Biofeedback in blood volume regulation during hemodialysis

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INTRODUCTION

Although our understanding of the underlying mechanisms has improved, cardiovascular instability with symptomatic hypotension is still one of the principal and most frequent complications occurring during dialysis therapy. Dialysis treatment involves the removal of fluid from the circulating blood with a view to bringing the hydration state back to normal in patients undergoing chronic treatment. During the dialysis sessions, together with the decreases in the patients body weight, there occur a series of hemodynamic events: 1) ultrafiltration induces a progressive reduction in the volume (BV) related to the entity of the ultrafiltration itself and to the rate of plasma refilling; 2) hemoconcentration is followed by a water shift from the intersticial and cellular spaces towards the vascular compartment; 3) initially, as in the course of hemorragic shocks, blood pressure is kept relatively constant thanks to the activation of the sympathetic system which induces a vasoconstriction, an increase in peripheral vascular resistances and an increase in heart rate. Maintenance of blood pressure is related to two mechanisms: BV preservation and cardiovascular compensation[1].

Arterial hypotension can appear when central hypovolemia determines an underfilling of the cardiac chambers, thereby compromising the circulatory load, while the vascular arteriolar or the venous tone falls or turns out to be inadequate in relation to the reduction of stroke volume[2]. Preventive measures have traditionally included an accurate evaluation of dry body weight, the avoidance of ultrashort and aggressive ultrafiltration, the use of bicarbonate as buffer, and an adequate sodium concentration in the dialysate. However, in the presence of severe vascular damage, left ventricular insufficiency, or severe cardiomyopathy, all these remedies prove only partially sucessful. Some aids to this difficult management can derive from the continuous monitoring and control of the hemodynamic variables involved in the genesis of dialysis-induced hypotension[3].

ON–LINE BV MONITORING

In the last few years, technological advances have led to the introduction of a series of instruments and methods that allow us to evaluate the BV variations during the dialysis session in order to prevent hypovolemia-induced symptoms and, above all, the onset of arterial hypotension[4-6].

At the basis of most of the indirect methods is the physical principle of the law of mass conservation: if the quantity of a substance x does not undergo variations during the dialysis treatment, then its variations are exclusively due to modifications in the volume of the fluid in which the substance has dissolved[7].

The relationship that allows for the calculation of the BV (BV) after any time interval (t), can be calculated from a mathematical formula that takes account of the variations in the x concentration at various times:

$$BV_t\ (\%) = \frac{BVt - BVo}{BVo} = \frac{Cx,o}{Cx,t}$$

The hematocrit, haemoglobin, plasma proteins and blood density are all variables to which the mass conservation principle can be applied for a continuous measure of the BV during the dialysis therapy.

A few years ago, we proposed a non-invasive probe to measure the haemoglobin concentration in a layer of whole blood flowing along the arterial line[5]. Today, this optoprobe is directly applied to a dialysis machine[8] and provides haemoglobin values by measuring the optical absorbance of monochromatic light (Hemoscan, Hospal-Dasco, Medolla, Italy).

The continuous surveillance of BV changes may allow for the identification of the critical individual level of hypovolemia in hypotension-prone patients with vascular refilling instability.

Furthermore, by means of the continuous measurement of volemia together with other hemodynamic parameters, it is possible to design statistical models that can be implement on a personal computer and can operate on-line during the dialysis session. Such models, based on mathematical equations, allow us to calculate discriminant indices, predictive of the appearance of a hypotensive event. However, one of their limits is the fact that they can only be used in particular classes of patients, and namely in those patients in whom a retrospective statistical analysis has been performed[3]. In practice, what is needed is a preliminary study on the patient which allows us to establish the coefficients and the constants of the equation that will, in future applications, allow for an alarm system designed to predict critical events.

Thus, on-line BV monitoring alone, although representing a great help, is not likely to solve the complex problem of vascular instability. The variables involved in the complex regulation of blood pressure, i.e. the vascular refilling, the cardiac output, the arterial and venous tone, can change erratically throughout the dialysis session[1]. We believe that, given the enormous inter- and intraindividual variability and the continuous appearance of some uncontrolled inputs during dialysis, only a biofeedback closed-loop system can either resolve or, at any rate, minimise the complications of cardiovascular instability during dialysis therapy.

