**Special Feature**

**Haemodialysis with on-line monitoring equipment: tools or toys?**

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**Abstract**

**Background.** On-line monitoring of chemical/physical signals during haemodialysis (HD) and bio-feedback represents the first step towards a ‘physiological’ HD system incorporating adaptive and logic controls in order to achieve pre-set treatment targets.

**Methods.** Discussions took place to achieve a consensus on key points relating to on-line monitoring and bio-feedback, focusing on the clinical applications.

**Results.** The relative blood volume (BV) reduction during HD can be monitored by optic devices detecting the variations in concentration of haemoglobin/haematocrit. BV changes result from an equilibrium between ultrafiltration and the refilling capacity. However, BV reduction has little power in predicting intra-HD hypotensive episodes, while the combination of the patient–dialysate sodium gradient, the relative BV reduction between the 20th and 40th minute of HD, the irregularity of the profile of BV reduction over time and the heart rate decrease from the start to the 20th minute of HD predict intra-HD hypotension with a sensitivity of 82%, a specificity of 73% and an accuracy of 80%. A biofeedback system drives the relative BV reduction according to desired values by instantaneously changing the ultrafiltration rate and the dialysate conductivity. This system has proved to reduce the incidence of intra-HD hypotension episodes significantly. Ionic dialysance is also a useful tool to monitor vascular access function, as it can be used to obtain serial measurements of vascular access blood flow. On-line urea monitors provide detailed information on intra-HD urea kinetics and delivered dialysis dose, but they are not in widespread use because of the costs related to the disposable materials (e.g. urease cartridge). The body temperature monitor measures the blood temperature at the arterial and venous lines of the extra-corporeal circuit and, thanks to a bio-feedback system, is able to modulate the dialysate temperature in order to influence the patient’s core body temperature, which can be kept at constant values. This is associated with improved intra-HD cardiovascular stability. The module can also be used to quantify total recirculation.

**Conclusions.** On-line monitoring devices and bio-feedback systems have evolved from toys for research use to tools for routine clinical application, particularly in patients with clinical complications. Conductivity monitoring appears the most versatile tool, as it permits quantification of delivered dialysis dose, achievement of sodium balance and surveillance of vascular access function, potentially at each dialysis session and without extra cost.

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Introduction

The development of haemodialysis (HD) ‘changed kidney failure from a fatal to a treatable disease, prolonging the useful lives of millions of patients’, as noted by the Albert Lasker Foundation when the 2002 Albert Lasker Award for Clinical Medical Research was awarded to Willem J. Kolff and Belding H. Scribner for their pioneering work in the development of HD [1,2]. Over the last few years, technological innovations in dialysis equipment and new modalities have improved the quality and safety of HD treatment. However, if we assume that the ideal of dialysis is to replace the function of the failed kidneys as completely as possible with full rehabilitation of the patient and minimal cost to society, we realize that we are still far from reaching this goal. In fact, among the many differences, the natural kidneys are capable of maintaining perfect homeostasis of the volume and chemical composition of the ‘internal milieu’, in a continuous time-constant fashion, via complex sensing and feedback mechanisms. Conversely, the traditional HD equipment is based on relatively fixed prescriptions throughout the sessions [constant hourly ultrafiltration (UF), constant patient–dialysate exchange gradients], which are modified only from time to time according to clinical evaluation and laboratory parameters. So many differences exist between the natural kidneys and artificial ones that Jacobs correctly wrote that ‘the true miracle is that these very primitive devices are able to provide several decades of survival time for the patients’ [3]. Although HD treatments have become much better tolerated because of progress in technology, intra-HD hypotension is still the most frequent complication of HD sessions and significantly interferes with the quality of life and the delivery of dialysis treatment in a non-negligible number of dialysis patients. This is also because of the characteristics of the modern dialysis population, which is getting older and sicker because of the many co-morbidity factors [4], and requires HD treatments to be as physiological and tolerable as possible.

From this need, together with the progress in the technology of HD machines, the concept of treatment profiling emerged. The rationale of dialysis profiling lies in the assumption that patients may undergo physiological variations during HD treatment so that the dialytic parameters set at the beginning of the session may not be adequate after a few hours of therapy. Hence, specific software programs have been designed to pre-set variable profiles of UF and dialysate sodium concentration. The main drawback of these approaches is that they are constructed on data from previous clinical observations and not on the response to the changes actually occurring in the patient during that particular treatment [5]. In other words, the limit of treatment profiling lies in the blind nature of the prescription, which is designed a priori and based on physiological assumptions. This is in contrast to the function of the natural kidneys, which are able to recognize immediately any deviation from the homeostatic condition. The requirement for on-line monitoring of physiological signals soon became evident in the perspective of evolving the dialysis machine to become an ‘intelligent’ artificial kidney.

This report focuses on the most important clinical applications of the on-line monitoring systems so far developed by the HD technology and is intended to appraise critically whether they should be still viewed as toys, or whether they can rather be used as tools in the dialysis panorama. The accord reached on key points is summarized.

