Continuous Blood Volume Monitoring and Ultrafiltration Control

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Continuous blood volume monitoring (CBVM) is believed to be a promising method for making the determination of patients' "dry weight" more objective, and ultrafiltration (UF) control more appropriate. Although blood volume response to UF and the interrelation between blood volume changes and changes in hemodynamic parameters are highly individual, certain principles of this response and interrelation can be identified and exploited for effective use of CBVM. The present work summarizes the authors' findings from practical CBVM application over the past 5 years and their opinions on the future development of this method.

Four distinct types of blood volume response to constant UF rate were identified: Type 1, flat line throughout the whole session; Type 2, flat line during the first part of dialysis, followed by a linear decrease during the remaining time; Type 3, linear decrease right from dialysis start; and Type 4, linear decrease first, followed by a flat line during the remaining time. The possibility of a shift from one type to the other was verified. Blood volume reduction due to UF was found to have a static and a dynamic component. The most important factors affecting both components were found to be, by sensitivity analysis of a three-pool kinetic model, degree of overhydration, vascular system compliance, and UF volume (for the static component); and UF coefficient of the capillary wall and UF rate (for the dynamic component).

Type 3 response, induced by more vigorous UF, was found to significantly decrease the volume of residual daily diuresis on the first postdialysis day. If confirmed, this finding may serve as a basis for the response type choice in patients with still significant residual renal function.

Exploitation of the existence of dynamic blood volume reduction component for the first generation of automated biofeedback UF controllers may be complemented by automated identification of patient's plasma refilling capacity and/or position of his/her point on the Guytonian pressure/volume characteristics curves, and thus may more advanced "intelligent" UF controllers be constructed in the future.

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Introduction

Management of fluid control in dialysis patients has traditionally been based on the concept of optimal "dry weight" (DW). However, correct determination of this parameter has also traditionally been considered critical in achieving adequate dialysis time. Overestimation of DW on a long-term basis contributes to hypertension. Underestimation, frequently leads to hypotensive episodes during dialysis. Due to the relatively short dialysis times used nowadays, patients may suffer hypotension far before they reach their optimal DW (see further the paragraph on dynamics of blood volume reduction). All this stimulates the search for an objective method of DW determination and fluid control management more than ever before.

As blood volume (BV) changes induced by ultrafiltration (UF) are by far the strongest stimulus of changes in hemodynamics during dialysis, continuous blood volume monitoring (CBVM), once made commercially available, was received by the dialysis community with great enthusiasm and expectation. The present article gives an overview of our findings and experience with this method in our unit over the past 5 years, and strives to provide a possible explanation of these findings, based on currently accepted physiological principles. In view of our current knowledge, the issue of automated UF control, based on biofeedback from a CBVM device, and its likely future development is also discussed briefly.

Physical principles and rationale of the CBVM method

The BV changes monitoring device used in our studies (Critline monitor, In-Line Diagnostics, Riverdale, UT, U.S.A.) evaluates relative BV changes from optically measured absolute values of hematocrit. Assuming the number of erythrocytes and their volume does not change during dialysis, one can write

$$Hct(0) * BV(0) = Hct(t) * BV(t) = const,$$

where Hct(0) and BV(0) denote Hct and BV at the beginning of dialysis, and Hct(t) and BV(t) denote the same parameters

at time *t* during dialysis. The equation can be rearranged to express the relative BV change

$$\Delta BV\ (\%) = 100 * [BV(0) - BV(t)]/BV(0)$$

$$= 100 * [Hct(t) - Hct(0)]/Hct(t).$$

Using the initial Hct value, Hct(0), stored in the memory, the instrument measures a new Hct value every 10 seconds and calculates the corresponding ΔBV (%) by means of the above equation.

As a matter of fact, the rate of BV change during dialysis reflects the balance between the applied ultrafiltration rate (UFR) and the plasma refilling rate (PRR):

$$dBV/dt = UFR - PRR.$$

If the PRR is able to compensate for the UFR there will be no change in BV. If not, BV will decrease. This indicates that *BV behavior gives information on the appropriateness of the UFR (not UF volume!)*. However, although the relation between BV changes and changes in hemodynamic parameters is causative in itself, it is influenced by a number of patient- as well as procedure-related factors.

