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Impact of biofeedback-induced cardiovascular stability on hemodialysis tolerance and efficiency

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Impact of biofeedback-induced cardiovascular stability on hemodialysis tolerance and efficiency.

Background. Hypotension is caused by a drop in blood volume during ultrafiltration, followed by vasoconstriction and reduced perfusion in some regions of the body.

Methods. We carried out a prospective controlled crossover study on 12 hypotension-prone patients with two different modalities: (*A*) acetate-free hemodiafiltration with standard ultrafiltration control, and (*B*) acetate-free hemodiafiltration with monitoring of blood volume and automatic biofeedback with machine-driven adjustments on ultrafiltration and dialysate conductivity. We measured urea Kt/V and equilibrated Kt/V (eKt/V), urea rebound, and urea removal. Hypotensive episodes and interventions were recorded.

Results. In group B, fewer hypotensive episodes were recorded (24 out of 72 in group B vs. 59 out of 72 in group A). Saline infusion was required in 57 cases in group A and 15 cases in group B. Urea Kt/V was 1.34 ± 0.08 in group A and was 1.26 ± 0.06 in group B; eKt/V was much higher in group B (1.12 ± 0.05) than in group A (1.03 ± 008). A significantly higher rebound was observed in group A (14.2 ± 2.7%) compared with group B (6.4 ± 2.3%).

Discussion. A greater solute sequestration seems to occur during hemodialysis with hypotension. This results in lower eKt/V, enhanced postdialytic rebound, and lower solute removal. Higher efficiency can be observed when dialysis is carried out smoothly and cardiovascular stability is maintained. We conclude that new systems for blood volume monitoring and automatic biofeedback may not only reduce the number of hypotensive episodes during dialysis, but may also contribute to significantly increase the efficacy of the treatment.

The ultimate goal of hemodialysis treatment is to achieve the highest level of efficiency in the presence of maximal clinical tolerance [1–12]. In recent years, reduced treatment times have resulted in higher ultrafiltration rates, thus enhancing the problems of patient tolerance to hemodialysis and the possibility of maintaining adequate dry body weight [13]. At the same time, studies on urea kinetics have demonstrated the importance of solute volume distribution calculation and possible double-pool effects [14–17]. It has been frequently observed that solute mass recovered in the spent dialysate is smaller than that one could expect based on changes of blood concentration in the patient. This phenomenon has been attributed to an apparent distribution volume for urea that is smaller than real [17–19]. Since transcellular equilibration for urea is almost instantaneous, it seems that intracellular trapping of urea is unlikely to be the primary factor involved in this phenomenon. Thus, this observation seems to depend on a very efficient solute removal from a smaller portion of the whole distribution volume deriving from an altered blood flow distribution in several regions of the body [20–29]. As a final consequence, postdialytic rebound of urea concentration takes place depending on the equilibration of urea between the sequestrated pool and the effectively dialyzed pool.

This mechanism may limit the efficiency of the treatment with an importance proportional to the size of the sequestrated pool. It has been suggested that vasoconstriction caused by hemodialysis and ultrafiltration may be the key factor in reducing the perfusion of some regions of the body where urea can therefore be sequestrated. Thus, an intracorporeal recirculation of dialyzed blood takes place in a central vascular loop, while peripheral regions remain poorly perfused with a progressive discrepancy between the content of urea in the two pools. Under these circumstances, hypotension may further affect tissue perfusion because of compensatory vasoconstriction. In a previous article, we observed that hypotension-prone patients present high urea rebound and lower equilibrated Kt/V [13]. From this viewpoint, efficiency of hemodialysis and clinical tolerance appear to be linked by a common denominator, which is tissue perfusion and vascular stability.

Intradialytic hypotension has been correlated with the

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rate of ultrafiltration and relative blood volume (BV) changes [30]. The reduction of circulating BV (ΔBV) depends on the discrepancy between the ultrafiltration rate and intravascular refilling rate [31, 32]. Today, there is the possibility of monitoring online relative BV changes using several methods, such as light absorption or scattering. Despite a large variability, most patients display a threshold for BV reduction; beyond this value, there is a high chance of hypotension. The curve of BV change may be used in an integrated system to drive the rate of ultrafiltration during treatment in the attempt to prevent hypotension. Further improvements may be obtained if a variable sodium concentration is applied to the dialysis solution [33, 34].