The concept of on-line monitoring and bio-feedback

During HD treatments, patient surveillance is normally limited to occasional measurements of body weight and blood pressure. As a consequence, therapeutic interventions are made only upon the appearance of symptoms and side effects. This may imply: (i) discomfort to the patient, with a risk of reduced compliance with the HD treatment itself; or (ii) interference with the delivery of the HD prescription (treatment time and dry body weight achievement). A more perceptive patient monitoring from a biochemical and physical standpoint may enable the early recognition of signs of intolerance and permit an early intervention.

The concept of on-line monitoring is based on the real time and repeated measurement of chemical/physical signals coming from the patient. Today, the different parameters for which on-line monitoring is possible are: blood volume (BV) changes, dialysate conductivity, urea kinetics and thermal energy balance.

The logical flow of on-line monitoring is the following: once the measurement of a given signal is taken, data are analysed and evaluated. If the parameter is within the desired values, the treatment continues unchanged. If the parameter is not satisfactory, an action to bring it back to the desired value is needed. This action can be operated manually (by the operator), semi-automatically (authorized feedback by a nurse or a doctor) or automatically by a bio-feedback loop built in the machine [6]. This is the concept of automatic bio-feedback. While any action performed by an operator necessarily implies a certain time lag, the power of the automatic feedback is that no lag is present between the analysis of the signal coming from the patient and the retroactive action to bring the parameter back to the desired value. The final result of automatic bio-feedback systems is that the control
variable varies gradually and smoothly along a pre-defined trajectory towards a pre-defined target. Indeed, the essence of physiology is regulation, and the human body has thousands of control systems interacting with one another, whose main aim is to keep the internal environment under such constant conditions as are comparable with cell life. Most of these control systems use negative feedback consisting of a series of changes that return the deviating factor towards its nominal value [7]. Similarly, on-line monitoring with automatic instantaneous bio-feedback will be the first step towards a ‘physiological’ dialysis, where the dialysis treatment parameters, such as weight loss rate, dialysate conductivity and dialysate temperature are not pre-set by the operator, but are changed continuously and dynamically by a dialysis delivery system incorporating adaptive and logic controls, in order to achieve the pre-set treatment targets.

Blood volume monitoring and modelling

The BV changes during HD are mainly a function of the UF rate and the patient’s vascular refilling. During HD, the fluid is removed by UF directly from the intravascular compartment, but it is finally derived from both the intravascular and the interstitial compartments and, in some cases, from the intracellular fluid space. This implies a continuous refilling of fluid from the extravascular to the plasma compartments, which avoids overt hypovolaemia. The plasma refilling rate can be calculated as the difference between the total fluid loss and plasma volume loss per time unit [8]. After an initial phase in which the fluid loss leads to a decrease in intravascular hydrostatic pressure, the increase in oncotic pressure secondary to haemocencentration enhances the plasma refilling from the interstitial compartment. As a consequence of this fluid shift, the plasma oncotic pressure declines, as does the interstitial hydrostatic pressure: the refilling will decrease until a new disequilibrium results because of the continuous water withdrawal across the dialyser [8].

In an attempt to find a relationship between the development of intra-HD hypotensive episodes and hypovolaemia, serial BV changes and the plasma refilling rate during HD were studied from the beginning of the dialysis era [9]. The early studies calculated the total BV from either the circulating plasma volume or the red blood cell mass obtained by a dilution technique (using iodinated serum albumin [131I] or red blood cells tagged with chromium [51Cr], respectively) and correcting for haematocrit. However, such dilution techniques are expensive, time-consuming and, obviously, unsuitable for clinical practice. More recently, indirect methods of measuring BV changes during HD have been proposed. They are based on the variation in concentration of intravascular substances whose pool can be assumed to remain substantially unchanged during HD, so that the variation in their concentration is due exclusively to the changes in BV. On-line optical devices have been developed which measure the optical absorbance of monochromatic light via an optprobe in the arterial line and provide a continuous monitoring of haemoglobin or haematocrit values (according to the Lambert–Beer law). They permit, via computer software, the continuous estimation of the percentage changes in BV during HD. It is important to stress that, in contrast to the dilution techniques, these devices do not give the absolute values of BV, but provide continuous monitoring of the percentage BV changes, which are graphically displayed in % BV changes–HD time curves and are available for use in routine clinical practice.

Blood volume monitoring and intra-HD hypotension

On-line BV monitoring permitted a more extensive and deeper insight into the pathogenesis of intra-HD hypotension. The importance of hypovolaemia in the determination of intra-HD hypotension was recognized early on by Kim et al. in 1970 [9] following the observation that, when BV fell below a given threshold, arterial hypotension appeared. However, subsequent studies were unable to demonstrate a close relationship and a temporal overlap between the maximal reduction of BV and the reductions in arterial pressure.