Among patient-related factors, importance of the patient's hydration status was recognized long ago [1]. Of great importance is vascular system compliance, although this is a very complex parameter. Hemodynamic reaction to BV changes is also influenced by the patient's medication (vasodilating or heart inotropism influencing antihypertensives). Biochemical parameters such as plasma protein content [2], and biophysical parameters such as the UF coefficient of the capillary wall also play a role.

Among procedure-related parameters, the most important is the session time, which for a given UF volume goal defines the value of UFR. Thermal balance has been rather a neglected factor but there is growing evidence that it may be a very potent factor in preserving cardiovascular stability [3,4]. Choice of dialysate sodium, and/or sodium and UF profiling may also play a role.

Due to all the above-mentioned factors, the patient's reaction to UF-induced BV changes is highly individual. Yet it is possible to identify certain principles in the patient's response that enable us to interpret and exploit the information provided by the CBVM.

Typing of blood volume response to constant UFR

When applying constant UFR throughout the whole dialysis session as the simplest UF strategy, we have found that BV response can be classified into four distinct types (Fig. 1): Type 1, constant BV, that is, a flat line throughout the whole dialysis; Type 2, constant BV during the first part of dialysis, followed by a roughly linear decrease during the remaining time; Type 3, linear decrease with an individually variable slope right from dialysis start until the end; and Type 4, a linear decrease during the first part of dialysis, followed by a constant line until the end.

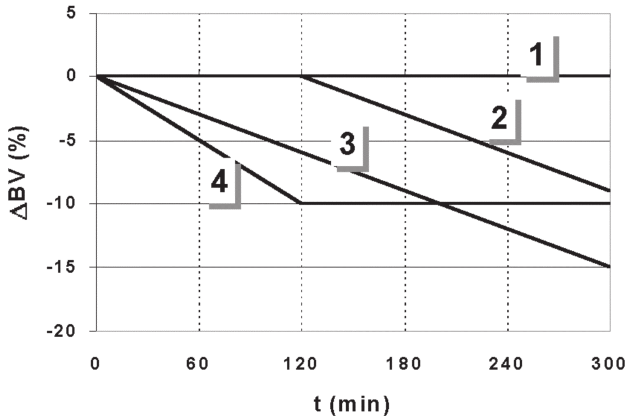

FIGURE 1 Types (1, 2, 3, and 4) of blood volume (BV) response to constant ultrafiltration rate. Horizontal axis indicates time during dialysis in minutes, vertical axis relative BV change (ΔBV) as a percentage of its value at dialysis initiation.

Figures 2 to 5 illustrate individual BV response types recorded during *in vivo* dialysis with the Critline device. The steep transient drop in BV at the flat part of BV response in Fig. 3 was caused by the patient's food intake – a typical phenomenon in most patients [5–7]. Sudden dips in the recordings in Figs. 2 to 5 are artifacts caused by short blood pump stops.

Both physiological and clinical interpretation of three of the above four types is clear to a great extent. In Type 1 (the flat line over the whole session), PRR is able to fully compensate for UFR due to fluid overloaded in the interstitial space. Using independent methods of hydration status assessment (whole-body, multifrequency bioimpedometry and ultrasound measurement of inferior vena cava diameter), we were able to prove that, clinically, Type 1 BV response indicates persistent overhydration [8]. At the start of CBVM use, this response type was seen in nearly one third of our patients; however, due to improved clinical management based on better understanding of fluid dynamics during hemodialysis, it is rarely seen today. Patients with Type 2 and Type 3 responses are certainly closer to their optimal DW. When the slope of the line begins to change due to lowered pressure gradient across the capillary wall, PRR is no longer able to fully compensate for UFR. However, the rate of BV change in response to a certain UFR, as well as the final ΔBV at a certain UF that an individual patient can tolerate without onset of hypotension, are highly individual. For Type 4 there is currently no generally accepted physiological and clinical interpretation. However, this response type is seen very rarely (in our recordings its occurrence was around 1%).

