

# Ultrafiltration and dialysate conductivity biofeedback in the prevention of dialysis-related hypotension

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## ABSTRACT

The progressive increase in mean age and comorbidity in chronic haemodialysis (HD) patients (especially those with cardiovascular diseases and diabetes) has significantly worsened patients' clinical status and tolerance to dialysis treatment. Moreover, constraints on resources (both economic and human), along with the need for shorter treatment times, have increased the risk of haemodynamic instability as well as inadequate dialysis.

In traditional dialysis session management, setting predefined treatment parameters, with active therapeutic interventions only in the event of complications, is definitely unsuitable for short-lasting treatments, often complicated by haemodynamic instability, especially in critically ill patients.

The first step towards improving dialysis session management is the use of continuous and noninvasive monitoring systems for the haemodynamic or biochemical parameters involved in dialysis quality. Special sensors for continuous blood volume measurement have

been developed over the past ten years. As a second step, some of these devices have been implemented in dialysis instrumentation, mainly with a view to preventing cardiovascular instability, but also in order to control dialysis efficiency (e.g. biofeedback control systems or closed-loop biological variable control systems).

The basic components of a biofeedback system are the plant, the sensors, the actuators and the controller. The plant is the biological process that we need to control, while the sensors are the devices used for measuring the output variables. The actuators are the working arms of the controller. The controller is the mathematical model that continuously sets the measured output variable against the reference input and modifies the actuators in order to reduce any discrepancies.

In practice, however, there are a number of conceptual, physical and technological difficulties that still need to be overcome. In particular, the patient-monitor system to be controlled is typically nonlinear and time-varying, with interactions between the actuators and the controlled variable. In these cases, more sophisticated control systems are needed, capable of identifying the behaviour of the process, and continuously updating the data while the control is being made. These complex systems are called adaptive controllers.

Biofeedback blood volume control is a system used in routine clinical dialysis around the world.

## ■ INTRODUCTION

Over the past four decades, haemodialysis has changed from a potentially life-saving therapy for a few patients with acute renal failure treated in teaching hospitals to an outpatient-based chronic treatment for patients with chronic disease, with an increasing majority of patients now dialysed without direct medical supervision. Nevertheless, complications can still occur.

Among the dialysis-induced symptoms, arterial hypotension is a common event, estimated to occur in up to 30% of dialysis sessions<sup>1</sup>, and associated with high acute morbidity<sup>2,3</sup> and an increased mortality risk<sup>4</sup>. The pathogenesis of intradialytic hypotension is multifactorial<sup>1</sup>. However, hypotension is often related to both an excessive or unduly rapid decrease in blood volume that results in decreased cardiac filling (which, in turn, causes a reduced cardiac output) and a lack of adequate vasoconstriction<sup>1,5</sup>. Indeed, today there has been a shift away from treatments aimed solely at patient survival to systems also capable of addressing patient rehabilitation and quality of life.

We have the chance to view dialysis treatment from a more all-inclusive standpoint, oriented to the “patient-system” through the application of methods and techniques more typical of bioengineering and through a wider use of sensors and computers<sup>5</sup>. The time has come to redefine the concept of the artificial “kidney” organ, endowing it with the capacity to adapt the functions of the device to the physiological, haemodynamic and metabolic needs of the organism with which it has to interact. In practice, it is now necessary to think in terms of biological closed-loop control (biofeedback), that is, a mechanism capable of measuring the organism’s physical-chemical status and reacting automatically to maintain it, or to restore its steady-state condition.

## ■ BLOOD VOLUME (BV) BIOFEEDBACK

BV behaviour during dialysis has been extensively described mathematically<sup>6</sup> and several factors influencing and modifying BV changes throughout dialysis treatment have been identified<sup>7</sup>.

Ultrafiltration and changes in the dialysate sodium concentration are, however, the major and the most important dialysis variables in the control of volaemia during dialysis treatment<sup>8</sup>. On the other hand, ultrafiltration profiling may have a beneficial impact on blood pressure behaviour during haemodialysis.

