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Dialysis
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Blood volume monitoring and control

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Introduction

Fluid volume control during and between dialysis treatments is an important factor in determining the adequacy of the dialysis delivered to the uraemic patients. Besides controlling fluid intake between treatments, curbing the blood volume decrease during dialysis may result in a reduced frequency as well as severity of dialysis hypotension. During haemodialysis the fluid is removed by ultrafiltration from the intravascular compartment, but it naturally derived from both the intravascular and interstitial volume. This implies a continuous refilling of fluid from the extravascular to the plasma compartments. The plasma refilling rate is the difference between the total fluid loss and plasma volume loss per time unit.

In order to minimize the impact of the blood volume decrease on the patient's haemodynamic stability during the treatment, and to reduce the incidence of hypovolaemia in the genesis of haemodialysis hypotension, the following points ought to be dealt with:

(1) fluid changes during haemodialysis;
(2) the measurement and monitoring of blood volume;
(3) the automatic control of blood volume.

Fluid changes during haemodialysis

Fluid exchange across the capillary walls was first described by Starling in 1909 [1]. He suggested that plasma–interstitial fluid exchanges are controlled by the interaction of microvascular hydrostatic pressure and colloid osmotic forces. In the following years this original hypothesis underwent an evolution. New concepts concerning hydraulic conductivity, capillary surface area, reflection coefficient for plasma proteins and the Péclet number, which couples the protein flux to the volume flow across the capillary walls, were introduced.

In 1984, Mitchel proposed a new version of Starling's hypothesis [2], taking into account the link between protein flux and filtrate concentration:

$$J_v = L_p S\left((P_c - P_{int}) - \sigma^2 \pi_p\left[\frac{1-e^{-Pe}}{1-\sigma e^{-Pe}}\right]\right)$$

where J_v is the transcapillary fluid rate, L_p is the hydraulic conductivity, S the capillary surface area, P_c and P_{int} are the capillary and interstitial hydrostatic pressures, respectively, σ is the reflection coefficient for plasma proteins, π_p is the plasma oncotic pressure and P_e is the Péclet number.

During haemodialysis, the continuous water loss by ultrafiltration acts as a disturbing factor in this complex equilibrium of different forces. After an initial phase in which the fluid loss leads to a decrease in intravascular hydrostatic pressure, the secondary increase in oncotic pressure enhances the plasma refilling from the interstitial compartment. As a consequence of the fluid shift, the plasma oncotic pressure declines, as does the interstitial hydrostatic pressure: the refilling will decrease until a new disequilibrium results because of the continuous water withdrawal across the filter.

The blood volume behaviour in response to ultrafiltration differs from patient to patient and in the same patient from session to session as a consequence of different vascular refilling capacities. In 1984, Kimura *et al.* [3] developed a computer model simulating the change of plasma volume in haemodialysis, by combining two models for transcapillary and transcellular fluid exchanges. Unfortunately, this model is based on assumed values for parameters such as arterial and venous capillary pressure, hydraulic permeability and interstitial space compliance, which continuously change during haemodialysis. Recently, Schneditz *et al.* [4] described a more realistic model examining the vascular refilling rate in terms of filtration coefficients that may be used to determine the rate at which the fluid excess can be removed.

During haemodialysis, several patient-related parameters (Table 1) and technique-related variables (Table 2), extensively described elsewhere [5], affect the refilling rate. At a constant and fixed ultrafiltration rate, the plasma refilling rate may vary throughout the treatment. Any reduction in the filtration coefficient increases the imbalance between the ultrafiltration rate and the vascular refilling rate. Modifications in blood

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Table1. Patient-related parameters affecting vascular refilling during haemodialysis

Body size
Fluid overload
Plasma volume
Regional blood flow distribution
Plasma protein concentration
Transcapillary pressure gradient
Plasma osmolality
Venous compliance

Table 2. Dialysis-related factors affecting vascular refilling during haemodialysis

Ultrafiltration
Sodium dialysate concentration
Dialysate buffer
Dialysate temperature
Dialyser membrane (?)

flow distribution [4] or tissue hydration [6] strongly affect changes in plasma volume.