The BV response type can be changed from Type 1 via Type 2 to Type 3 merely by increasing the applied UFR, that is, by decreasing the patient's prescribed DW. We have also

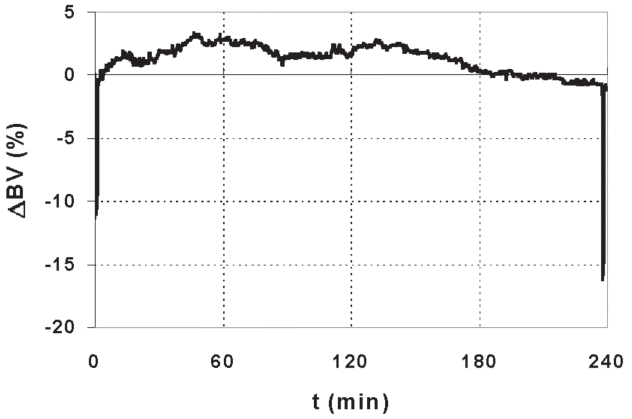

FIGURE 2 *In vivo* recorded example of Type 1 response. Horizontal axis indicates time during dialysis in minutes, vertical axis relative blood volume change (ΔBV) as a percentage of its value at dialysis initiation.

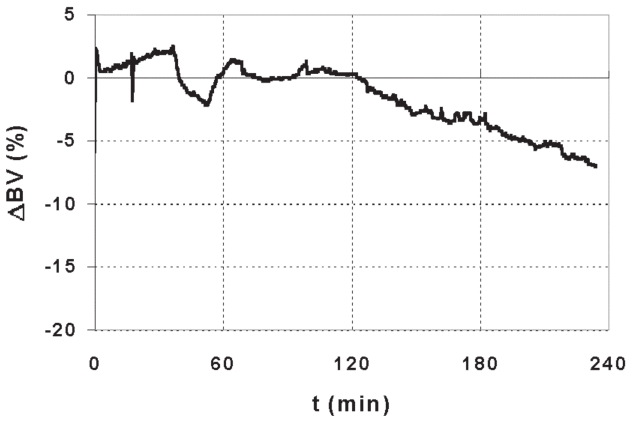

FIGURE 3 *In vivo* recorded example of Type 2 response. The steep transient drop in blood volume (BV) at the flat part of BV response between 40 and 60 minutes was caused by patient's food intake. The sudden dip at 20 minutes is an artifact caused by stopping the blood pump. Horizontal axis indicates time during dialysis in minutes, vertical axis relative BV change (ΔBV) as a percentage of its value at dialysis initiation.

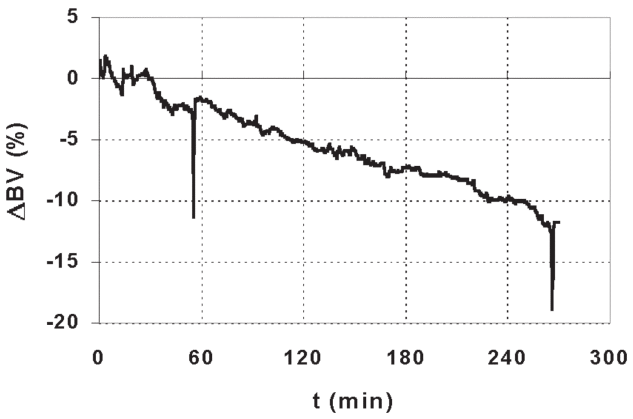

FIGURE 4 *In vivo* recorded example of Type 3 response. The sudden dips in the curve are artifacts caused by stopping the blood pump. Horizontal axis indicates time during dialysis in minutes, vertical axis relative blood volume change (ΔBV) as a percentage of its value at dialysis initiation.