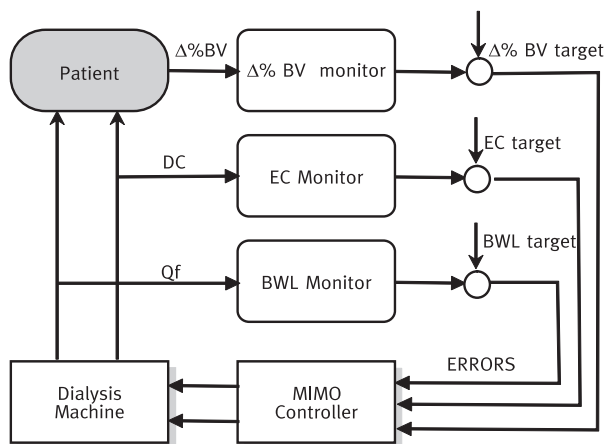
However, models based on ultrafiltration alone are limited to adapting the rhythm of plasma water removal to the patient’s refilling capacities. The major limitation to these models is their inability to keep control over the total planned weight loss within the preset treatment times<sup>7</sup>. Increased dialysate sodium can promote greater fluid mobilisation from the extravascular compartment, thereby reconstituting a greater portion of the plasma volume lost during ultrafiltration<sup>9</sup>, helping reduction in the desired body-weight loss.

Moreover, on the one hand, the modification of the intravascular sodium concentration can increase plasma refilling, while on the other it can increase the activity of the autonomic nervous system, with a consequently better haemodynamic response from the peripheral vascular resistances. However the intradialytic sodium balance has to be always borne in mind to avoid sodium and fluid overload in the interdialytic period. In this light, in collaboration with the Gambro-Hospal research group we have modified our first automatic BV control system based on variable ultrafiltration<sup>10,11</sup>. The new feedback control system is based on an adaptive controller, capable of forcing the spontaneous volaemia trends along preselected trajectories by means of ultrafiltration as well as sodium. From a modelling standpoint, the model proposed is an example of a closed-loop system (Fig. 1), with a dependent output or controlled variable, i.e. volaemia or BV, and two independent or control variables, i.e. ultrafiltration and conductivity<sup>12</sup>.

The relative BV changes are measured continuously during dialysis by an optical absorbance system<sup>13,14</sup>.

At the same time, the following parameters are continuously calculated:

- 1) the mathematical coefficients linking the controlled variable to the control variables;
- 2) the differences in the actual BV trajectory (measured during HD) as compared with the ideal one (defined at the beginning of the HD session);



**Figure 1**

The blood volume (BV) biofeedback with the multi-input and multi-output controller (MIMO controller).

The BV biofeedback system aims at three clinical targets:

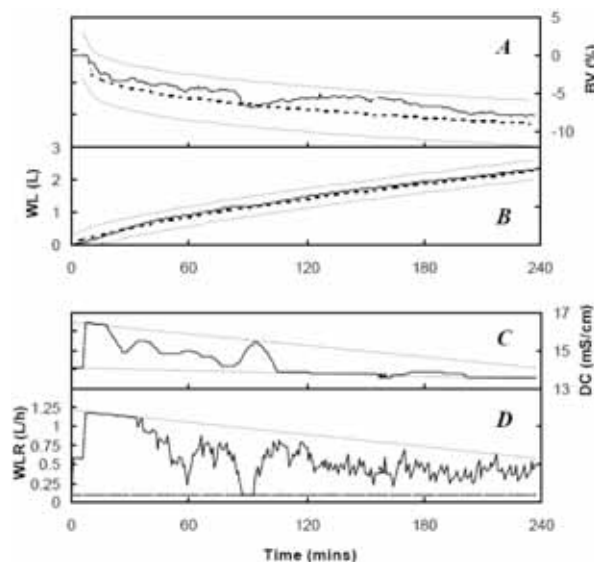
- body weight loss (BWL) for the restoration of the dry body weight;
- variation of blood volume for the preservation of cardiovascular stability;
- equivalent dialysate conductivity (DC) to maintain a desired sodium balance.