THE CONCEPT OF BIOFEEDBACK

Ever since the dawning of human kind, control has always meant a form of power over man's environment. Although *control* is sometimes equated with the notion of feedback control (involving the transmission and return of information), modern usage tends to favour a broader meaning of the term. For instance, the control and regulation of machines, the *control* of prosthetic devices, general aspects of coordinated activity in the social sphere, such as the optimisation of business operations, the *control* of economic activity by means of government policies and even the *control* of political decisions by democratic processes.

Biofeedback is widespread in nature and, in physiology, the term is synonymous of a servosystem, which controls a biological process such as muscular co-ordination and metabolism. A classic example is that of body temperature regulation, which is kept constant independently of the external temperature. Thermoreceptors continuously measure the core and surface temperatures and send this information to the integration centres. The integration centres, via descending pathways, control the state of the effector, the skin blood flow, the sweat rate and shivering, and keep the body temperature constant in spite of great changes in the outside temperature.

Learning a lesson from nature, bioengineering has codified the basic components of a biofeedback (figure 1): the process, the sensing elements, the actuators and the controller.

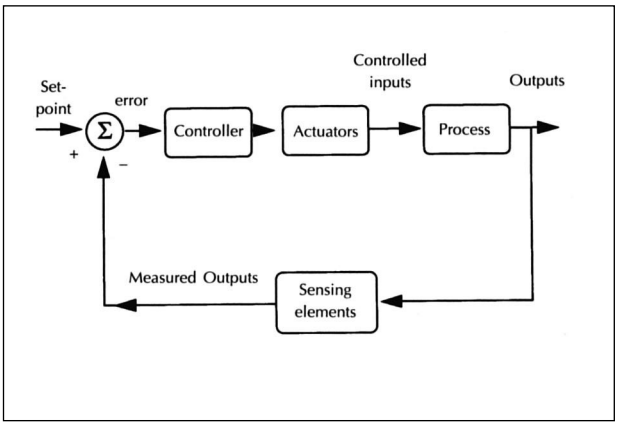

Fig. 1.—The components and relationships of the program in a feedback control system.

The process in the system that we would like to control, while the sensing elements are devices for measuring the output variable. This is the variable that is measured and compared to the input, i.e. the output's reference value.

The controller consists of a mathematical model that continuously sets the measured output variable against the reference input and modifies the actuators in order to reduce the differences between them.

The scientific formulation of a control problem is based on two kinds of information: a) the behaviour must be described in a mathematically accurate way; b) the purpose of the control and the environment (noise) must be specified, again a mathematically accurate way.

This is the theory, while, in practice, the development of feedback systems has several conceptual, physical and technological difficulties to overcome. Often, the process to be controlled and the quantification of the desired effects may not be properly understood. Indeed, the behaviour of what is to be controlled may be non-linear and time-varying and, lastly, the controlled variable may interact with the actuators.

BIOFEEDBACK AND BV

The BV behaviour during dialysis has been extensively described mathematically[9] and several factors influencing and modiflying BV changes throughout dialysis treatment have been identified[10].

Ultrafiltration and changes in the dialysate sodium concentration are, however, the major and the most important dialysis variables in the control of volemia during dialysis treatment[5]. On the other hand, ultrafiltration profiling can have a beneficial impact on blood pressure behaviour during hemodialysis.

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 maintain control over the total planned weight loss within the pre-defined treatment times[11, 12]. Increased dialysate sodium can promote greater fluid mobilisation from the extra-vascular compartment, thereby reconstituting a greater portion of the plasma volume lost during ultrafiltration[13], helping the reduction in the desired body-weight loss.

Moreover, on the one hand the modification of the intravascular sodium concentration can increase the activity of the Autonomic Nervous System, with a consequently better hemodynamic response from the peripheral vascular resistances. In this light, we have recently[14] modified our first automatic BV control system, based on variable ultrafiltration. The new feedback control system (figure 2) is based on an adaptive controller, capable of forcing the spontaneous volemia trends along pre-selected trajectories by means of both, ultrafiltration as well as the sodium. From a modelling point of view, the model proposed is an example of a *closed loop system* with a dependent output variable or *controlled variable*, i.e. volemia, and two independent or *control variables*, i.e. ultrafiltration and conductivity[14].