From our personal observations in over 1000 dialysis sessions with blood volume monitoring and a constant and fixed ultrafiltration rate, four main typical trends have been observed (Figure 1). In approximately 60% of the sessions, blood volume changes have a biexponential trend, with an early period lasting about 30 min, characterized by a rapid reduction due to the direct water withdrawal from the intravascular compartment; after that there follows a second phase, less steep, during which the plasma refilling rate almost equals the ultrafiltration rate and blood volume tails off linearly and slowly up until the end of dialysis. This kind of trend is generally observed in patients with cardiovascular stability and a gradual decrease in blood pressure. In about 25% of the cases, the blood volume reduction is linear and progressive during haemodialysis, reaching a reduction of 20–25% by the end of

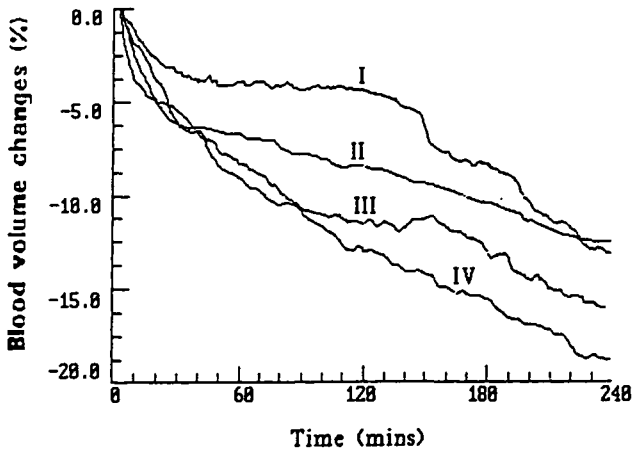


Fig. 1. Different individual patterns of blood volume decrease during haemodialysis sessions with constant ultrafiltration rate. The overall frequency of appearance is 7.12% for pattern I, 58.9% for pattern II; 9.3% for pattern III and 24.65% for pattern IV. See text for other comments.

the treatment. This trend is often accompanied by haemodynamic instability that can be controlled by volume expansion. The other two much less frequent trends are characterized by brusque changes in the slope of the blood volume curve. These changes, which are the expression of intradialytic modifications of the vascular tone as well as of changes in the filtration coefficient, tend to favour the appearance of hypotension [5].

However, there is no one typical, characteristic blood volume pattern which always leads to hypotension. On the other hand, changes in arterial and venous vascular tone, which are the appropriate response to a blood volume reduction, may account for cardiovascular stability even in the presence of a substantial volume depletion. Of the total blood volume, 75% is contained in the venous vascular system, with the veins able to alter their capacity over a wide range. Moreover, translocation of blood from the unstressed to the stressed compartment by active or passive venoconstriction may enhance venous return and maintain an adequate stroke volume.

However, it may actually be true that in *some* hypotension-prone patients there is a threshold level of hypovolaemia, beyond which hypotension can appear. Nevertheless, in such patients it is hard to understand whether the blood volume reduction is the actual cause of hypotension or whether it is only a warning signal of a stressed cardiocirculatory system. In any case, it is precisely in these patients that continuous intradialytic blood volume monitoring could turn out to be an efficient tool in predicting and preventing dialysis hypotension.

Measurement and monitoring of blood volume

The circulating plasma volume or the red blood cell mass can be obtained by a dilution technique [7] using, respectively, iodinated (^{131}I) human serum albumin or red blood cells tagged with chromium (^{51}Cr). Total blood volume is then derived either from the plasma volume and the haematocrit or from the red blood cell volume and the haematocrit.