According to the biofeedback architecture, similar parameters are continuously measured: variations in blood volume, total weight loss and equivalent conductivity. With this information the physiological controller continuously adjusts the ultrafiltration rate and the dialysate conductivity. Adapted from<sup>10</sup>.

- 3) the differences in the body weight loss first prescribed and then achieved and their relationships with BV reductions;
- 4) the average dialysate conductivity and its error, *vis-à-vis* the equivalent conductivity.

In the presence of substantial errors, the model is able to automatically update both the ultrafiltration and the conductivity with a view to minimising any discrepancies there may be between the ideal volemia trajectories and the experimentally obtained ones, as well as any relevant errors in the patients' body weight reductions.

At the heart of the system is a MIMO, i.e. a multi-input, multi-output controller, in which all the branches are linearly controlled with adapted parameters (Fig. 1). The adaptive controller handles three kinds of error: errors in volemia, but also ones in the total weight loss and dialysate conductivity. For greater safety during the treatment, ultrafiltration and conductivity, i.e. the two independent variables,



**Figure 2**

Time course of the BV% reductions (panel A), total weight loss (WL, Kg, panel B), dialysate conductivity (DC, mS/cm, panel C) and weight loss rate (WLR, L/h, panel D) during a dialysis session with biofeedback control of blood volume.

According to the desired pattern for blood volume and total weight loss (the thin dashed line in the top panel), the weight loss rate and the dialysate conductivity change time by time to reduce discrepancies between the desired and observed values. The WLR and DC are in any case constrained within safety limits (dotted lines in the bottom plot). Adapted from<sup>11</sup>.

may fluctuate only within a well-defined upper and lower limit, set at the start of the treatment according to the patients' clinical characteristics (Fig. 2).

Moreover, the overall system, apart from allowing for the regulation of the BV profile according to desired trajectories, makes it possible to prescribe adequate ultrafiltration to achieve the ideal body weight in individual patients along with a personalised intradialytic sodium balance.

From a clinical standpoint, biofeedback in BV regulation has several aims:

- i) to avoid reaching serious and major contractions in BV; reductions over 25% should be avoided owing to the greater risk of intradialytic hypotension;
- ii) modelling the volemia curves and reducing intratreatment variability (ups and downs in BV) in patients with plasma refilling instability during dialysis;

- iii) to avoid, in patients with cardiovascular instability, the reaching of their own critical hypovolaemia thresholds, independent of their absolute value;
- iv) to modulate the sodium balance and patient fluid removal in order to reach the ideal post-dialysis body weight.

Biofeedback blood volume controlled HD is now possible with this system in routine dialysis, allowing for the delivery of a more physiologically acceptable treatment.

## ■ CLINICAL RESULTS

The largest clinical validation of blood volume tracking is represented by a multicentre study trial involving, in addition to our own Centre (where the system was conceived and piloted), a further nine Italian Nephrology Units. In this study<sup>15</sup>, carried out in 36 patients with a high degree of cardiovascular comorbidities and suffering from frequent dialysis-induced hypotensive episodes, cardiovascular instability during dialysis was compared in two different treatments: conventional dialysis (treatment A) and dialysis with blood volume tracking (treatment B). Each patient served as his/her own control, and was randomly assigned to either an A-B-A-B or a B-A-B-A sequence, with each period lasting four weeks. At the end of the study, a 30% reduction in the dialysis hypotension incidence resulted from dialysis with the BVT system. The effect was particularly evident in patients with the highest number of hypotensive events in conventional dialysis (in these patients the reduction of hypotension was up to 65%). The results concerning the treatment haemodynamic tolerance were reinforced by observing a 10% overall reduction in interdialysis symptoms (e.g. thirst, cramps, fatigue, etc.). Interdialytic body weight gains, predialysis blood pressure and Kt/V did not differ during the periods with the two treatments.