Based on these premises, we may hypothesize that hemodialysis carried out with "guided" ultrafiltration profile and variable dialysate sodium (driven by ΔBV) may not only result in better clinical tolerance but also in a higher treatment efficiency. The last effect should be caused by a reduced solute compartmentalization and a reduced rebound effect.

The aim of our present study was to evaluate the impact on vascular stability and treatment efficiency of a new biofeedback system characterized by online BV control through instantaneous corrections of ultrafiltration rate and dialysate conductivity (DC). For this purpose, a series of hemodialysis sessions carried out with and without a biofeedback loop was compared in the same chronic hemodialysis patients.

METHODS

Study design

This was a prospective, randomized, crossover study carried out on 12 hypotension-prone patients (8 males and 4 females) for a total of 144 hemodialysis sessions that used either standard controls (schedule A) or a biofeedback system (schedule B).

Population

Patients were on hemodialysis for more than six months at the beginning of the study, and all had a well-functioning internal arteriovenous (AV) fistula. Their ages were between 35 and 72 years, and body weights varied from 45 to 94 kg. All of them were recruited on the basis of the clinical history recorded over the previous month. The selection criteria were the following: presence of symptomatic hypotension in more than 70% of the last 12 sessions, interdialytic weight gain greater than 3 kg, and normal hydration status as determined by a bioelectrical impedance analysis. All of the patients were treated with acetate-free biofiltration, one of the most sophisticated types of hemodiafiltration, characterized by the absence of acetate in the dialysate and a complete correction of buffer balance by postdilutional infusion of bicarbonate-based replacement solution [35].

Treatment schedules

Schedule A was as follows: acetate-free biofiltration, blood flow of 350 mL/min, dialysate flow of 500 mL/min, using an automatic ultrafiltration control system and manual adjustment of ultrafiltration rate if required throughout the session. Schedule B was as follows: acetate-free biofiltration carried out with the same parameters plus a biofeedback-driven automatic adjustment of ultrafiltration rate and dialysate conductivity (Hemocontrol™, Hospal, Mirandola, Italy).

The scheduled time for both sessions was 220 ± 5 minutes. Each patient was studied for four weeks. Each treatment schedule was carried out for two weeks (6 sessions) and the, AB – BA sequence was randomized in each patient.

Measurements

Urea concentration was measured in blood before, at the end, and after 30 minutes from the end of the session. Single-pool Kt/V, postdialytic rebound, equilibrated Kt/V, and urea mass removed were calculated using the formulas reported in the literature [29]. Urea mass removed was measured by continuous partial collection of spent dialysate with a specifically designed device [Quantiscan™ (QTSC), Hospal, Mirandola, Italy]. In the first 30 sessions, a parallel measurement was performed by total collection of spent dialysate [direct dialysate quantification (DDQ)] to obtain a validation of the QTSC method.

Recruitment and clinical assessments

Preliminary assessment was done with bioelectrical impedance to ensure an adequate patient hydration status. Once the hydration parameters resulted within normal values, the patient was recruited for the study after obtaining informed consent. The study was also licensed by the local ethical committee.

Hypotension episodes, symptoms, and medical or nursing interventions during each hemodialysis session were carefully recorded. Effective treatment duration and total weight loss were also recorded. Hypotension was defined by a drop in systolic blood pressure of greater than 40 mm Hg from the starting value or by a lower drop in the presence of symptoms. We reported the number of dialysis sessions with hypotension over the total number of dialysis sessions analyzed. Dialysis with hypotension was considered in those sessions in which at least one episode of hypotension was detected.

Study end points

The end points of the study were the following: (*1*) difference in cardiovascular stability measured by the

