Chapter (20)

Biofeedback Systems and Their Application in the Hemodialysis Therapy

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CHAPTER OUTLINES

- Introduction
- The Biofeedback Concept
- Monitoring and controlling hemodialysis
- Biochemical monitoring and control
- Conclusion

CHAPTER OBJECTIVES

- Define the concept of Biofeedback system.
- Discuss various Types of Biofeedback systems.
- Understand the importance of on-line monitoring devices.

KEY TERMS

- Biofeedback
- Open-loop Control System
- Closed-Loop Control System
- Multi-Input Multi-Output systems
- Actuators
- Adaptive Controllers
- On-line monitoring
- Blood volume
- Body temperature
- Ultrafiltration
- Blood Pressure
- Biochemical
- Hemodynamic

ABSTRACT

The traditional control of the dialysis session comes about by means of an open-loop system. At the beginning of the session some parameters are set, such as the kind of dialyzer, the blood flow, the ultrafiltration rate, the dialysate conductivity and the dialysate temperature. Generally speaking, these parameters are not modified unless there occur complications in the patient that call for adjustments to be made. The biofeedback concept, which is synonymous with a closed-loop control of biological variables, presupposes, on the other hand: the continuous measurement of a variable thanks to a specific sensor its evaluation by a sort of expert system - the

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so-called controller and a series of means - the actuators - that allow the behavior of the variable to be directly or indirectly influenced. In clinical practice, different biofeedback systems are emerging, addressed to the control of blood volume, body temperature, and blood pressure. Each one of these systems has been successfully utilized, especially in the management of "difficult" patients unstable from the hemodynamic point of view. However, the future will be an integrated system that sees a complex adaptive, multi-input, multi-output controller which, with a great simplicity of use and low costs, will allow renal replacement therapy to be increasingly physiological and more efficient.

20.1 INTRODUCTION

The progressive increase in the mean age and the growing conditions of co-morbidity, especially of cardiovascular pathologies and diabetes, has significantly worsened the patients' clinical status and tolerance to the hemodialysis (HD) treatment. On the other hand, the demand for short treatment times enhances the risk for hemodynamic instability as well as for inadequate depuration.

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

The first step to improve the management of the dialysis session is the utilisation of continuous and uninvasive monitoring systems for hemodynamic or biochemical parameters involved in the dialysis quality. Special sensors for the continuous measurement of blood volume, blood temperature, blood pressure, heart rate, electrolytes, have been realized throughout the last 10 years. As a second step, some of these devices have been implemented in the dialysis instrumentation, mainly with a view to preventing cardiocirculatory instability but also to control the dialysis efficiency (biofeedback 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 variables under control. 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.

Yet, in practice there are a number of conceptual, physical and technological difficulties to be overcome. In particular, the behaviour of what is to be controlled may be non-linear and time-varying, with interactions between the actuators and the controlled variable. In these cases, more sophisticated control systems are needed, which must be capable of identifying the behaviour of the process, and continuously up-date information data while the control is on. These complex systems are called adaptive controllers.

At present, there are three biofeedback systems routinely used in clinical dialysis (Santoro et al. 2003a; Locatelli et al. 2005; Azar 2008). All of them are aimed to improve the cardiovascular stability during HD, that is, at present, one of the main problem limiting on the one hand the tolerance to treatment by the patient, and on the other hand, the quality of HD in itself. One is the biofeedback control of blood volume, one is the biofeedback control of thermal balance, and the third is the biofeedback control of blood pressure.

Renal replacement therapies have enjoyed an exceptional development in the past few decades. Indeed, there has been a shift away from treatments aimed solely at the survival of the patient to systems capable of interacting with the various functions of the organism to such an extent as to be capable of addressing attention also to the patient's rehabilitation and quality of life.

Today 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. 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, hemodynamic and metabolic needs of the organism it has to interact with. In practice, it is now necessary to think in terms of biofeedback, which is a mechanism capable of measuring a physical-chemical status of the organism and react automatically to maintain it, or to bring it back to a condition of equilibrium.

The human organism is an extremely complex system of controls integrated with one another that operate at different hierarchical levels in order to maintain internal homeostasis also when faced with substantial variations in the environmental conditions in which it made to live. Historically speaking, bioengineering is a science that has set itself the primary objective of studying and reproducing the various organs and their main functional principles by means of non-organic devices. The concept

of being able to substitute the diseased organ, besides merely being able to heal it, has brought about an outright revolution in the therapeutic and rehabilitative field.

20.2 THE BIOFEEDBACK CONCEPT

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 co-ordinated 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 means of democratic procedures.

In the language of engineering, a control system is the set of interconnected components capable of providing the desired response by a given system. As a function of the configuration of the components, control systems are subdivided into two large categories: direct action controls (so called 'feed-forward' or open chain) and 'feedback' control. Examples of such control systems are present in many human activity applications: in the car sector all the anti-sliding control systems (ABS), the traction control and the speed cruise, as well as in the sector of heating and cooling (air-conditioning) or in the control of industrial processes. Some of these systems are in actual fact already present on the dialysis monitors: the temperature of the dialysis bath, the conductivity or the ultrafiltration are variables controlled by feedback systems. In order to understand the need to extend such control techniques to biological systems it is necessary to recall some salient characteristics of the control systems in open-chain or feedback.

The open-chain systems are generally easier to manufacture industrially, they do not necessarily require a sensor to measure the controlled variable, but have as a downside a less accurate regulation and a greater sensitivity to the variations in the environmental conditions in which they operate (noise) if the laws that govern the system to be controlled are not known in detail.

Given, therefore, the law that describes the controlled variable as a function of time and the control variable ($y = f(t,u)$), it is sufficient to apply the forcing action u_0 to obtain the desired response y_0. For example, having to warm up a room, if the external temperature and the thermal

resistance to the passage of the heat towards the outside are known, it is enough to apply a fixed thermal power in order to take the temperature internal to room to the desired value. However, if there appears a variation in the external temperature or a thermal resistance of the room, the law describing the system is modified; thus, with thermal power being equal, the internal temperature will be different.