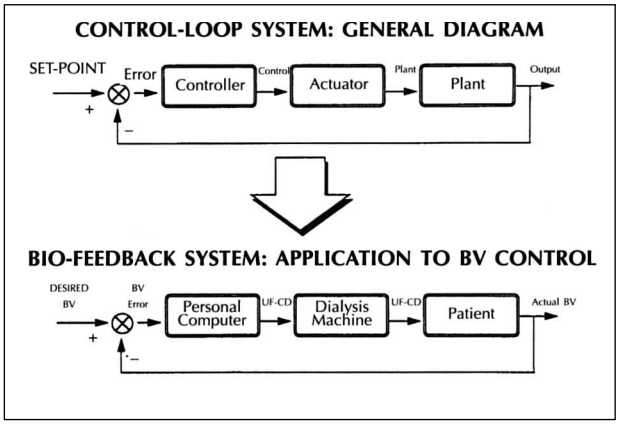

Fig. 2.—Schematic representation of the automatic closed loop regulation of blood volume during dialysis therapy.

The relative BV changes are measured continuously during dialysis by an optical absorbance system[8].

At the same time, the following are continuously calculated:

1) the mathematical coefficients that link the controlled variable to the control variables;
2) the instantaneous errors in the actual BV trajectory compared to the ideal one;
3) the differences in the body weight loss first prescribed and then obtained.

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 (figure 3) and the experimentally obtained ones, as well as any relevant errors in the patients' body weight reductions.

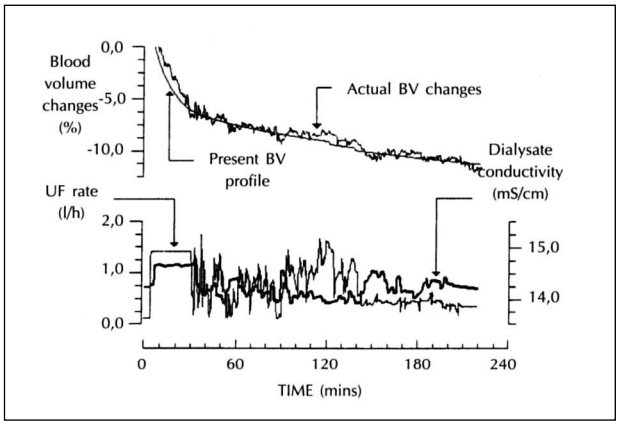

Fig. 3.—An example of a dialysis session with BV tracking: the blood volume changes during the dialysis session following the desired BV trend thanks to continuous changes in the ultrafiltration rate and dialysate conductivity. These changes are regulated by the controlled that continuously measures the errors of actual BV in relation to the prescription, modifying the operative values of the two actuators UF and DC.

The heart of the system is a MIMO (figure 4) multi-input, multi-output controller in which all the branches are linearly controlled with adapted parameters. The adaptive controller manages three kinds of error, errors on the volemia, but also ones on the total weight loss and on the sodium balance. Actually, together with the automatica model there operates a kinetic two-compartment sodium model, as described by Pedrini[15], which continuously calculates the theoretical systemic concentration of the patients' sodium.. The model's degree of predictive ac-

curacy has been verified by a laboratory control of the plasma sodium concentration values at various times both during and at the end of dialysis treatment. The correlation between the measured plasma sodium concentration values and those predicted (figure 5) by the model proved excellent with an SE of the mean equal to 0.389 mEq/L ($r = 0.88$, $p < 0.001$).

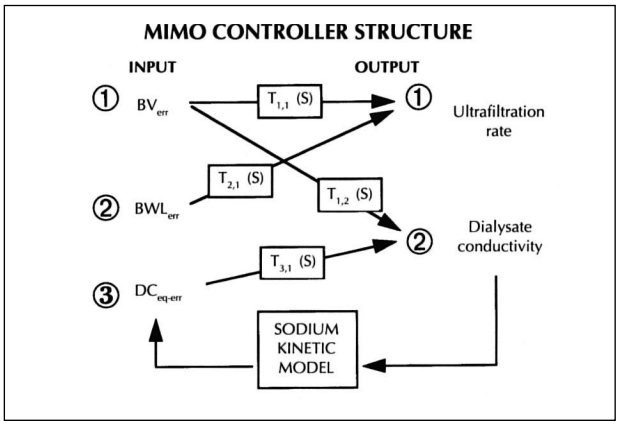

Fig. 4.—The structure of the MIMO controller, which, during the dialysis session, manages three kind of error (differences between the prescription and the actual results obtained): BV errors, body weight loss errors and equivalent dialysate conductivity errors. On the basis of the estimated errors, the controller modifies the instantaneous values of ultrafiltration rate and dialysate conductivity.