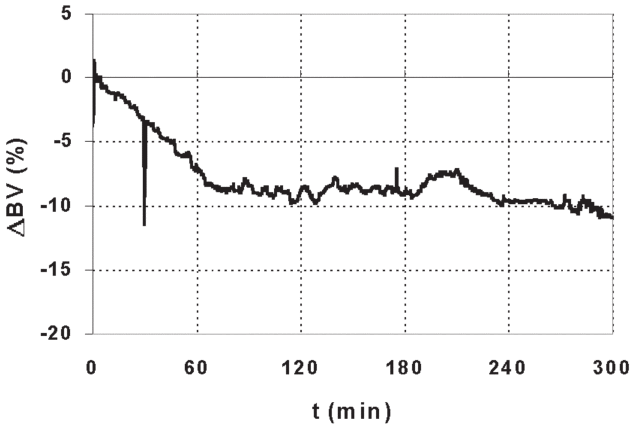

FIGURE 5 *In vivo* recorded example of Type 4 response. The sudden dip at 30 minutes is an artifact caused by stopping the blood pump. Horizontal axis indicates time during dialysis in minutes, vertical axis relative blood volume change (ΔBV) as a percentage of its value at dialysis initiation.

found that a shift from Type 3 to Type 2 response can be made by applying exponential sodium profile in dialysate (Fig. 6). A stable patient was first dialyzed against constant sodium and a reference response of Type 3 was obtained. During the second dialysis, with basically the same UF conditions, the exponential profile was applied and the patient responded with Type 2. The third dialysis was again performed with constant sodium and the patient returned to Type 3 response, very close to the original response.

Which blood volume response type? The "residual diuresis hypothesis"

While it is clear from the data in the previous paragraph that Type 1 response of BV is not to be strived for, it is less clear whether Type 2 or Type 3 should be generally preferred. In this respect, we have made an interesting finding [9]. On asking patients for their subjective feelings on different types of responses, repeated complaints of lowered diuresis during the immediate 24 hours post-dialysis were noted.

The daily diuresis was, therefore, recorded on the first, second, and third days of the interdialytic interval in a small group of patients (n = 10) dialyzed twice weekly because of significant residual diuresis (ranging from 600 to 1100 mL/day on the immediate predialysis day). By manipulation of their prescribed DW, these patients were shifted from a Type 2 to a Type 3 response, or *vice versa*, during this study. To accomplish this, changes of 0.5 – 1.0 kg

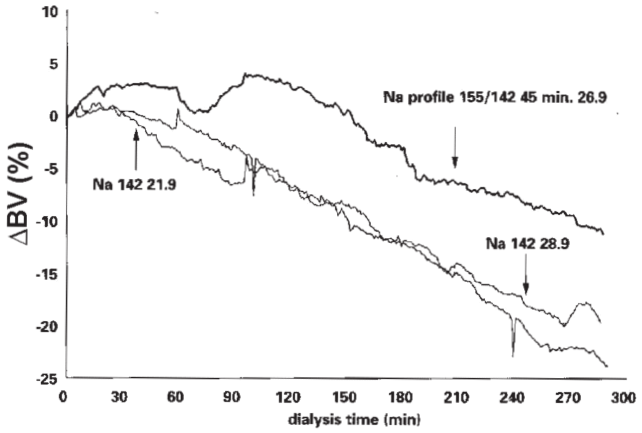

FIGURE 6 *In vivo* recorded example of change in blood volume (BV) response from Type 3 to Type 2 response due to exponential sodium profile. Horizontal axis indicates time during dialysis in minutes, vertical axis relative BV change (ΔBV) as a percentage of its value at dialysis initiation.

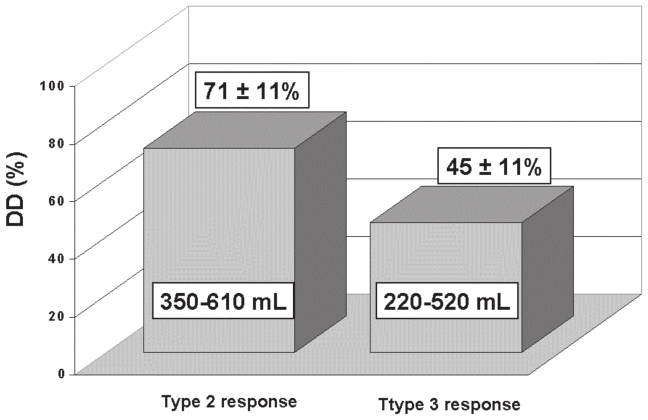

FIGURE 7 Evaluation of daily diuresis (DD) on the first postdialysis day.