The feedback systems function according to the principle of error minimisation between the desired value of the variable to be controlled and its direct measurement (see Fig. 20.1). These are more complex systems to be manufactured industrially, and require a sensor for the measurement of the controlled variable. However, they do not require a detailed knowledge of the laws governing the system to be controlled, they are more insensitive to the noise and guarantee a greater accuracy and control precision. For these reasons, the feedback techniques are more promising in the applications to biological systems, in that the law governing the system is not always known, the system parameters to be controlled are time-variable, the initial conditions in which the biological system functions are not known. Going back to the previous example, a thermoregulation system is definitely more effective in that also in the presence of variations in the external temperature or in the thermal resistance they are always capable of reaching the desired internal temperature.

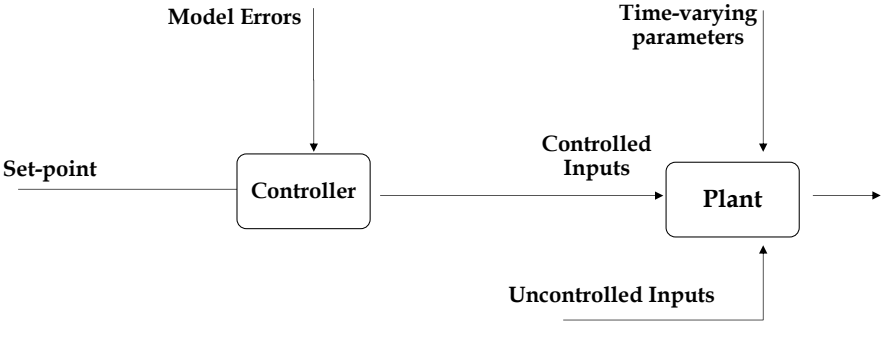

Fig 20.1 Schematic representation of an open-loop control system. The control parameters are set at the beginning of the process in order to obtain a desired change in the plant. However, model errors or time-varying parameters or uncontrolled inputs can modify the plant response during the process control and thus the result.

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 effectors, the skin blood flow, the sweat rate and shivering, and keep the body temperature constant in spite of large changes in the outside temperature. Learning a lesson from nature, bioengineering has codified the basic components of a biofeedback: the process, the sensing elements, the actuators and the controller.

The process is 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 in 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 wholly 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.

A problem that is posed in the biofeedback systems is that of the system's stability. If indeed the size of the biofeedback is too low (the ring gain is small) the control can prove to be ineffective, whereas if it is too high, the control can prove to be unstable and give rise to unwanted behaviours.

In dialysis, over the last few years, it has been relatively easy to realise some biofeedback systems, since a series of sensors have been developed for the online monitoring (Santoro 1995). The dialysis machines have become increasingly sophisticated and capable of providing accurate adjustments and this has turned them into powerful actuators. Furthermore, the internal computers are equipped with are also capable of hosting complex controllers of a multi-input and multi-output type.

20.3 MONITORING AND CONTROLLING HEMODIAYSIS (HD)

The need of new systems to check and possibly improve the quality of the dialysis treatments mainly derives from the characteristics of the present patient population on chronic dialysis treatment. In fact, the progressive increase in the mean age and the growing conditions of co-morbidity, especially of cardiovascular pathologies and diabetes, has significantly increased the patient's critical status. On the other hand, the demand for short treatment times enhances the risk for hemodynamic instability as well as for inadequate depuration.

The traditional management of the dialysis session presupposes the setting of pre-defined session parameters, and the active therapeutic interventions are limited to those situations in which complications occur. At the end of the pre-set time, often without taking account of the so-called recovery times and with no chance to check the "quality" of the depuration, the treatment is interrupted. Its efficacy is occasionally checked or else only when belated clinical complication appear. This kind of approach, acceptable in conventional treatments lasting 4-5 hours, is instead definitely unsuitable for short-lasting treatments, especially if they are complicated by phases of hemodynamic instability, or they are used in critical patients.

A technological response has followed, namely in the development of systems for on-line intradialytic monitoring, aiming to prevent critical situations and to continuously measure various physiological parameters of the patient, both of a hemodynamic kind and of a biochemical kind. The on-line monitoring systems have been most useful in high-efficiency, short-lasting dialysis techniques, since the risk of being "unphysiological" is so much greater when the treatment times are shortened while at the same time increasing the efficiency. In such conditions and in critical patients there is the need to have a continuous flow of information that guarantees at least two objectives:

- the adequacy of the cardiocirculatory *response* in terms of the progressive withdrawal of the fluids that guarantee a certain degree of hemodynamic stability;
- the overlapping of the actually delivered dialysis dose with the scheduled one;

An essential pre-requisite for reaching these objectives is that of disposing of adequate measurement devices and "sensors" for continuous measures during the dialysis sessions. Thus, besides a high degree of reliability and the continuity and accuracy of the measure, essential characteristics are relative simplicity of use, sterility and biocompatibility (for the sensors

that come into direct contact with the blood), the possibility to interface the measurement system with a computer and, lastly, an acceptable cost that will not further inflate dialysis treatment costs that are already high enough. But the indispensable pre-requisite for a sensor to be used in hemodialysis is its absolute non-invasiveness and utmost tolerability on the part of the patient.

Some devices for continuous hemodynamic or biochemical monitoring can be implemented in the dialysis instrumentation with a view to preventing cardiocirculatory instability (acute hypotension, arrhythmias) or controlling and improving the dialysis efficiency.

Hemodialysis is in fact no doubt the best area of application of the new servo-control systems, since it is not a static but a rather dynamic process, with rapid and continuous changes in both the solute and fluid distribution, as well as in the acid-base balance and hemodynamics. This kind of process needs a continuous monitoring of a number of parameters (both of a biochemical and a hemodynamic kind) to improve surveillance, but also needs a retroactive control aiming to keep the process back to an equilibrium state and reduce the unphysiology of the treatment.

However, the development of a biofeedback system for hemodialysis is not at all easy, because it presupposes a deep knowledge of the variables to be controlled, the construction of suitable sensors, the definition of the actuators and the realisation of an expert system overlooking, that is managing all the variables involved (input and output variables). In other words, they should be true and proper adaptive controllers.