However, in routine haemodialysis both these methods are impracticable. Indeed, the need to inject radiolabelled substances as well as the need to perform impossible continuous measurements make them of little use in measuring blood volume during haemodialysis. More recently, indirect methods of measuring blood volume changes have been proposed [8–11]. The measurement of the concentration (C) of substances whose pool (Q) can be assumed to remain substantially unchanged during haemodialysis may serve this purpose. Throughout the dialysis treatment the variation of the concentration is exclusively due to changes in total volume. The mathematical relation allowing us to calculate blood volume from the specific C is:

$$BV_t = \frac{TBV_t - TBV_0}{TBV_0} = \frac{C_0}{C_t} - 1$$

where BV = blood volume change, TBV = total blood volume, and 0 and t indicate the moment of dialysis start and the actual moment, respectively.

The systems that respond to this general principle in measuring blood volume exploit the measure of various parameters, such as haemoglobin [8], haematocrit [9], plasma proteins [10] and plasma conductivity [11].

A few years ago we proposed a non-invasive probe to measure the haemoglobin concentration in a layer of whole blood flowing in the arterial line [12]. Today, this optoprobe is directly applied to a dialysis machine [13], and provides haemoglobin values by measuring the optical absorbance of monochromatic light (Hemoscan, Hospal-Dasco, Medolla, Italy). Light propagating through a solution containing haemoglobin will be partially absorbed by the haemoglobin (Figure 2) and its intensity, after travelling through the medium, is provided by the Lambert–Beer law. In whole blood, along with the absorption phenomenon, there is also a multiple reflection of the light band on the cellular walls of the red blood cells. This phenomenon, known as scattering, is complexly linked to the mean volume of the red blood cells (MCV). In this case, the intensity of the received light (I_t) depends not only on the intensity of the incident light (I_0) and the haemoglobin concentration [Hgb], but also on the intensity of the scattered light (I_r).

$$I_t = I_0 \times e^{f[Hgb]} + \mathrm{err}(MCV)$$

Minimization of the scattering factor may be achieved thanks to an optical design obtaining the confinement of the radiant energy, and a disposable dedicated tract in the arterial blood line.

The resulting system has the following features:

(a) very low sensitivity to changes in osmotic pressure (maximum error 0.7% for wide change in plasma sodium, from 136 to 154 mEq/l);

(b) very low susceptibility to changes in hydraulic pressure and blood flow (maximum error 1.8% for blood flows from 200 to 400 ml/min);

(c) low sensitivity to changes in oxygen saturation (maximum error 1.6%).

The haemoglobin concentration determined by the optical probe compared with the concentration achieved using traditional laboratory method gives an excellent correlation (Figure 3) in *ex vivo* studies ($r = 0.996$, SE = 0.14 g/dl).

Continuous measurement of haemoglobin using the mathematical algorithm described above was performed during haemodialysis to estimate the percentage changes in blood volume. In actual fact, the opportunity of continuously and non-invasively measuring spontaneous blood volume variations during treatment offers several important prospects with a view to improving dialysis therapy. From a strictly theoretical point of view, continuous surveillance of blood volume might turn out to be useful in certain kinds of patients and under certain circumstances, such as the following.

(1) Hypotension-prone patients with a tendency to hypovolaemic hypotension. In such patients there is an evident cause and effect relationship between hypovolaemia and hypotension onset. The correction of hypovolaemia usually resolves the hypotension in this case.

