 ml/h/kg, while for the Swedish patients it was 10.2 ml/h/kg. The second factor is the post-haemodialysis rebound of water and sodium in the vascular space from the interstitial space, which is greater in short haemodialysis, as it is with other substances. Measurement of the vena cava has proven that this phenomenon is significantly greater in short haemodialysis [18]. Furthermore, with high concentrations of sodium in the dialysate, its passage from the dialysate to the patient may induce the passage of sodium into the intracellular space, with a decrease in the Na⁺-K⁺ pump activity. This cytosolic sodium increases could also have an effect on vascular tone. The clearance of substances which can affect the membrane transporters and, therefore, the sodium interchange may also be another associated factor [19].

The third factor is the sodium balance, a factor which is usually overlooked. The first component of sodium balance is the ingestion of sodium, which should be limited in the majority of patients. The second component is the elimination of sodium through haemodialysis, fundamentally carried out through UF. In short dialysis, a high sodium level in the dialysate is usually used to improve tolerance. The passage of sodium by diffusion from the dialysate to the patient counteracts part of the sodium eliminated by UF. The insufficient negative sodium balance is reflected by greater thirst in the interdialytic period and higher weight gain. The Tassin patients gained less weight than the Swedish patients: 2.2 ± 1.9 and 3.2 ± 1.5 kg, respectively, in spite of their fairly ‘free’ diet. A fundamental element in the control of adequate ECV is the sodium in the dialysate, which should be measured monthly, at least. The European Pharmacopoeia permits a variability of ± 2.5% in sodium concentration of commercial concentrate solutions for haemodialysis.

**Must we return to long haemodialysis or daily haemodialysis to control BP?**

The answer to the above question is: not in the majority of the patients, but only in those in whom adequate ECV, and therefore proper BP control, is not achieved, always taking into account the lag phenomenon of several weeks [14]. The first step in hypertensive patients on haemodialysis should be to eliminate antihypertensive drugs and to educate the patient in the control of sodium ingestion while maintaining a good nutritional status. At the same time, the sodium concentration in the dialysate should be reduced to ≤138 mmol/l, making sure that an adequate dialysis dose (Kt/V ≥ 1.2 adjusted for the urea rebound in all haemodialysis, averaging at 1.3) is achieved. Isolated UF can also be useful. Finally, good haemodialysis tolerance should be maintained, with the use of special techniques such as AFB, low temperature, etc. If adequate tolerance is not achieved, haemodialysis should be prolonged until proper tolerance is reached.

**References**