In actual fact, the feedback systems that have ended up having a practical routine application are substantially three: the blood volume biofeedback, the temperature biofeedback and the arterial pressure biofeedback.

20.3.1 Blood Volume (BV) Biofeedback

The BV behaviour during dialysis has been extensively described mathematically (Kimura et al. 1984) and several factors influencing and modifying BV changes throughout dialysis treatment have been identified (Scheneditz et al. 1992).

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 (Mancini et al. 1993). 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 (Santoro et al. 1992; Mann et al. 1990). 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 (Kouw et al. 1991) helping the reduction in the desired body-weight loss.

Moreover, on the one hand the modification of the intra-vascular sodium concentration can increase plasma refilling, while, on the other, it 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 modified, along with the Gambro-Hospal research group, our first automatic BV control system based on variable ultrafiltration (Santoro et al. 1994). The new feedback control system 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 sodium. From a modelling point of view, the model proposed is an example of a *closed loop system* (see Fig. 20.2), with a dependent output variable or controlled *variable*, i.e. volemia, and two independent or control variables, i.e. ultrafiltration and conductivity (Santoro et al. 1998).

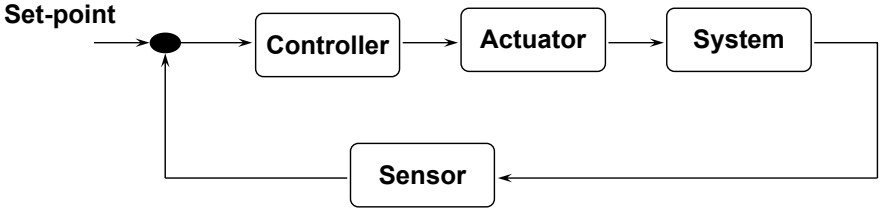

Fig. 20.2 Schematic representation of a closed-loop system

As shown in Fig. 20.2, in a closed-loop system, the variable to be controlled is continuously measured by a sensor and the action on the controller is determined by the difference between the desired and the measured value of the system variables. In this case, it is not necessary to know in detail the model of the system to achieve the desired point. Often, only the knowledge of a simplified input-output relationship is sufficient. This way is in general much less sensitive to external noise as well as to internal system variations, because the deviations from the imposed set values are first

measured then compensated for by the action of the controller on the system inputs.

The relative BV changes are measured continuously during dialysis by an optical absorbance system (Paolini et al. 1995). At the same time, the following parameters are continuously calculated:

i. The mathematical coefficients that link the controlled variable to the control variables;
ii. The instantaneous errors in the actual BV trajectory as compared with the ideal one;
iii. The differences in the body weight loss first prescribed and then achieved and their relationships with BV reductions.

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 core of the system is a MIMO, multi-input, multi-output controller in which all the branches are linearly controlled with adapted parameters (see Fig. 20.3).

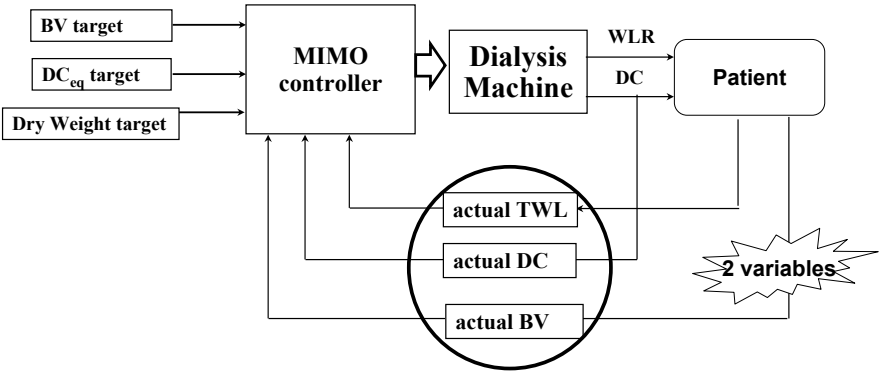

Fig. 20.3 The blood volume biofeedback with the multi-input and multi-output controller (MIMO controller)

As shown in Fig. 20.3, the BV biofeedback system consists in the setting of 3 clinical objectives:

- The Total Weight Loss (TWL) for the restoration of the dry weight;
- The variation of the blood volume (BV) for the preservation of cardiovascular stability;

- The equivalent dialysate conductivity (DC) to maintain a desired sodium balance.

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

The adaptive controller manages three kinds of error; errors on the volemia, but also ones on the total weight loss and dialysate conductivity. For greater safety during the treatment, ultrafiltration and conductivity, i.e. the two independent variables, can fluctuate only within a well-defined range, established at the start of the treatment according to the patients' clinical characteristics (see Fig. 20.4).