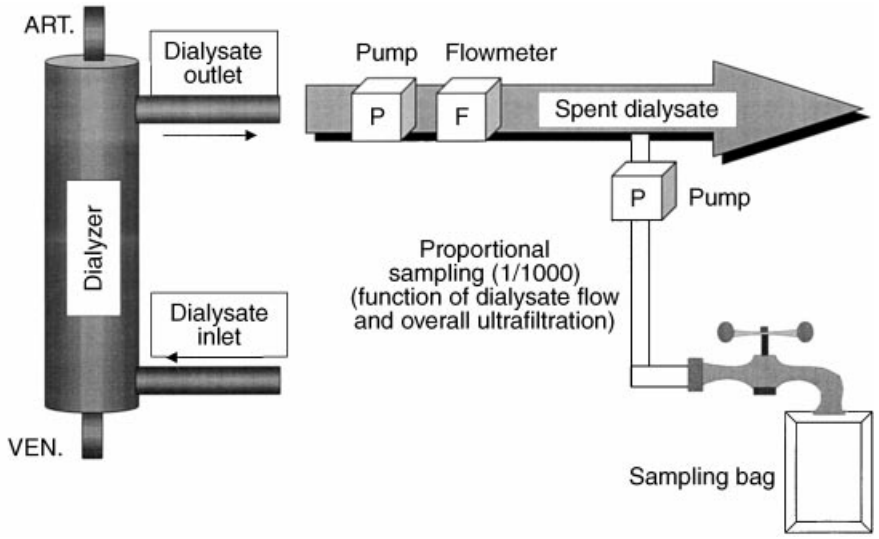

Fig. 1. Schematic representation of the system for partial dialysate collection. A continuous proportional spilling is made from the line of the spent dialysate. The quantity is regulated by a pump, and it is scaled down from the spent dialysate flow, which includes the amount of ultrafiltration. The system can collect a fraction of the total spent dialysate flow. In such a manner, the collected liquid will be representative of the whole, thus giving the physician the possibility to make any sort of analysis.

number of intradialytic hypotension episodes, symptoms, or medical-nursing intervention; and (*2*) differences in urea kinetics measured by single-pool Kt/V, postdialytic rebound, equilibrated Kt/V, and urea mass removed.

Paired *t*-test, linear regression test, and the Bland Altman test were used to analyze the obtained data.

Technological details

Continuous partial collection of dialysate. The system utilized in the study is designed to collect a fraction of the total spent dialysate. The proportional sample collected permits calculation of the total amount of spent dialysate and its average solute concentration. Thus, total solute removal can be calculated without the need to collect enormous amounts of fluid.

The system is composed of a sampling peristaltic pump, fully integrated into the machine, that draws a fraction of spent dialysate at a very low flow rate [in accordance with the dialysate flow rate, weight loss rate (WLR), and infusion flow rate settings] into a plastic bag (Fig. 1). During the collection, the sampling flow (Qs) is computed by the following formula:

$$Qs = K * (Qd + Quf + Qd)$$

where K is a coefficient in accordance to the dialysate flow rate (at 500 mL/min K = 1/1000).

The functioning principle is based on the high stability and accuracy achieved by the flow control system on the dialysis machine and on the stability of the sampling peristaltic pump over a dialysis treatment period. The system maintains its accuracy with dialysate flow rates between 350 and 1000 mL/min. Dialysate flow rate and Qs stability are guaranteed by the manufacturers with a variability of less than 1%.

The system measures waste dialysate volume (WDV) and collection time (CT), and transfers the information on the machine's screen. Solute concentration (SC) can be measured in the collected fluid (mmol/L), allowing the calculation of solute mass removed (SC × WDV, mmol).

Our study used the system in an automatic mode: The sampling pump automatically ran to obtain the representative sample of the waste dialysate considering the settings of the treatment and any subsequent variations in the scheduled parameters, including dialysate bypass, alarms, and others.

Biofeedback system. This system is a software loop designed to actuate a biofeedback response based on signals derived online from the patient/machine complex. The integrated multi-input-multi-output controller and its software are the heart of this biofeedback system. The main targets that are involved are weight loss, equivalent conductivity and ΔBV. The monitored discrepancies between the instantaneous value and the instantaneous target for BV change, conductivity, and weight loss represent the input parameters for the controller. The control variables utilized as outputs parameters are the dialysate conductivity (DC) and weight loss rate (WLR; Fig. 2).

Starting from the integrated monitoring of BV, based on an optical absorption biosensor (Hemoscan™; Hospal, Mirandola, Modena), the system can read and manage this physiological parameter, as it is linked to the removed water and to the physiological refilling of the patient.

After a learning phase for any single patient to understand the standard morphology of the BV curve, the target for this parameter can be set from the beginning of the session, and be included in the prescription of the treatment.