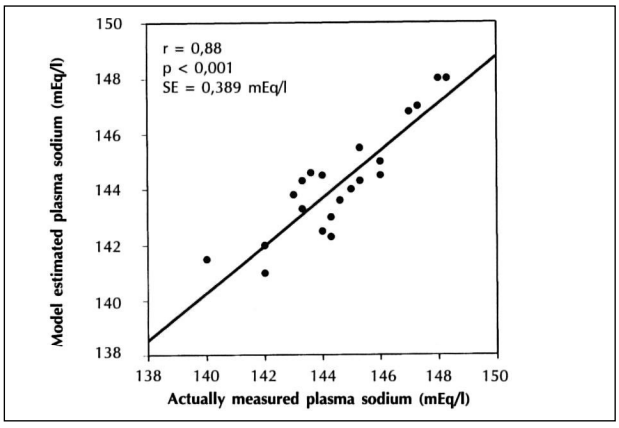

Fig. 5.—Relationship between patient's measured end-dialysis plasma sodium values and the ones predicted by the kinetic model.

The sodium kinetic model allows a continuous control of the sodium balance, bringing it back to its during a standard dialysis session with constant ultrafiltration.

The model considers the systemic sodium concentration as a function of time, and has been validated by comparing computer simulation results with experimental data. The correlation we obtained between plasma sodium levels actually measured at the end of the dialysis session, and the ones predicted by the model, is highly statistically significant.

However, besides the sodium model, whose only output variable is the equivalent dialysate conductivity, for greater safety during the treatment, ultrafiltration and conductivity, the two independent variables, can fluctuate only within the scope of a well-defined range, established at the star of the treatment on the basis of the patients' clinical characteristics.

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 and a personalised intradialytic sodium balance.

From a clinical point of view, biofeedback in BV regulation has several aims:

1) to avoid reaching serious and major contractions in BV. Reductions over 25% should be avoided owing to the greater risk of intradialytic hypotension;

2) modelling the volemia curves in patients with plasma refilling instability and non-homogeneous and non-linear plasma trends during dialysis;

3) to avoid, in patients with cardiovascular instability, the reaching of critical hypovolemia thresholds independently of their absolute value.

Recently, is a small group of patients with well-defined critical levels of hypovolemia who were highly simptomatic, we carried out a study comparing standard dialysis with a BV-controlled sessions. As shown in figure 6, the hipovolemia reduction at

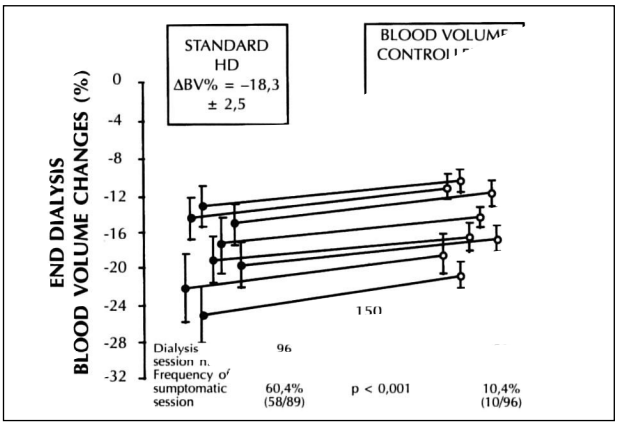

Fig. 6.—Effects of BV-controlled sessions on the end-dialysis reduction in BV and also intradialytic symptoms (hypotension, cramping, light-headedness) in 8 dialysis patients.

the end of treatment, an average of only 3 per cent (–18% in standard dialysis, and –15% in automatic BV-controlled sessions), was accompanied by a significant reduction in dialysis-related symptoms (e.g. hypotension, cramping, ligh-headedness). The frequency of symptomatic sessions fell from 60 per cent to 10.4 per cent.

On the whole, the control of BV via biofeedback can improve intra-treatment hemodynamic stability during dialysis sessions with hypovolemia as cause of hypotencion. It remains to be seen whether this advantage will be maintained over the long-run, resulting in a concrete sense of well-being for hemodynamically unstable patients.

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