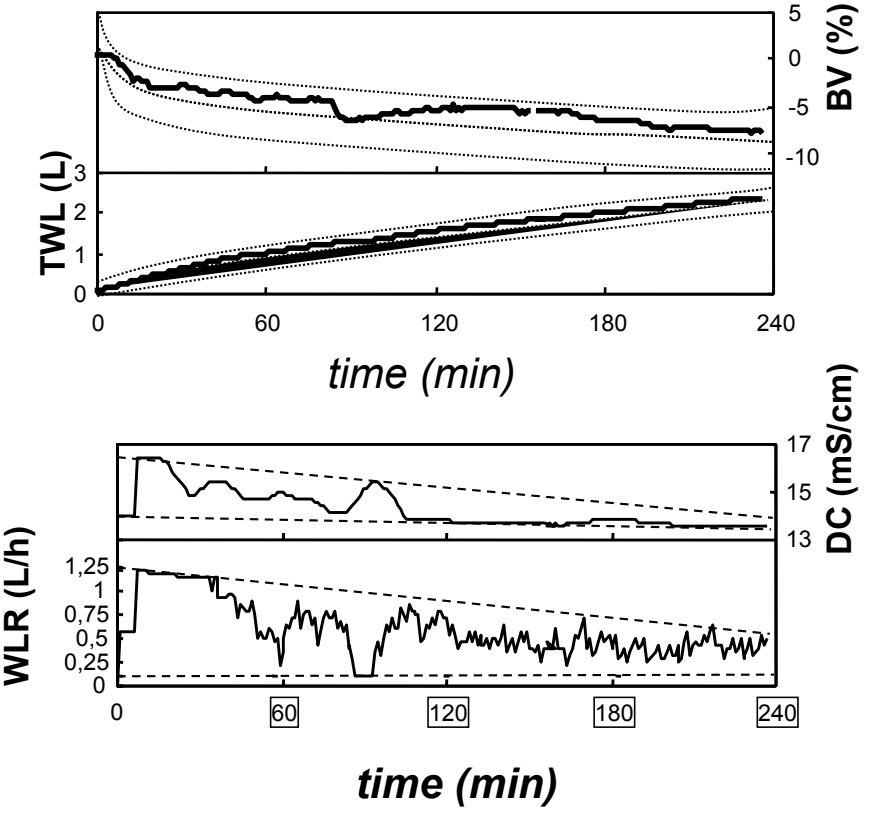

Fig. 20.4 Time course of the blood volume reductions (BV, %), total weight loss (WL, Kg), dialysate conductivity (DC, mS/cm) and weight loss rate (WLR, L/h) during a dialysis session with the biofeedback control of blood volume.

As shown in Fig. 20.4, according to the desired pattern for blood volume and total weight loss (the thin dashed line in the top plot), the weight loss rate and the dialysate conductivity change time by time to reduce the error between the desired and observed values. The WLR and DC are in any case constrained within safety limits (dotted lines in the bottom plot).

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 in order to achieve the ideal body weight in the individual patients along with personalised intradialytic sodium balance. From a clinical point of view, 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 in patients with plasma refilling instability and non-homogeneous and non-linear plasma volume trends during dialysis;
iii. To avoid, in patients with cardiovascular instability, the reaching of critical hypovolemia thresholds independently of their absolute value;
iv. To modulate the sodium balance and the patient's dehydration.

Biofeedback blood volume controlled HD is now possible with this system in routine dialysis, allowing the delivery of a more physiologically acceptable treatment. The largest clinical validation of Blood Volume Tracking is represented by a multicenter study protocol involving our Centre, where the system was born and experienced, and other 9 italian Nephrology Units. In this study (Santoro et al. 2002) carried out in 36 patients with a high degree of cardiovascular co-morbidity and suffering from frequent dialysis-induced hypotensive episodes, the cardiocirculatory stability during dialysis was compared in two different treatments: conventional dialysis (A treatment) and dialysis with Blood Volume Tracking (B treatment). Each patient served as his/her own control, and was randomly assigned either to a sequence A-B-A-B or B-A-B-A, each period lasting 4 weeks. At the end of the study a 30% reduction of dialysis hypotension incidence resulted in 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 hemodynamic tolerance were reinforced by the observation of a 10% overall reduction in interdialysis

symptoms (thirst, cramps, fatigue, etc.). Body weight gain, pre-dialysis blood pressure, and Kt/V did not differ between the two treatments.

A confirmation of our results comes from Basile's experience (Basile et al. 2001) who also compared conventional bicarbonate dialysis with biofeedback equipped dialysis in 19 HD patients, in the short-medium term. He found out a reduction of both acute hypotension and muscle cramps and a significant difference in post-dialysis asthenia. The residual percentage reduction in 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 capacity of refilling in dialysis with BV control. Once again the BVT systems proves less "unphysiological" compared to conventional treatment. The continuous adaptation of both theultrafiltration rate and dialysate conductivity to the instant vascular refilling capacity preserves more water in the interstitital fluid compartment or reduces the intracellular shift: vascular refilling is in any case maximally safeguarded and enhanced.

Ronco et al (2000), besides observing similar results in terms of hypotension prevention, reported also better values of equilibrated Kt/V in BV controlled HD, with a striking reduction in post-dialysis percentage urea rebound (6.4 $\pm$ 2.3 % *vs* 14.2 $\pm$ 2.7 %, in BV controlled and standard HD, respectively). Hence, the better hemodynamic 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 dialyser is greater, and greater is the amount actually removed. McIntyre et al (2003) have applied blood volume biofeedback to 15 stable, non-hypotension-prone HD patients and they found an increasing tolerability, reducing intradialytic fluid gains and enhancing urea clearance.

20.3.2 Body Temperature Biofeedback

Apart from blood volume, intradialytic hemodynamics can now be improved thanks to a blood temperature monitor. The theoretical assumption for such a system is that the thermal exchange processes between blood and heated dialysate may have an impact on different hemodynamic parameters of patients undergoing HD.

The standard dialysate temperature setting of approximately 37°C does not take into account that most uremic patients tend to be slightly hypothermic. Consequently, in several HD treatments, an unwanted positive

thermal energy balance is applied to patient, which in a certain number of cases, may provoke or contribute to symptomatic hypotension by eventually forcing the thermoregulatory system of the patient into a redistribution of the available blood volume from the central vassal system into the peripheral circulatory system.

In earlier studies by Maggiore et al (1985) an improved vascular response was observed during cooled dialysate or during isolated ultrafiltration in comparison with conventional hemodialysis. Recently, Rosales et al (2000) have shown that the amount of thermal energy to be removed for an isothermic HD correlates with ultrafiltration. The prevalence of symptomatic hypotension is comparable in hemodialysis and isolated ultrafiltration, if the core temperature is stabilized.

Unlike uraemic solutes, which accumulate between treatments, there is some potential for thermal energy to accumulate within a hemodialysis treatment. Basically, there are three possibilities for intradialytic heat accumulation: i) delivery of thermal energy by the extracorporeal system; ii) increase in the metabolic rate; iii) decreased dissipation of heat from the body surface during hemodialysis and ultrafiltration.