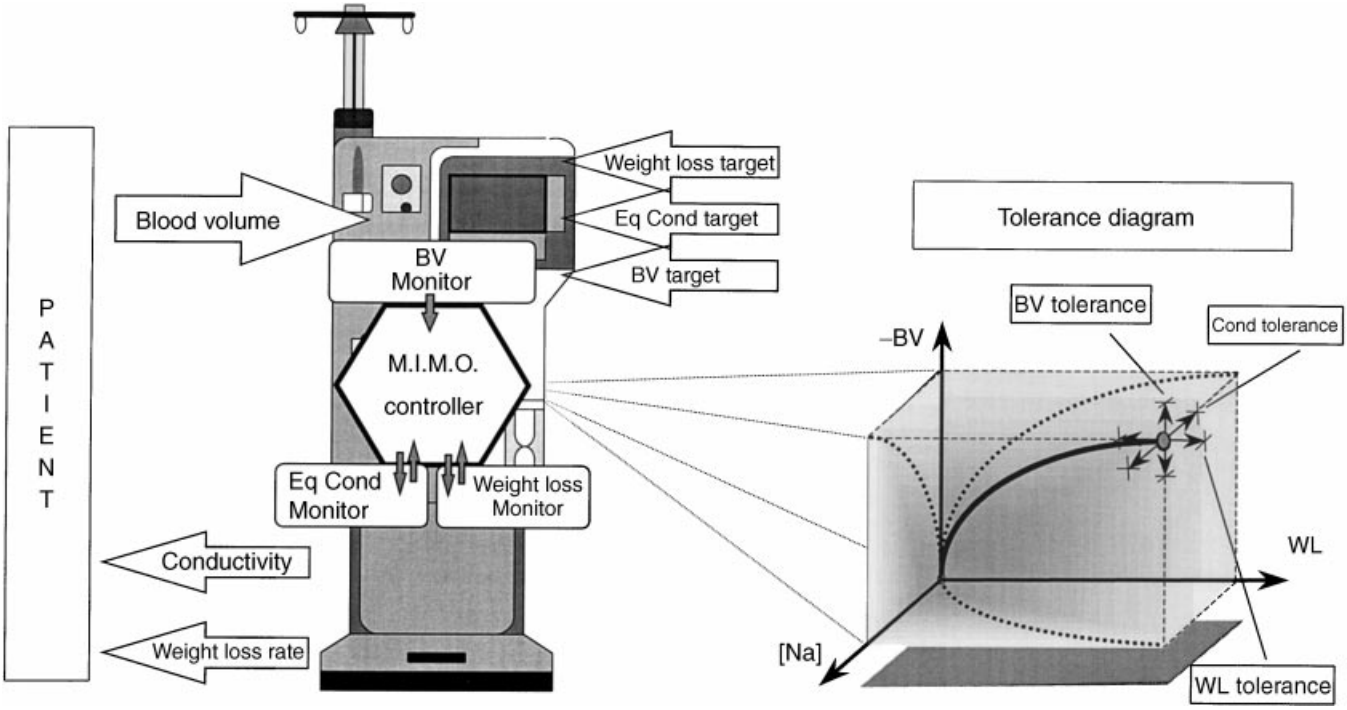

Fig. 2. Schematic representation of the multi-input–multi-output control system that characterizes the biofeedback loop. Starting from an integrated monitoring of BV, based on a optical absorption biosensor, the system can read and manage this physiological parameter, linked to the removed water and to the physiological refilling of the patient, that is known as one of the most important in the genesis of the intradialytic hypotension. This means that after a learning phase for any patient of the BV curve, it is possible to find a target for this parameter and include it in the initial prescription of the treatment. Beyond the weight loss target and the equivalent conductivity (Na) target, we have now the BV target that will be managed through a closed loop system. The integrated multi-input–multi-output controller and software are the heart of this biofeedback system: It can accept different monitored variables like inputs (in this case 3) and can have different control variables like outputs, in this case 2, DC and WLR. The goal of this biofeedback management is to reach the best compromise among the multiple targets of the treatment.

Hence, besides the target weight loss and the target equivalent conductivity (that is, the desired sodium concentration at the end of the session), the target BV can be prescribed. This is managed through the closed-loop biofeedback system.

The goal of biofeedback management is to reach the best compromise among the various targets, considering that these target values (given as inputs) can be in conflict one against the others. To correct a large BV change, one solution could be to reduce WLR, but this cannot be done below certain limits without indefinitely prolonging the duration of the session. On the other hand, increasing the dialysate sodium in an attempt to obtain higher refilling rates is also limited by physiological ranges and the consequent sense of thirst of the patient.