A confirmation of our results comes from the experience of Basile<sup>16</sup>, who also compared conventional bicarbonate dialysis with biofeedback equipped dialysis in 19 HD patients in the short-medium term. He found a reduction in both acute hypotension and muscle cramps and a significant difference in postdialysis fatigue. The percentage residual BV divided by the percentage change in extracellular fluid volume

(measured by a bioimpedance technique) was significantly higher during HD with biofeedback, suggesting a better refilling capacity in dialysis with BV control. Once again the BVT system proves less “antiphysiological” than conventional treatment. The continuous adaptation of both the ultrafiltration rate and dialysate conductivity to the instant vascular refilling capacity preserves more water in the interstitial fluid compartment or reduces the intracellular shift: vascular refilling is, in any case, maximally preserved and enhanced.

Ronco *et al.*<sup>17</sup>, in addition to observing similar results in terms of hypotension prevention, also reported better values in equilibrated Kt/V in BV controlled HD, with a striking reduction in postdialysis percentage urea rebound ( $6.4 \pm 2.3\%$  vs.  $14.2 \pm 2.7\%$ , in BV controlled and standard HD, respectively). Hence, the better haemodynamic stability obtained thanks to the biofeedback reflects positively in terms of HD efficacy: it reduces solute compartmentalisation and favours a better blood flow distribution within the body. As a consequence, the amount of urea accessible to the dialyzer is greater, and so is the amount actually removed.

Several other studies have addressed the use of such a blood volume tracking system in different dialysis populations. For instance, Wolkotte *et al.*<sup>18</sup> have investigated the plasma sodium level and the intradialytic weight gain in an unselected group of 16 patients crossed between standard and BVT dialysis. The percentage of hypotensive episodes was  $15.75 \pm 18.27\%$  and  $6.33 \pm 11.28\%$  in standard and BVT, respectively<sup>18</sup>.

McIntyre *et al.*<sup>19</sup> have applied blood volume biofeedback to 15 stable, nonhypotension-prone HD patients, the majority of the dialysis population, finding an increasing tolerability (a reduction of percentage of dialysis complicated by severe hypotension from 10% in conventional dialysis to 1.5% in BVT system,  $p < 0.001$ ), reducing the need for intradialytic fluid restoration (number of saline infusions,  $2 \pm 0.6$  in conventional HD and  $0.13 \pm 0.13$  with the BVT system). They also found an enhanced urea clearance (assessed by equilibrated KT/V ( $1.01 \pm 0.03$  and  $1.13 \pm 0.03$  for conventional and BVT system, respectively,  $p < 0.01$ ) to the same extent as Ronco<sup>17</sup>.

Franssen *et al.*<sup>20</sup> aimed their study at understanding the potential benefits of the BVT system on blood

pressure control during and after dialysis by measuring ambulatory 24-hour blood pressure in 12 nonhospitalised hypotension-prone patients (need for nursing intervention in >50% of dialysis sessions in the previous six months). Dialysis hypotensions necessitating nursing intervention went down from 67±32% in conventional haemodialysis, to 37±21% and 28±21%, respectively ( $p<0.01$ ). Moreover, the systolic and diastolic blood pressure was better preserved during dialysis in the BVT system than conventional dialysis, especially in the second half of the sessions ( $p<0.05$ ). Higher systolic blood pressures values were also seen in the next 16 hours following dialysis (on average a difference of 6-8 mmHg) disappearing in the subsequent 16-24 hours. The same effect on blood pressure was also investigated by the same authors in a randomised parallel groups study comparing conventional vs BVT haemodialysis in 28 hypertensive patients<sup>21</sup>. In that study the authors investigated whether BVT was able to adjust the volume status and to reduce the predialysis blood pressure. Intradialytic hypotension episodes and other intradialysis symptoms were secondary end points of this study. They concluded that, despite a reduction in predialysis blood pressure (22.5 mmHg for the systolic and 8.3 mmHg for the diastolic) accompanied by a reduction in the number of hypotensive events per week, they were unable in either study to explain the improvement in treatment tolerability. They argued that, as observed by Santoro *et al.*<sup>15</sup>, the improved tolerance could be the effect of a lower variability in the relative blood volume reduction. Moreover, the shape of the BV decline through the dialysis session in itself is another factor playing a specific role in improving the blood pressure trend. In fact, by means of the automatic blood volume control, a favourable trend in BV reduction with positive repercussion in terms of haemodynamics is attainable: a sharp fall in the first minutes due to the high water removal rate, compensated for by a higher dialysate sodium content, and a smoother time pattern in the second half on the treatment.