The reduced transfer of metabolic heat from the body core to the body shell is essentially caused by cutaneous vasoconstriction as a compensation for ultrafiltration-induced hypovolemia. However, if the heat accumulation increases beyond a critical threshold, the increase in the thermoregulatory drive will lead to an increase in cutaneous blood flow and blood volume which will reduce peripheral resistances, leading to a fall in blood pressure, and an increased risk of intradialytic morbid events. This additional cardiovascular stress can be avoided by the controlled adaptation of dialysate temperature to the individual needs of an individual patient. According to the present knowledge the target should be a negative extracorporeal heat balance throughout the treatment. A manual adjustment of the dialysate temperature is not practical for routine application. However, the availability of microprocessor controlled equipment permits the development of closed loops to influence the extracorporeal thermal balance in a defined way according to the medical prescription.

The dialysate temperature should then be individualized and chosen with regard to actual patient temperature, blood flow and treatment modality. Above all, it is not sufficient to maintain a constant dialysate temperature throughout the treatment, but to continuously adjust the dialysate temperature to keep a pre-defined patient temperature. In practice, it is necessary to realise a biofeedback system. A practical realisation is now available with the BTM, short for blood temperature monitor, by Fresenius. Short sections

of the extracorporeal circulation are inserted into arterial and venous measuring heads equipped with sensors to measure arterial and venous temperature (see Fig. 20.5).

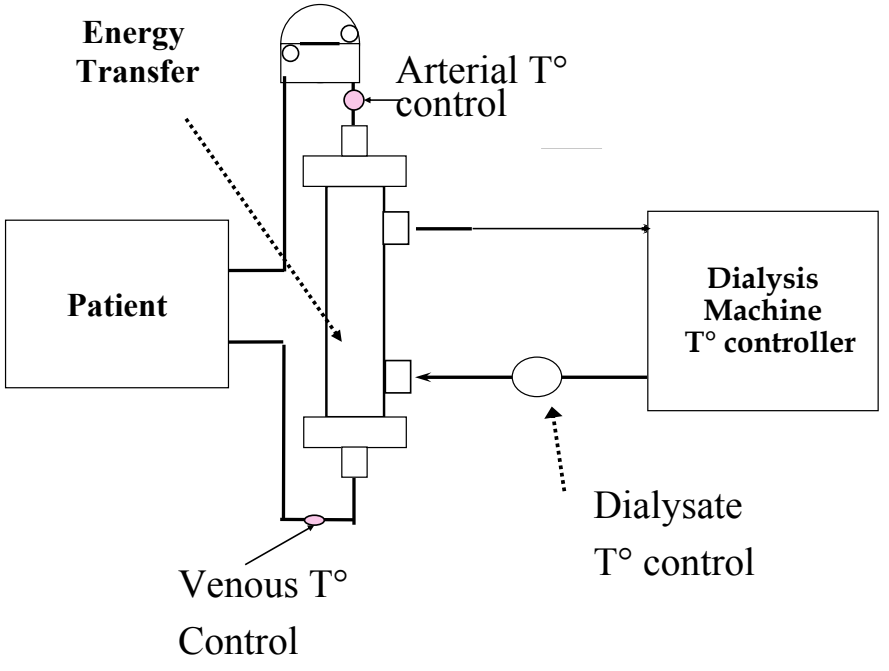

Fig. 20.5 The extracorporeal circuit of the blood temperature monitor which shows the measuring points of the temperature and the temperature controller.

The function of body temperature control is exerted by a controller. The controller uses the error signals between the desired and actual changes in temperature to actuate a bounded change in dialysate temperature which changes the temperature of the venous blood returning to the patient, thereby changing the extracorporeal heat flow.

Two active operational modes are possible with the BTM used as a closed-loop device: E-control and T-control. In the E-control modality the BTM controls the thermal energy balance of the extracorporeal circuit. A positive energy balance means transferring energy into the patient; on the contrary, a negative energy balance represents heat removal (cooling) and a zero extracorporeal heat balance means that the thermal state of the patient is not at all influenced by the extracorporeal circuit. The desired energy balances are keyed into the BTM by selecting a certain heat flux in KJoule/hour over the treatment time (internal limits: -500 kJ/h and +200 kJ/h). From the

therapeutical point, E-control with a set parameter of 0 kJ/h is a useful tool, if the medical intention is to exclude any thermal influence from an extracorporeal circuit.

In T-control mode, the BTM tries to influence the patient's body temperature directly by assessing the body temperature of the patient and applying the respective dialysate temperature changes according to a pre-set temperature goal. This goal can be keyed into the BTM's panel by setting a certain body temperature change per time ($\pm$ x°C/h; internal limits: -2°C/h and +1°C/h). Setting the BTM goal to $\pm$ 0°C consequently stabilizes the patient's body temperature at the temperature level which was present when the active control program was started.

In a prospective study (on 95 hypotension-prone patients), (Maggiore et al. 2002) have documented the hemodynamic benefits in terms of reduction of hypotension episodes of isoenergetic dialysis as compared with the thermo-neutral treatment mode. In isoenergetic treatment the patient temperature was keep constant throughout the treatment. Moreover, patients with left ventricular hypertrophy (LVH) seem to have more benefit from "cold" hamodialysis compared to patients without. In fact, a reduction in the dialysis hypotension incidence was observed in as much as 86% of the patients with LVH (left ventricular mass > 125 gr/m^2), and in 62 % of the patient without LVH, which was a statistically significant different (see Fig 20.6) (personal unpublished observations).