Within the operative logic of the artificial kidney, the three main parameters (BV, plasma sodium, and weight loss) are driven through a precise curve during the treatment aiming at the best compromise among the three targets; this operation is performed with a given range of tolerance for each parameter. This is a safety feature of the monitor that reacts with specific alarms and information to the operator when the prescribed compromise cannot be achieved.

Starting from the numeric values of each target given as an input, the system automatically designs the trajectory for each single target, considering the range of tolerance. In detail, by combining the WL and the BV trajectory in a bidimensional domain, a graphic description of the instantaneous condition of the treatment can be obtained, which illuminates whether the prescribed targets will be reached (Fig. 3). At the same time, the graph shows the distance to reaching the target values and how the initial prescription can be modified to achieve each goal. All of these graphs and information are displayed on the machine monitor (Fig. 4).

RESULTS

In the presence of similar ultrafiltration rates and required weight losses, the cardiovascular tolerance was significantly improved in the biofeedback-driven sessions. In particular, the number of hypotension episodes was significantly lower with the biofeedback system, and the symptoms were markedly reduced even in the case of hypotension. In Table 1, the hemodialysis parameters relevant to ultrafiltration and the clinical parameters pertaining to the cardiovascular response to ultrafiltration

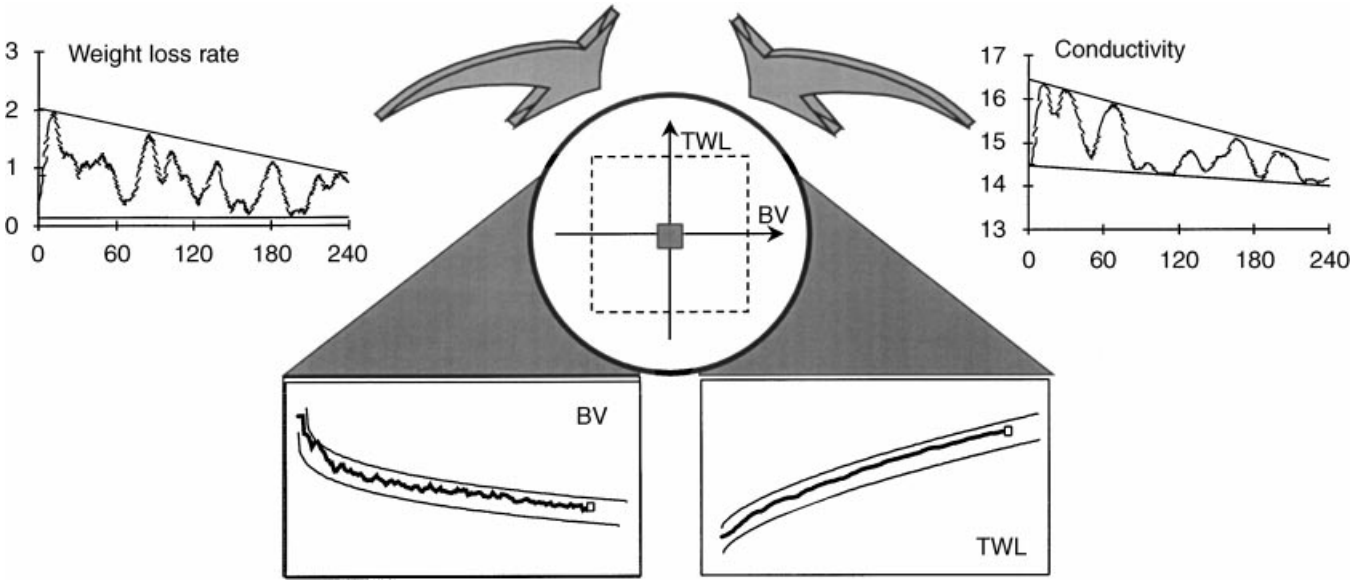

Fig. 3. Starting from the numeric target that we give like input, the system automatically designs the trajectory for each single target, considering also the tolerance. Combining the WL and the BV trajectory, we can observe during the session a kind of cruciform graph inside which the graphic bullet tells whether the final target can be reached and how far we are from it. To drive the BV, the machine controls minute by minute the two control variables that are the WLR and the conductivity.

are reported for the two modes of dialysis. Because the target of the system is to provide a hypotension-free dialysis session, the results are reported describing the number of sessions with clinically relevant hypotension compared with the total number of studied dialysis sessions. It should be emphasized that the overall weight loss and the rate of ultrafiltration did not differ between the two dialysis modes. In contrast, the number of hypotensive episodes decreased significantly with the use of biofeedback. A general well-being was recorded in sessions carried out with biofeedback, and surprisingly, even in the presence of hypotension, the patients displayed a reduced symptomatology and required less medical or nursing intervention. These results are probably correlated with a progressive correction of the BV variations by an immediate variation in the rate of ultrafiltration and DC in the biofeedback-driven sessions. This, in turn, may result in a less dramatic alteration of the intravascular filling pressure and permitted easier adaptations of the vascular tone to such conditions.