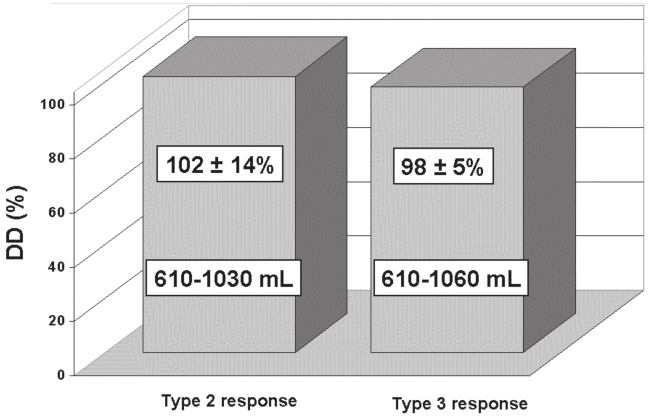

FIGURE 8 Evaluation of daily diuresis (DD) on the third postdialysis day.

were usually sufficient. While the mean daily diuresis on the first postdialysis day was 45% (220 – 520 mL) of the diuresis on the second day in patients with the Type 3 BV response (Fig. 7), it was over 70% (350 – 610 mL) in cases of Type 2 response. Daily diuresis during the third postdialysis day was about the same in both cases and did not differ significantly from 100%, that is, from the value of the second day (Fig. 8).

The latter finding suggests that the glomerular filtration reached maximum, and tubular reabsorption reached minimum, in residual nephrons on the second day. The drop in daily diuresis seen on the first postdialysis day may thus be attributed to lowered glomerular filtration and higher tubular reabsorption, induced most probably by lowered perfusion of the kidneys, which in turn could be attributed to lowered BV. Under otherwise comparable conditions, BV reduction is always higher in Type 3 response than in Type 2 response. Furthermore, it may be speculated that inappropriately high UF (underestimated DW) in some patients may contribute via this mechanism to accelerated loss of residual renal function after initiation of chronic dialysis, a phenomenon that has been reported from chronic hemodialysis programs, but is not believed to be the case in peritoneal dialysis. Should this be true, Type 2 would be preferred, at least in patients with significant residual renal function. However, since the above observation has been made on only a small group of patients, it will need to be confirmed in larger groups of patients.

What BV reduction and BV reduction slope? Dynamics of BV reduction

When assessing the issue of acceptable slope and end-value of BV reduction, it is necessary to realize that BV reduction at any moment in a dialysis session results from the sum of static and dynamic components. Dynamic component is that part of the BV reduction that levels out after stopping UF, while the static component is preserved.

The existence of both components is well documented in Fig. 9. The UFR was changed significantly twice during dialysis. In both cases, equilibration of the dynamic component of BV reduction followed, after which BV continued to decrease with a slope corresponding to the lower UFR.

It is difficult to understand BV dynamics from measured BV data alone because of the number of parameters involved. Therefore, a three-pool mathematical model (intracellular space, interstitial space, plasma) was devised including Guyton's nonlinear pressure/volume characteristics for the interstitial compartment [10]. The so-called sensitivity analysis of the model was then performed; that is, a series of repeated simulations of BV response was performed in which the value of only one parameter was changed in small increments, and the influence of this change on BV response behavior observed. Using this procedure, the most important