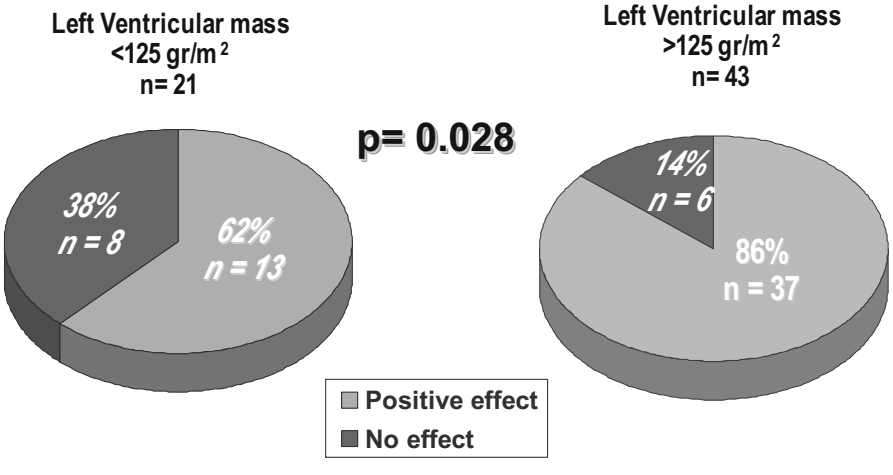

Fig. 20.6 Comparison of the effect the "cold" dialysis on the incidence of dialysis hypotension in patients without and with left ventricular hypertrophy (LVH). The positive effect was significantly higher in patients with LVH compared to patients without.

A hypothesis for this different effect could be seen in the fact that hypertrophic ventricle may present, during HD with concomitant UF, an inadequate filling, secondary to impaired relaxion. The reduced peripheral venous pooling, due to the cold-induced increase in venous tone, may favour the venous return to heart and the filling of the cardiac chambers, thereby maintaining an adequate cardiac output (which, on the contrary, could decrease to a critical level), and blood pressure. Different thermal balance characterizes convective and diffusive treatments, with the more negative one observed in cold hemodialysis (dialysate 35.5°C) and post-dilution hemofiltration (infusate 37°C) (Santoro et al. 2003b).

20.3.3 Arterial Blood Pressure Biofeedback

The arterial pressure control is definitely the most ambitious objective in the management of a dialysis session. Unfortunately, in order to exert a feedback control online, the essential prerequisite is the continuous measurement of the variable that should be controlled and in this case it is necessary to measure the arterial pressure. The continuous arterial pressure systems are, however, at least until now, only of an invasive kind and it is not thinkable that they can be applied in the routine dialysis and on a day patient. So we must be content with the oscillometric systems with external cuff that is periodically deflated and inflated in order to monitor the height and the width of the sphygmic wave. Many patients, however, do not like this continuous disturbance during the dialysis session and so we are only able to have the measures at pre-set time intervals that are no longer than a quarter of an hour. The company B Braun have created a measuring system of arterial pressure that is a little more sophisticated than the normal cuff instruments and a feedback control of arterial pressure based on ultrafiltration as the actuator.

The feedback control provides for the measurement of arterial pressure and its trend during the treatment and an accurate regulation of ultrafiltration finalised to the maintenance of an adequate blood volume. The system controller is based on fuzzy logic. Fuzzy logic does not work on the binary logic but allows for continuous and gradual transitions from 0 to 1. The fuzzy controller allows the modulation of ultrafiltration proportionally to the variation trend in the arterial pressure and so small variations in blood pressure are matched by small variations in ultrafiltration or the maintenance of a constant ultrafiltration, while large pressure variations are matched by large variations in the ultrafiltration. As reported in Fig. 20.7, when the controller highlights a negative trend in the blood pressure it reduces the ultrafiltration to the extent of reducing it to zero when there is no pressure recovery.

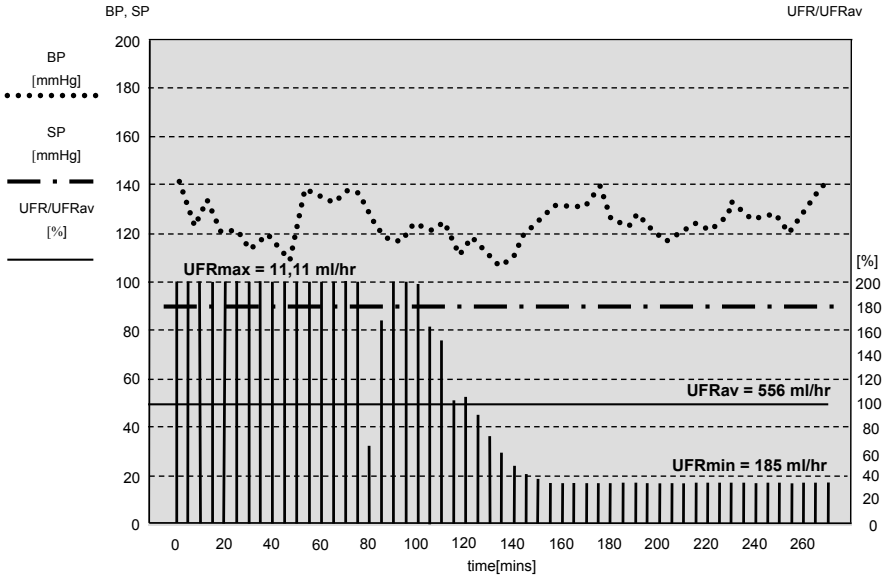

Fig. 20.7 The figure shows the behaviour of the Ultrafiltration rate (UFR, vertical bars) and blood pressure (BP, dotted line) trend during a dialysis session with the automatic blood pressure stabilisation system. The critical systolic pressure (SP, dashed line) set-point was 90 mmHg (top horizontal line) and was not changed since BP never reached that level. The UFR was maintained constant (1111 ml/h) until a BP reduction was recorded (80 minutes), when it was automatically reduced. During the 3rd and 4th hour the UFR was progressively reduced until a minimum value of 185 ml/h (bottom horizontal line). The mean UFR resulted equal to 556 ml/h (middle horizontal line).

Obviously, a system limitation may be, having to respond categorically to given constrains such as the duration of the session and the total ultrafiltration (total patient fluid loss). If rigid limits are set upon these parameters, then in some patients the control becomes more difficult by the system. We are performing a clinical multicenter, prospective, controlled, randomised trial, based on the application of this system, better known as APBS (Automatic Blood Pressure Stabilisation System) in a group of patients with pressure instability. Although the study is not yet complete, the preliminary results show an efficacy of the system vis-à-vis symptomatic intradialytic hypotension. In particular (see Fig. 20.8), the most severe hypotensive episodes are significantly statistically reduced; this is likely to be linked to the large reductions in the blood volume (Mancini et al. 2003).