The effects of the achieved cardiovascular stability were paralleled by an improved efficiency of treatment. A lower rebound was observed in the biofeedback sessions, resulting in a higher equilibrated Kt/V. In Table 2, the urea kinetic parameters are displayed for the two dialysis modes. Single-pool Kt/V was higher in the sessions carried out with the standard controls. At the same time, probably because of the high frequency and the severity of hypotension, postdialytic rebound for urea was also higher in this dialysis mode. These data were associated with a significantly higher equilibrated Kt/V in the sessions carried out with biofeedback. Therefore, despite an apparently higher efficiency in the manually controlled sessions (group A), the real efficiency was superior in the biofeedback-driven sessions (group B). The explanation of this observation lies in the artificially small urea distribution volume observed in sessions with hypotension. As the blood purification process could only have access to a reduced volume, urea remained sequestrated in high concentrations in peripheral regions. As a result, urea concentrations fell remarkably during treatment, but a significant rebound was observed in the minutes following the end of the session. This phenomenon can explain the results obtained in terms of urea removal in the two groups of sessions. Solute removal results from the product (clearance $\times$ concentration). In the presence of similar clearances but different apparent distribution volumes, the amount of solute removed will be lower in the treatment in which blood concentration displays a greater reduction.

In our study, total urea removed in the two groups was significantly different (Table 2). The accuracy of total removal measured by partial dialysate collection (QTSC) was demonstrated by its high coefficient of correlation ($r = 0.982$, $P < 0.0001$) with the measure obtained by total dialysate collection (DDQ). The statistical comparison of the two methods, carried out with the Bland Altman test, is reported in Figure 5.

Instantaneous urea clearance measured in the two dialysis modes did not differ significantly, with an average