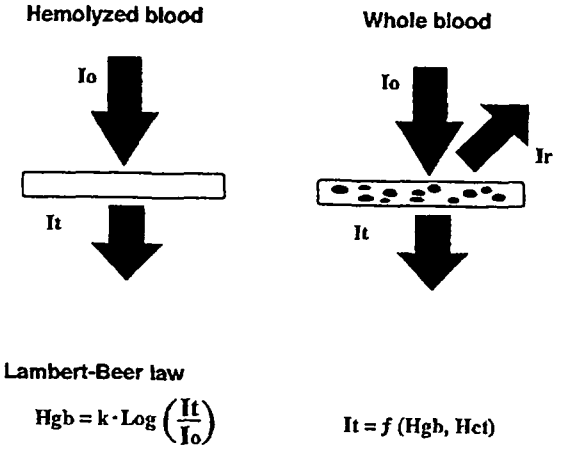


Fig. 2. The attenuation of an incident light propagating through blood is different in haemolysed and whole blood. In haemolysed blood (left), the attenuation of the incident light is only due to absorption by haemoglobin; in whole blood (right), the attenuation of light is the result of both absorption and scattering by the red blood cell surface. In this case, the degree of the attenuation is a function not only of the incident light and the haemoglobin concentration, but also of the haematocrit. I_0 = incident light; I_r = light scattered by the surface of the red blood cells; I_t = light received by the photodetector; Hgb = concentration of haemoglobin; Hct = haematocrit; k = constant depending on the physicochemical characteristics of the medium.

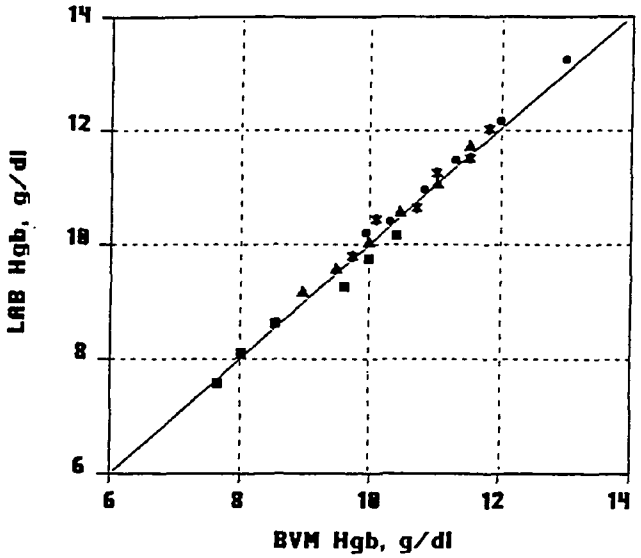


Fig. 3. *Ex vivo* validation of haemoglobin measurement by the optical monitor. In the figure, the haemoglobin values determined with the blood volume monitor (BVM Hgb) in four different haemodialysis study sessions are plotted against the standard laboratory values (LAB Hgb). The coefficient of correlation is 0.996 and the standard error is 0.14 g/dl.

(2) Patients with instability and disordered vascular refilling: (a) diabetic patients with microvasculature damage and autonomic nervous system insufficiency; (b) patients with poor nutritional status; (c) underhydrated patients with compromised tissue hydration. The combination of blood volume and extracellular fluid volume monitoring by conductivity [14] might make it possible to evaluate the influence of the hydration state on the refill capacity. The dry body weight could be corrected in order to improve tissue hydration.
(3) Patients with cardiomyopathy and reduced diastolic compliance. As suggested by Ritz *et al.* [15], left ventricular malfunction might predispose to dialysis hypotension. In such patients, hypovolaemia induced by ultrafiltration might in fact worsen the already compromised ventricular filling.

In our opinion, these three groups of patients could well obtain concrete benefits from the continuous monitoring of their blood volume during treatment. However, our impression is that an absolute and objectively critical level of hypovolaemia does not exist, in that such a level has a great inter-individual variability, i.e. changing from patient to patient. Each hypotension-prone patient should be studied several times in order to assess his or her own 'critical' threshhold.

Nevertheless, it must be said that the identification of an individual degree of critical hypovolaemia will not solve the complex problem of the dialysis hypotension. In fact, any change in the variables involved in the vascular refilling regulation, serum osmolality, electrolyte and protein concentrations, changes in body position and eating during dialysis, can unpredictably modify the value of the 'critical level'.