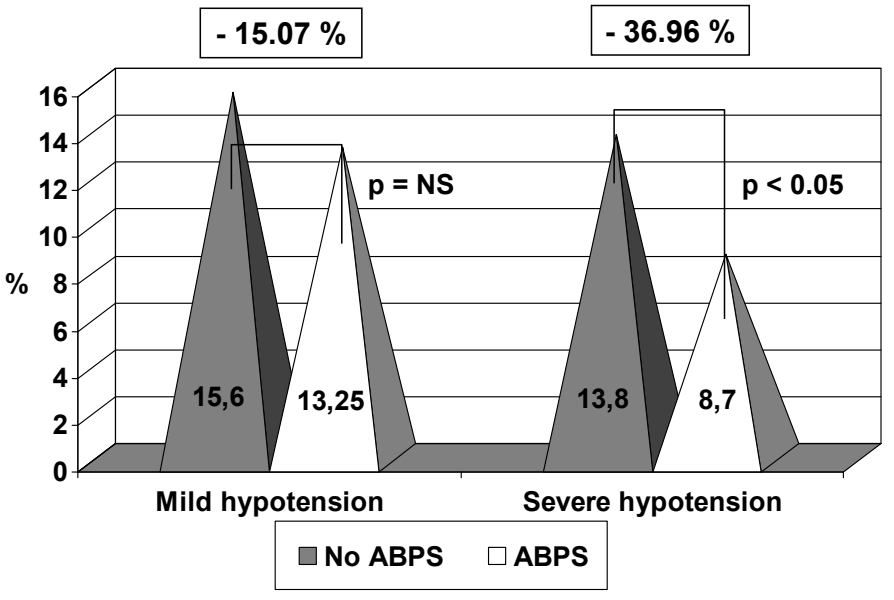

Fig. 20.8 Comparison of the frequency of hypotension episodes (severe and mild) in dialysis sessions without and with the automatic blood pressure stabilisation system (ABPS). A significant difference between the two modalities was observed in the appearance severe hypotension events (-36.96% in ABPS dialysis).

20.4 BIOCHEMICAL MONITORING AND CONTROL

The need to verify the quality of the actually delivered treatment can only be satisfied by the use of systems aimed at the real-time monitoring of actual urea clearance (dialysis efficiency) and solute removal (dialyzer performance), using special biosensors.

An indirect measurement of the urea clearance can be obtained with the ionic dialysance (total effective dialysance) that can be measured conducimetrically. Conducimetric dialysance measured by the conductivity technique in the dialysate represents the effective dialyzer clearance, which does not take the vascular access and cardiopulmonary recirculation into account, so it can be usefully used to monitor the fluctuations in the clearance.

Further possibilities for monitoring dialysis efficiency, with indirect measurements of the effective clearance, can only be superseded by the

real-time monitoring of urea concentration, made possible by using dedicated urea sensors measuring urea directly on the extra-corporeal circuit.

Continuous urea monitoring can now be carried out on the ultrafiltrate by means of a devised that can only be used during Paired Filtration Dialysis, a dialysis technique in which there is a continuous production of ultrafiltrate (UF), and where the urea concentration is wholly comparable to the plasma water concentration. The measurement system consists of:

i. a conductivity cell measuring UF conductivity;
ii. a urea sensor containing urease, an enzyme inducing the complete hydrolysis of UF urea with production of ammonium ions;
iii. a second conductivity cell which detects the UF conductivity changes induced by the ammonium ions.

The conductivity difference between the two cells correlates well to the UF urea concentration. The continuous intradialytic measurement of the urea concentration allows us to calculate kinetic parameters, such as Kt/V and dialytic time averaged urea concentration. Hence, there is this is a true and “quality control" of the treatment, with the possibility to check, in real-time, that the prescribed and the administered dialysis dose do actually overlap, and, eventually, modify the parameter prescription in order to avoid situations of underdialysis.

20.5 CONCLUSIONS

The technological innovation that has come about in the dialysis field in the past few years has allowed for the realisation of sophisticated biofeedback systems, based on the continuous measurement of the physical variables such as body temperature or haemodynamic variables such as the blood volume and the arterial pressure. These systems have been implanted and used successfully in the day-to-day dialysis practice, above all in the management of the “difficult” and unstable patients.

In our opinion, however, the future must look to an integration of the already existing system and the completion with other physical and chemical variables that are essential for a physiological dialysis (see Fig. 20.9).

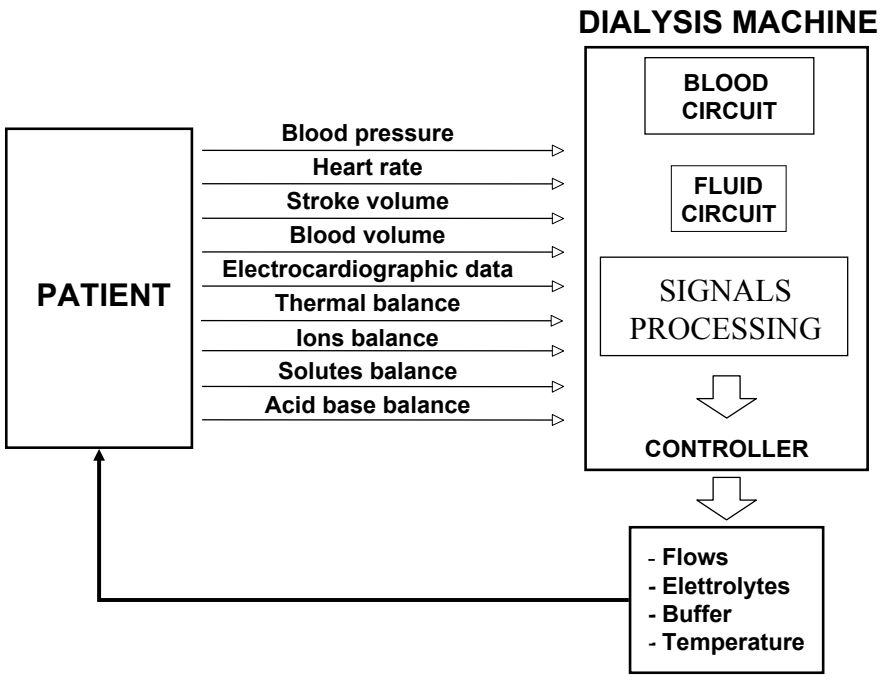

Fig. 20.9 Integrated adaptive control with a schematic view of the monitored variables and the controller dedicated to signal processing and dialysis machine control.