Moret *et al.*<sup>22</sup> investigated the effect of sodium profiling and biofeedback system on plasma conductivity and sodium mass balance in a group of 12 hypotension-prone patients randomised to a sequence of four different dialysis treatments: conventional dialysis as the control treatment, a sodium profiled dialysis session and two haemodialysis schemes using biofeedback technologies on blood volume and plasma conductivity. The authors were unable to find

any statistically significant difference as regards the treatment tolerance (a secondary end-point) between the four types of dialysis. However, there was a trend favouring the biofeedback systems. The lack of significant results could be partially accounted for by the limited number of patients enrolled in the study.

Positive results were obtained by Deziel *et al.*<sup>23</sup> in a parallel group randomised trial comparing standard HD vs. BVT dialysis in 57 hypertensive patients. Again the study was aimed at investigating the potential capability of reducing the hypertensive status of the patients by using the BVT system. Despite a reduction in systolic and diastolic blood pressure after six months using both therapies (no statistically significant difference), the patients in the BVT arm experienced a significant decrease in the number of the dialysis sessions complicated by hypotension (from 34.8% to 19.4%), while those in the standard HD arm showed an increase (from 22.8% to 32.2%).

## ■ CONCLUSIONS

The continuous increase in critical clinical conditions of the dialysis patient population and the fact that performing long or daily dialysis sessions is impracticable for many patients in most dialysis centres obliges us to find new ways to make dialysis treatments lasting 4-4.5 hours more physiological. One solution to this problem comes from new technology that, by means of the development of biosensors and continuous monitoring systems, allows us to better monitor the patient and adapt dialysis to each patient's individual needs in that specific dialysis session. The reduction in the intradialysis symptoms, in particular intradialysis hypotension, has some beneficial repercussions on the dialysis patient's morbidity and is also reflected in the patient's outcome. The blood volume control system (which presupposes the automatic control of ultrafiltration and dialysate conductivity during dialysis in order to stabilise and personalise the intradialysis BV reduction trends) is now feasible and safe in haemodialysis patients. Many clinical studies have already demonstrated its usefulness in reducing hypotension episodes as well as in increasing dialysis adequacy.