Automatic control of blood volume

Dialysis comfort of the patients might be further improved when blood volume control is combined with intradialytic sodium and ultrafiltration profiles. Increased dialysis fluid sodium can promote greater fluid mobilization from the extravascular compartments, thereby reconstituting a greater portion of plasma volume lost during ultrafiltration. On the other hand, profiling the ultrafiltration rate during haemodialysis can have a beneficial influence on blood pressure behaviour [16]. The control of the two variables should be combined together in order to achieve, apart from haemodynamic stability, an ideal post-dialysis body weight and an adequate sodium balance.

In point of fact, we have developed a blood volume control system based on an adaptive controller. During haemodialysis, the blood volume changes and the coefficients that link them to the controlling variables, the ultrafiltration rate and the dialysate conductivity, are continuously calculated [17]. These two variables are thus modified according to a mathematical model, so that any discrepancy between the pre-set blood volume profile and the one actually obtained during haemodialysis can be offset (Figure 4). During the treatment the independent variables, the ultrafiltration rate and dialysate conductivity, can only fluctuate within well-defined limits (Figure 5). Furthermore, the automatic blood volume control system works together with a kinetic sodium model with two subcompartments, as suggested by Pedrini [18]. The model considers the systemic sodium concentration (or sodium content) as a function of time, and has been validated by comparing computer simulation results with experimental data. The correlation between the plasma

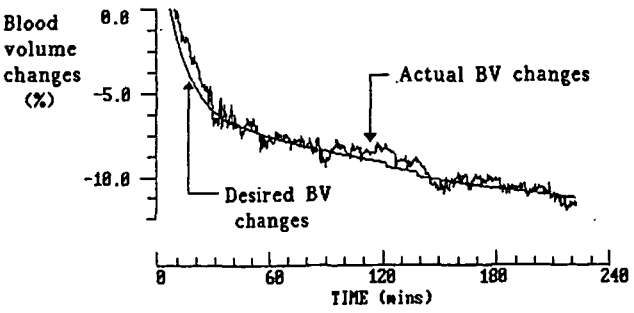
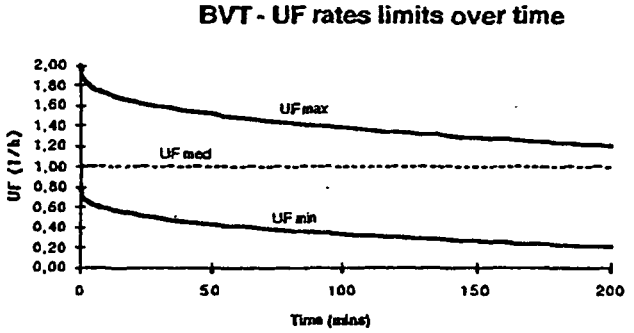


Fig. 4. An example of a dialysis session with blood volume (BV) tracking. The actual blood volume changes, obtained by the retroactive modulation of both the ultrafiltration rate and dialysate conductivity, follow the desired trend very closely.



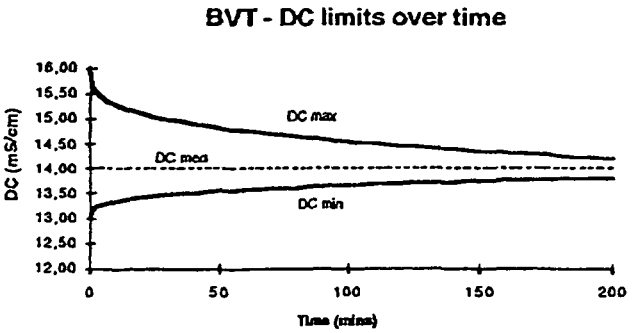


Fig. 5. Variability ranges of the ultrafiltration rate (UF, top), and dialysate conductivity (DC, bottom) during a haemodialysis session with blood volume tracking (BVT). Despite this variability, by the end of the session the mean values of both the ultrafiltration rate and dialysate conductivity are equal to the ones that would have been obtained during conventional haemodialysis with constant ultrafiltration and dialysate conductivity.