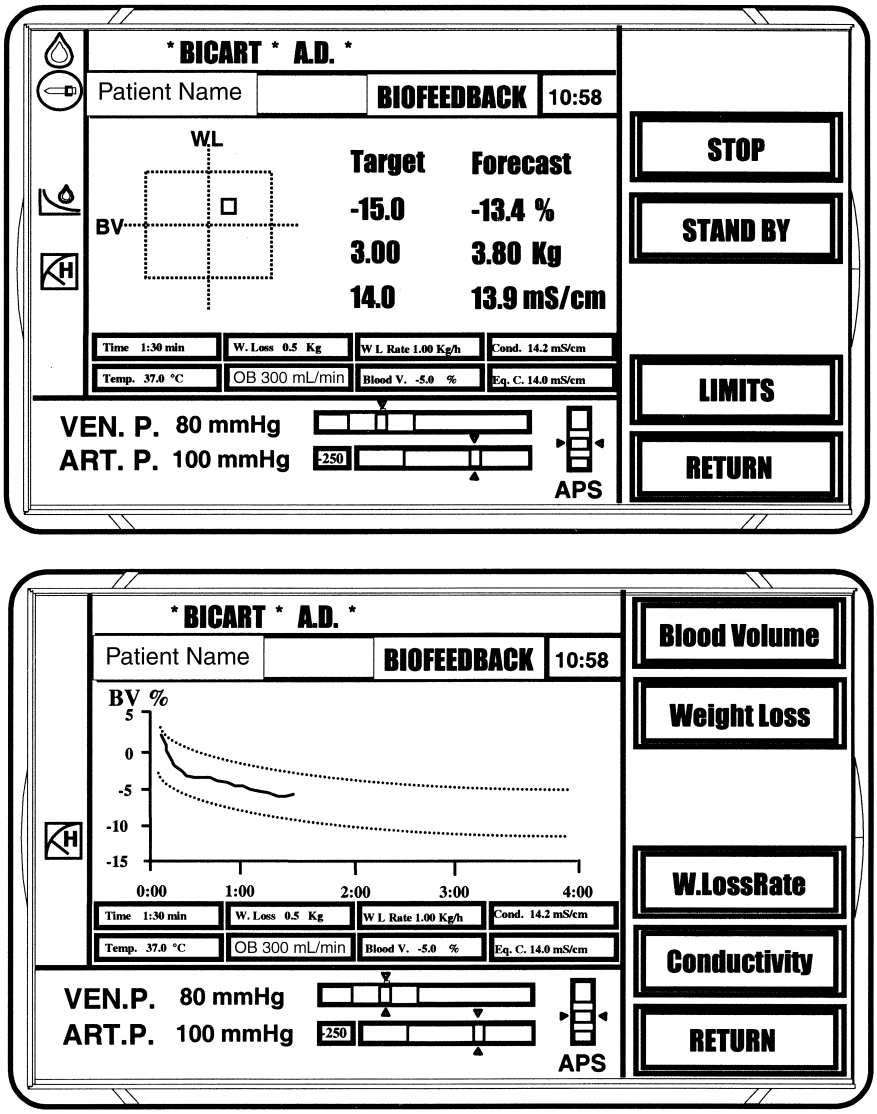

Fig. 4. An example of two typical screens during a biofeedback guided hemodialysis session. In the top panel, the detailed trajectory for BV and WL and the curve of WLR and conductivity show how the system works in relationship to the relative tolerances and limits. In the bottom panel, numerical and graphical representations give practical and clinical information on the screen about the parameters involved in the biofeedback loop.

Table 1. Cardiovascular tolerance

	Standard	Biofeedback	*P*
Weight loss/session *g*	3646 ± 684	3710 ± 710	NS
Ultrafiltration rate *mL/min*	16.6 ± 3.6	16.9 ± 3.7	NS
Hypotension episodes	59/72	24/72	< 0.001
Presence of symptoms	55/72	15/72	< 0.001
Interventions/infusions	57/72	15/72	< 0.001

Table 2. Urea kinetics

	Standard	Biodfeedback	*P*
Single pool Kt/V	1.34 ± 0.08	1.26 ± 0.06	< 0.005
Equilibrated Kt/V	1.03 ± 0.08	1.12 ± 0.05	< 0.001
Urea rebound %	14.2 ± 2.7	6.4 ± 2.3	< 0.001
Urea removal *g*	30.4 ± 4.1	35.4 ± 3.7	< 0.005
Solute removal index	1.77 ± 0.15	2.01 ± 0.23	< 0.005

value of 200 ± 18 mL/min in group A and 204 ± 19 mL/min in group B. The predialysis urea concentrations were almost identical for each patient in the studied sessions with the two dialysis modes (90 ± 18 mg/dL in group A and 91 ± 20 mg/dL in group B). These data suggest that differences in total solute removal are only due to a different profile of solute concentration in the blood during the treatment. The removal values were also normalized by the amount of solute present in the body at the beginning of the session. The resulting values calculated in a weekly period (solute removal index) were significantly higher in the biofeedback-driven sessions.

DISCUSSION

The primary goal of hemodialysis is to achieve an adequate blood purification and dry weight control with

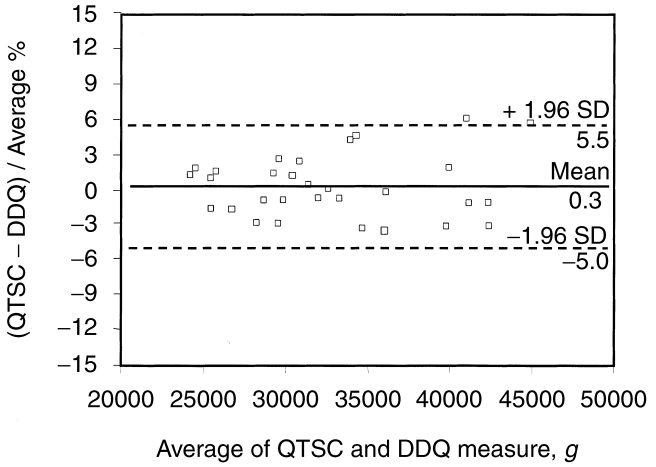

Fig. 5. Quantiscan measure of urea mass removal versus direct dialysate quantitation (total dialysate collection). Comparison of the two methods is shown.

the highest degree of clinical tolerance and patient well-being. In the past, these two aspects were frequently considered separate and independent variables. In our article, we suggest that cardiovascular stability and treatment efficiency can, at least to a certain extent, be definitely linked.