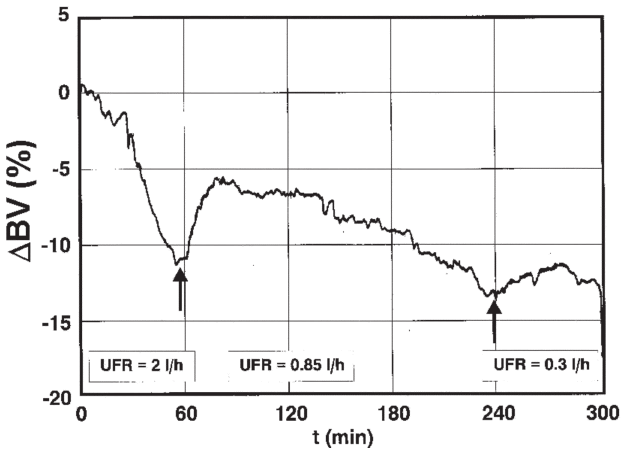

FIGURE 9 *In vivo* record of blood volume (BV) changes with expressed equilibration of dynamic component. The ultrafiltration rate (UFR) was significantly changed twice during dialysis. In both cases, an equilibration of the dynamic component of BV reduction followed, after which BV continued to decrease with a lower slope, corresponding to the lower UFR. Horizontal axis indicates time during dialysis in minutes, vertical axis relative BV change (ΔBV) as a percentage of its value at dialysis initiation.

patient- and procedure-related factors affecting both the static and dynamic components of BV reduction were identified.

For the static component, the two most important patient-related factors were compliance of the cardiovascular system (this may need refinement into several independent parameters in case of deeper analysis) and plasma protein content. Both of these factors also determine what portion of the interdialytic fluid overload will be stored in the plasma compartment, and what will go to the interstitial space. From the treatment-related parameters, the static component of BV reduction is determined by UF volume.

The dynamic component of BV reduction is, on the other hand, determined almost exclusively by capillary wall UF coefficient (KUF). However, only a few studies have addressed the issue of interindividual and intradialytic changes of this parameter [11,12]. Among the treatment-related parameters, the dynamic component of BV reduction is influenced by UF rate.

An example of a computer simulation visualizing the impact of vascular system compliance and capillary wall KUF in short and long dialysis is shown in Fig. 10. The influence of UFR is visualized by short and long dialyses performed with the same total UF, that is, with higher UFR for a shorter dialysis time. Because the same volume is ultrafiltered in both short and long dialysis, BV reduction after equilibration (i.e., its static component) is the same regardless of the value of KUF (see the two bottom curves for a patient with a compliant vascular system, and the two upper curves for a patient with a noncompliant vascular system, Fig. 10). Comparison of both short dialysis curves with long dialysis curves demonstrates the influence of UFR and KUF on BV rebound (i.e., dynamic component of BV reduction). Noteworthy also is the lower slope of BV reduction in the patient with a noncompliant vascular system compared to the patient with a compliant system, for both low and high KUF values. This is caused by a greater decrease in hydrostatic pressure in the noncompliant vascular system under the same UFR, resulting in faster mobilization of fluid from the interstitial space. The simulation assumed that the saline used for priming the extracorporeal circuit is discarded when filling of the circuit with blood begins. Blood volume thus lost from the vascular system to the extracorporeal system starts to be immediately compensated by refilling from the interstitial space, that is, total circulating BV tends to increase. This is counteracted by UF. Depending on the compliance of the vascular system and the KUF, the net change in BV immediately after dialysis starts may range from a steep decrease (see the bottom curve of the patient with a compliant system and low KUF under high UFR caused by short dialysis, Fig. 10), up to a transient increase over the initial value (the upper curve of the patient with a noncompliant vascular system and easy refilling from the interstitial space due to a high KUF).

The influence of biochemical factors, namely of the predialysis value of total plasma proteins (TPP) and of the intradialytic increase of plasma sodium (ΔCP_{Na}), was investigated using *in vivo* data in an unselected group of about 100 dialyzed patients [13]. Linear regression analysis of ΔBV/UF versus predialysis TPP and ΔCP_{Na}, respectively,