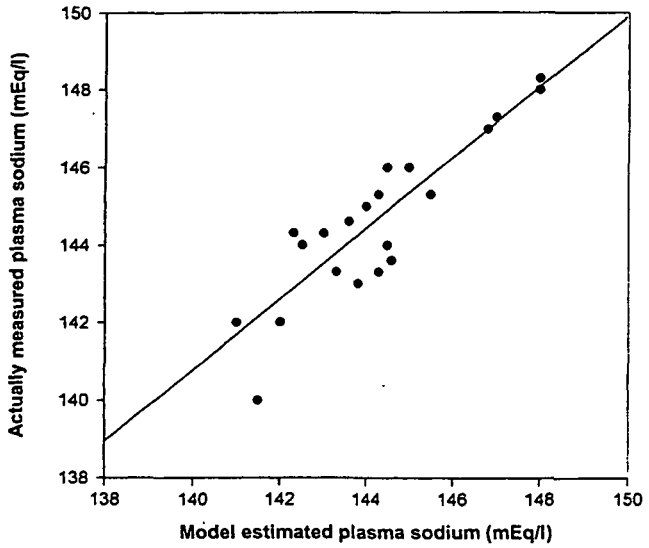


Fig. 6. Linear relationship between the intradialytic values of plasma sodium predicted by the control model and the values actually measured by standard methods ($n=23$, $r=0.88$, $P<0.0001$, SEM = 0.957 mEq/l).

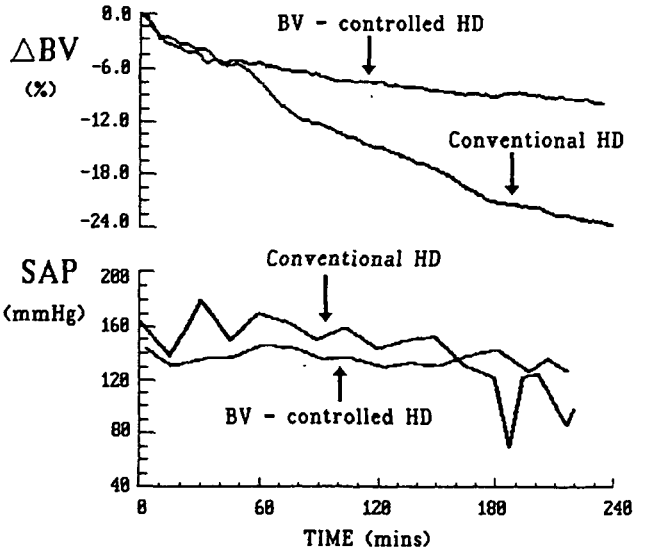


Fig. 7. Blood volume (BV) and systolic arterial pressure (SAP) trends during two different haemodialysis (HD) sessions in the same patient, and with the same weight loss. During conventional haemodialysis, the ultrafiltration rate and dialysate conductivity were constant throughout the treatment, and blood volume decreased about 24%. During blood volume-controlled haemodialysis, the ultrafiltration rate and dialysate conductivity were automatically changed in order to keep the blood volume variations as near as possible to the desired variation. The different blood volume behaviour is reflected in a striking difference in systolic arterial pressure.

sodium concentration values actually measured during dialysis and the ones predicted by the model is excellent ($r=0.88$, SEM = 0.957 mEq/l) (Figure 6).

With this system, which allows for the regulation of the blood volume profile according to a desired trajectory, it should be possible to prescribe an adequate ultrafiltration and a personalized intradialytic sodium balance. The possibility to smooth out the acute and sudden reduction in blood volume that can appear during dialysis, consequent to a transient imbalance in the patient's vascular refill capacity, should minimize the risk that the acute hypovolaemia might lead to an acute hypotension episode (Figure 7).

On the whole, the control of blood volume throughout haemodialysis can improve intra-treatment haemodynamic stability, at least in certain categories of patients. It remains to be seen whether this advantage can be maintained over the long term as well, and whether the personalization of the sodium balance coupled with an improved arterial pressure stability during haemodialysis is positively reflected in the patient's inter-dialytic well-being.

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