Two events have modified the scenario of dialysis therapy over the past decade: the progressive increase in the population of aged patients with concurrent morbid conditions (such as cardiovascular diseases, diabetes, etc.), and the substantial increase in dialysis efficiency and efficacy [36, 37]. These two events are neither easy to reconcile, nor are they compatible. Aged and critically ill patients are unstable and prone to dialysis-related cardiovascular intolerance. On the other hand, high-efficiency dialysis, particularly if associated with short treatment times, is more unsettling and less well tolerated compared with less aggressive therapies.

All of these phenomena, together with the understanding that each patient may present specific requirements and needs, suggested the prescription of an individualized hemodialysis treatment. In several cases, however, treatment personalization was not sufficient to achieve satisfactory results, and further technological advancements had to be planned. Starting from this requirement, the concept of treatment profiling emerged in the dialysis scenario. Patients may undergo physiological variations during the treatment, and the dialytic parameters set at the beginning of the session may not be adequate after a few hours of therapy. Hence, specific software programs have been designed to preset variable profiles of ultrafiltration and dialysate sodium concentration. Very soon, however, this approach displayed its limits, and the success was lower than expected. The limit of treatment profiling in fact lies in the blind nature of the prescription, which is designed a priori and is based on physiological assumptions. The requirement for online monitoring of physiological signals soon became evident [38–44].

During dialysis, patient assessment is normally limited to occasional measurements of body weight and blood pressure, with therapeutic intervention only upon the appearance of symptoms or side effects. A more perceptive patient monitoring from a biochemical and physical standpoint might enable the early recognition of signs of intolerance and might permit an early intervention.

Today, online monitoring is possible for different parameters, such as conductivity, urea kinetics, BV changes, thermal balance, and access recirculation [45, 46].

For some time, online monitoring devices had been considered mere toys for advanced research rather than real tools for routine clinical application. Today, several of these new devices are increasingly displaying their clinical utility. At the same time, the advances in technology permit a reduction in the cost of these important and sophisticated accessories. It seems, therefore, that a new generation of dialysis machines will be incorporating different sensors and online monitoring devices. The subsequent step is the generation of a smart dialysis machine able to mimic what happens in nature where rapid feedback occurs in response to physiologic signals. With this perspective, an automatic biofeedback loop has been proposed to improve dialysis tolerance [47]. In an attempt to prevent the occurrence of dialysis hypotension, signals such as BV changes and conductivity measures have been integrated in a multi-input controller capable of providing, via software, a series of output signals that result in variations of the treatment parameters. Corrections are practically effected by changes in the rate of ultrafiltration and in the dialysate inlet conductivity. Instead of waiting for a manual feedback operated by the nurse, the multi-input–multi-output controller tends to reach the selected target of intradialytic weight loss and maximal tolerance by a continuous compromise between ultrafiltration, conductivity, and actual weight loss. This article presents our experience with this type of automatic biofeedback in multiple sessions.

The present study demonstrates the efficacy of a biofeedback system in reducing the rate of intradialytic hypotension in hypotension-prone patients. Even in the presence of hypotension, patients experienced remarkable well-being and fewer symptoms in sessions carried out with biofeedback. Improved cardiovascular stability has a positive impact on urea kinetics and treatment efficiency. In particular, because of a reduced solute compartmentalization and a better blood flow distribution within the body, urea rebound is reduced, and equilibrated Kt/V is improved. At similar levels of predialysis urea concentration and fluid gain, the amount of urea removed is increased because of a steadier blood concentration throughout the session. Blood temperature was

only monitored as it is done routinely to detect significant prepost hemodialysis variations. The system unfortunately does not include a noninvasive blood temperature monitor, and therefore, thermal balance could not be measured. It has been suggested that improved vascular stability can be observed when neutral thermal balance is achieved or even more when the temperature of dialysate is reduced. In hemodiafiltration, a further component concerning temperature may monitor the infusion of replacement solutions at room temperature. This may have a beneficial impact on hemodynamic stability; however, it should be noted that sessions carried out with biofeedback and sessions carried out without biofeedback were performed in the same room and in the same patients. Therefore, there is no reason to expect a significant variation in the thermal balance in the two treatment modalities. It seems, however, that the integration of a blood temperature monitor in the system could present some further advantages.

New horizons may be seen from the present results, and newer options for combining cardiovascular stability and treatment efficiency can be undertaken thanks to the emerging technology in the field of hemodialysis.

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