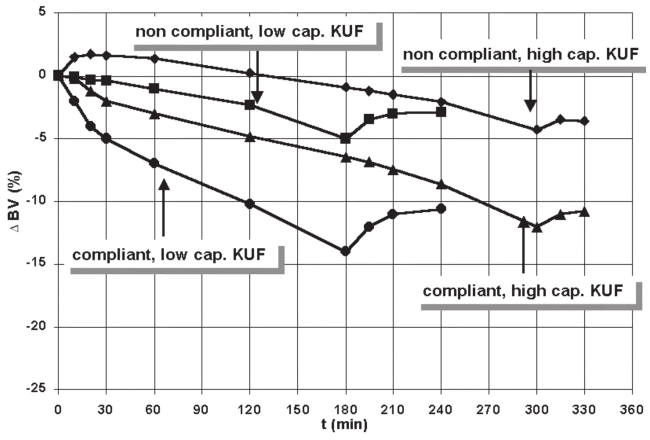

FIGURE 10 Examples of computer simulation of blood volume (BV) dynamics for two different values of vascular system compliance and ultrafiltration coefficient of capillary wall (cap. KUF). Under equal ultrafiltration rate, BV reduction is higher in the patient with compliant vascular system due to lower drop in hydrostatic pressure in vascular system with ultrafiltration, and thus less refilling from the interstitial space. Also, lower KUF causes higher BV reduction because of hindered influx of fluid from the interstitial space. Horizontal axis indicates time during dialysis in minutes, vertical axis relative BV change (ΔBV) as a percentage of its value at dialysis initiation.

provided the following data:

- A difference of 10 g/L in predialysis TPP increases BV reduction under otherwise comparable conditions by 1.44 percentage points per 1 L of UF. (The predialysis TPP value in the group ranged from 56 to 77 g/L, and the range of applied UF ranged from 0.5 to 3.5 L per session.)
- Similarly, an intradialytic increase in plasma sodium of 5 mmol/L will diminish the total BV reduction by about 1 percentage point. (Intradialytic plasma sodium level changes seen in the group ranged from 1 to 9 mmol/L.)

The figures of 1.44 percentage points per 10 g/L difference in TPP and 1 percentage point per 5 mmol/L increase in plasma sodium level are, however, merely averaged statistical data, and as such should be applied with caution in an individual. Smaller transient changes may appear on the CBVM record in response to some situations or maneuvers during dialysis (change in position, food intake, etc. [5,7]).

Automated CBVM-based UF control

Although current knowledge of BV dynamics and its relation to cardiovascular stability is far from complete, it has proven to be sufficient for construction of the first generation of automated UF controllers (Hospal SA, Lyon, France; Fresenius AG, Bad Homburg, Germany). These controllers are based on a trial-and-error approach to determine maximal permissible BV reduction [14] at which the patient becomes symptomatic, and on the existence of the dynamic component of BV reduction. The patient is vigorously ultrafiltered until the allowed ΔBV limit (set by a safety margin above the maximal permissible BV reduction determined previously) is reached. At that moment UF is automatically switched off and BV is allowed to equilibrate for a few percentage points. As soon as the preset increase is reached, UF is switched on again, and so forth. These automatic controllers have already been approved for marketing and clinical use [for instance by the German Testing Association (TÜV)].

Future "intelligent" UF controllers with biofeedback can be expected to include more advanced features. The current CBVM devices give merely a relative value of BV reduction. Should the absolute value of BV be known, a patient's plasma refilling capacity at any moment during dialysis could easily be evaluated. This seems to be accomplishable by means of evaluation of BV response to a stepwise change in UFR [15]. Although not enough is known currently on PRR changes during dialysis, a certain relation to patient hydration status can reasonably be expected. A technically very "clean" and tempting solution for an intelligent UF controller is automated detection of a "patient's point" on the Guytonian pressure/volume curves [10]. This would enable us to follow a patient's shift from the edematous part of the characteristics to the normohydrated part, and stop UF prior to entering the hypohydration region. Such a device could presumably work even without an *a priori* estimated value of DW.

Another promising concept is represented by mathematical models describing the relationship between fluid volume changes in the organism and its hemodynamic response [16,17].

Conclusions

CBVM is an extremely useful tool for investigating factors contributing to hypovolemia-induced intradialytic hypotension. At present, the method enables unambiguous detection of overestimated dry weight. Basic BV response typing has been revealed, and the most important factors affecting both the static and the dynamic components of BV reduction were identified. Although the first generation of CBVM-based UF controllers still need an *a priori* estimation of dry weight, application of more advanced control and modeling techniques may do away with this "traditional need" of dialysis treatment strategy in future generations of intelligent UF controllers.

Acknowledgment

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