**Conflict of interest statement.** None declared.

## References

1. Zucchelli P, Santoro A. Dialysis-induced hypotension: a fresh look at pathophysiology. *Blood Purif* 1993;11:85-98.
2. Schortgen F. Hypotension during intermittent hemodialysis: new insights into an old problem. *Intensive Care Med* 2003;29:1645-1649.
3. Davenport A, Cox C, Thuraisingham R. Blood Pressure Control and Symptomatic Intradialytic Hypotension in Diabetic Haemodialysis Patients: A Cross-Sectional Survey. *Nephron Clin Pract* 2008;109:c65-c71.
4. Shoji T, Tsubakihara Y, Fujii M, Imai, E. Hemodialysis-associated hypotension as an independent risk factor for two-year mortality in hemodialysis patients. *Kidney Int* 2004;66: 1212-1220.
5. Santoro A. On-line monitoring. *Nephrol Dial Transplant* 1995;10:615-618.
6. Kimura G, Van Stone JC, Baven J. Model prediction of plasma volume change induced by hemodialysis. *J Lab Clin Med* 1984;104:932-938.
7. Schneditz D, Roob J, Oswald M, Pogglitsch H. Nature and role of vascular refilling during hemodialysis and ultrafiltration. *Kidney Int* 1992;42:1425-1433.
8. Mann H, Stiller S, Gladziwa V, Konig F. Kinetic modelling and continuous on line blood volume measurement during dialysis therapy. *Nephrol Dial Transplant (Suppl 1)*1990;144-146.
9. Kouw PM, Olthof CG, Gruteke P, deVries PMJM. Influence of high and low sodium dialysis on blood volume preservation. *Nephrol Dial Transplant* 1991;6:876-880.
10. Santoro A, Spongano M, Mancini E, Rossi M, Paolini F, Zucchelli P. Parameter estimator and adaptive controller to regulate intra-dialytic blood volume trends. *Kidney Int* 1992;41:1446.
11. Santoro A, Mancini E, Paolini F, Spongano M, Zucchelli P. Automatic control of blood volume trends during hemodialysis. *ASAIO J* 1994;40:M419-422.
12. Santoro A, Mancini E, Paolini F, Cavicchioli G, Bosetto A, Zucchelli P. Blood volume regulation during hemodialysis. *Am J Kidney Dis* 1998;32(5):739-748.
13. Paolini F, Mancini E, Bosetto A, Santoro A. Hemoscan: a dialysis machine-integrated blood volume monitoring. *Int J Artif Organs* 1995;18(9):487-494.
14. Mancini E, Santoro A, Spongano M, Paolini F, Rossi M, Zucchelli P. Continuous on-line optical absorbance recording of blood volume changes during hemodialysis. *Artif Organs* 1993;17(8):691-694.
15. Santoro A, Mancini E, Basile C, Amoroso L, Di Giulio S, Usberti M, Colasanti G, Verzetti G Rocco A, Imbasciati E, Panzetta G, Bolani R, Grandi F, Polacchini M. Blood volume controlled hemodialysis in hypotension-prone patients: a randomized, multicenter controlled trial. *Kidney Int* 2002;62:1034-1045.
16. Basile C, Giordano R, Vernaglione L. Efficacy and safety of hemodialysis treatment with the Hemocontrol biofeedback system: a prospective medium-term study. *Nephrol Dial Transplant* 2001;16:328-334.
17. Ronco C, Brendolan A, Milan M, Rodeghiero M, Zanella M, La Greca G. Impact of biofeedback-induced cardiovascular stability on hemodialysis tolerance and efficiency. *Kidney Int* 2000;58:800-808.
18. Wolkotte C, Hassell DR, Moret K. Blood Volume Controlled Biofeedback and Dialysis-Induced Symptomatology. *Nephron* 2002;92:605-609.
19. McIntyre CW, Lambie SH, Fluck RJ. Biofeedback controlled hemodialysis (BF-HD) reduces symptoms and increases both hemodynamic tolerability and dialysis adequacy in non-hypotension prone stable patients. *Clin Nephrol* 2003;60(2):105-112.
20. Franssen C, Dasselaar J, Sytsma P, et al. Automatic feedback control of relative blood volume changes during hemodialysis improves blood pressure stability during and after dialysis. *Hemodial Int* 2005;9:383-392.
21. Dasselaar J, Huisman RM, De Jong PE. Effects of relative blood volume-controlled hemodialysis on blood pressure and volume status in hypertensive patients. *ASAIO Journal* 2007;53:357-364.
22. Moret K, Aalten J, van den Wall Bake, et al. The effect of sodium profiling and feedback technologies on plasma conductivity and ionic mass balance: a study in hypotension-prone dialysis patients. *Nephrol Dial Transplant* 2006;21:13-144.
23. Deziel C, Bouchard J, Zellweger, et al. Impact of Hemocontrol on Hypertension. Nursing Intervention and Quality of Life: A Randomized, Controlled Trial *Clin J Am Soc Nephrol* 2007;2:661-668.

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