Only by means of a more accurate and complete monitoring and adaptive control of the patient during the dialysis session will it be possible to make the process of renal replacement therapy more physiological, with traditional times and methods. A similar system, integrated into the dialysis machine, is today impossible to create. However, the challenge that industry and researchers must face and conciliate is the technological complexity of the system with an extreme simplicity of use and extremely low running costs. The alternative, which however does not exclude a careful "instrumental" surveillance of the patient, is the recourse to dialysis techniques with a greater weekly frequency (such as daily dialysis) or with a longer duration (diurnal or nocturnal long-duration dialysis) that come closer to the continuous physiological purification ensured over the 24 hours by the human kidney.

Unfortunately, the continuous increase in demand for R.R.T. and the even lower availability of economic resources hamper the diffusion of long dialyses and extremely frequent ones, so it is quite likely that we should increasingly look to technology for a helping hand.

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ESSAY QUESTIONS

1. Define the concept of biofeedback system
2. List the basic components of a biofeedback system
3. Define the plant, the actuators and the controller.
4. List the two kinds of information which the scientific formulation of a control problem is based on.
5. List the major types of biofeedback systems routinely used in clinical dialysis.
6. What are the most important dialysis variables for controlling volemia during dialysis treatment?
7. What is the main problem of the biofeedback systems?
8. What is the major limitation of BV Biofeedback models based on ultrafiltration alone?
9. What are the main objectives of the BV biofeedback system?
10. List the main possibilities for intradialytic heat accumulation.
11. Differentiate between the active operational modes of the BTM.

MULTIPLE CHOICE QUESTIONS

Choose the best answer

1. In a biofeedback system what is a sensor?

A. A device used to define the changes in the work of the actuators
B. A device used to measure the variable under control
C. A device used to calculate the distance between the target and the actual value

2. In a biofeedback system what is the role of the "actuators"?

A. They are the arms of the control process and actually work to reach the target
B. They are the systems to measure the variations of the variable under control
C. They are the heart of the mathematical model

3. Which one of the following is not a characteristic of a sensor dedicated to dialysis?

A. Continuity and accuracy of the measure
B. Non-invasiveness
C. Off-line continuous measurement

4. Which one of the following is a target for biofeedback systems for chronic hemodialysis patients?

A. Improve the efficacy of anticoagulation
B. Improve the cardiovascular stability
C. Improve the functioning of the vascular access

5. In the biofeedback system controlling blood volume changes during hemodialysis which one of the following is an actuator used to pilot blood volume?

A. Dialysate temperature
B. Dialysate sodium concentration
C. Dialysate flow rate

6. Besides blood volume, what are the other goals for the blood volume biofeedback system?

A. Kt/V and urea reduction
B. Water removal and equivalent conductivity
C. Electrolyte mass removal

7. How is the trend of the ultrafiltration rate during a dialysis session with the biofeedback control system of blood volume?

A. Continuously changing, higher at the beginning
B. Continuously changing, lower at the beginning
C. Continuously changing with a step profile (ups and downs)

8. What is the vascular refilling rate?

A. The rate of the fluid shift from the vessels to the interstitium
B. The rate of the fluid shift from the interstitium to the vessels
C. The rate of the fluid shift from the interstitium to cells

9. What is the effect on the blood volume trend of increasing the dialysate conductivity?

A. Favouring fluid mobilisation towards the cells
B. Favouring fluid mobilisation towards the circulation
C. Favouring fluid mobilisation towards the heart

10. In many uremic patients the body temperature tends to be…

A. Lower than in non-uremic subjects
B. Higher than in non-uremic subjects
C. Comparable to non-uremic subjects

11. The cutaneous vasoconstriction induced by ultrafiltration-induced hypovolemia is responsible for…

A. Enhanced dissipation of the heat accumulated
B. Reduced dissipation of the heat accumulated
C. No relationship between heat and blood volume

12. BTM stands for…
    A. Blood temperature monitor
    B. Body temperature modifier
    C. Blood temperature maintenance

13. During a dialysis session with BTM, which temperatures are measured?
    A. Arterial and venous
    B. Arterial, venous and dialysate
    C. Venous and dialysate

14. During a dialysis session with BTM, where is the first effect of the change in the dialysate temperature?

    A. In the arterial line of the extracorporeal circuit
    B. In the venous line of the extracorporeal circuit
    C. In the vascular access

15. During a dialysis session with BTM, setting the BTM goal to 0°C implies:
    A. Isothermic dialysis
    B. Isoenergetic dialysis
    C. Isovolemic dialysis

16. Which one of the following dialysis strategies has the more negative thermal balance?
    A. Bicarbonate dialysis dialysate 36.5°C
    B. Post-dilution Hemodiafiltration, infusate 37°C
    C. Pre-dilution hemodiafiltation, infusate 37°C

17. One of the following is not a feature of the BTM system…

    A. Temperature control
    B. Energy control
    C. Volume control

18. The system called ABPS is dedicated to…

    A. The prevention of acute hypotension
    B. The prevention of insufficient depuration
    C. The prevention of vascular access problems

19. What are the actuators in ABPS?

A. Dialysate sodium concentration and dialysate temperature
B. Dialysate sodium concentration and ultrafiltration
C. Ultrafiltration alone
D. Dialysate sodium concentration alone

20. A real-time monitoring of urea concentration in the extracorporeal circuit may help to…

A. Monitor the dialysis efficiency
B. Prevent cardiovascular instability
C. Monitor the reduction in plasma volume