The implementation of on-line BV monitoring has shown that: (i) different individual patterns of BV decrease are observed during HD sessions with a constant UF rate; (ii) although a certain correlation may exist between UF rate and development of hypotension, an absolute and objectively critical level of hypovolaemia that triggers intra-HD hypotension does not exist, because of great variability in the predisposition to hypotension, not only among individuals but also within the same individual; and (iii) the relationship between UF rate and BV changes, and between the latter and hypotension, is variable. These findings can be explained by: (i) vascular refilling capacities differing from patient to patient, within the same patient from session to session and within the same session from time to time, in relation to various parameters affecting vascular refilling during HD (patient-related factors, i.e. body size, fluid overload, plasma volume, regional blood flow distribution, plasma protein concentration, transcapillary pressure gradient, plasma osmolality and venous compliance; and dialysis-related factors, i.e. UF, dialysate sodium concentration, dialysate buffer and dialysate temperature [8]); (ii) the cardio-vascular response to hypovolaemia (increased arterial tone, venous vasoconstriction with centralization of the BV and increased pre-load, increased heart rate and contractility), which is also variable and may offset the BP reduction induced by a wide range of hypovolaemic states [10].

A recent study by Andrulli et al. [11] provided important information on the role of relative BV reduction, as continuously monitored by means of an optical device, in the genesis of intra-HD hypotension in a large number of patients (n = 123). The patients
were divided \textit{a priori} into three groups: normotensive, hypotension-prone and hypertensive. The duration of the study was 1 week. The intra-HD BV reduction was similar in the three groups (−13.8 ± 7.0%). Of note, in the patients experiencing intra-HD hypotension, this occurred at a relative BV reduction (−13.9 ± 6.4% at a dialysis time of 159 ± 56 min) that was not different from that recorded at the same time in dialysis sessions without hypotension (−12.7 ± 5.2%). No critical relative BV reduction level for the appearance of symptomatic hypotension could be found, as already reported by others [12]. Regardless of the curve of BV reduction, in all three groups, the greatest reduction in relative BV occurred during the first 40 min of dialysis, while the greatest rate of reduction in systolic BP occurred during the first 20 min. The different break times suggest that the BP response to dehydration was maximal before refilling was fully established and point to the role of cardiovascular compensatory mechanisms, in addition to vascular refilling, in determining cardiovascular stability during UF-induced hypovolaemia.

The most original part in the study by Andrulli \textit{et al.} was the assessment, in a multivariate logistic model, of the independent predictors of intra-HD hypotensive episodes. They included: the group to which the patients were originally assigned, as predicted [relative risk (RR) of hypotensive group vs normotensive: 7.26, \( P < 0.001 \)]; baseline plasma–dialysate sodium gradient, also as predicted (for each 1 mEq/l increase) (RR 1.13, \( P < 0.001 \)); relative BV reduction from 20 to 40 min of dialysis (for each 1% decrease) (RR 1.23, \( P = 0.03 \)); irregularity of the relative BV reduction over time (RR 3.13, \( P = 0.001 \)); and heart rate decrease from start to the 20th minute of HD (for each 1 beat/min decrease) (RR 0.95, \( P = 0.017 \)). When only relative BV between 20 and 40 min of dialysis was considered, the model had a sensitivity of 30% in predicting hypotension. Conversely, the multivariate model increased the predictive power to a sensitivity of 82%, a specificity of 73% and an accuracy of 80%, and included variables easy to obtain and relating to the first 40 min of HD, when hypotension is still preventable. The take-home message is that the interplay of UF and vascular refilling, reflected in the relative BV reduction curve, is only a part of the complex puzzle of the model predicting intra-HD hypotension, which must necessarily include other clinical variables related to additional compensatory mechanisms to gain clinical reliability.

If one considers the variations of heart rate as an index of the sympathetic system response, the reduction in heart rate during the first 20 min of HD—when the inhibition caused by the recumbent position probably exceeded the stimulation caused by the reduction in relative BV—can be viewed as an indirect index of preserved sympathetic function: those who had a reduced bradycardic response in the first 20 min of HD probably had an impaired autonomic function also predisposing them to hypotension in response to dehydration. Total relative BV did not have any predictive power for intra-HD hypotension, while a greater reduction in relative BV between the 20th and 40th minute of HD was an independent predictor of hypotension. This may be related to the timing of refilling, which may be delayed in hypotension-prone patients. Finally, apart from the expected variables (initial group of assignment and plasma–dialysate sodium gradient), the most powerful predictor of intra-HD hypotension was the irregularity of the relative BV over time: those patients whose time line was irregular had a 3.13 times greater risk of experiencing intra-HD hypotension. This indicates the importance of a ‘smooth’ and physiological BV reduction during HD and is in accordance with the findings that HD sessions performed with the aid of feedback systems aimed at controlling the BV reduction over time are at lower risk of intra-HD hypotensive episodes [13,14].

**Blood volume modelling**

Starting from the integrated monitoring of BV via an optical absorption bio-sensor, a bio-feedback system has been built based on an integrated multi-input–multi-output (MIMO) controller whose targets are prescribed total body weight loss, equivalent dialysate conductivity and relative BV change [8,15]. The monitored discrepancies between the instantaneous actual value and the instantaneous desired target for BV change, dialysate conductivity and weight loss represent the input parameters for the controller. The control variables, used as output parameters, are the instantaneous dialysate conductivity and weight loss rate, which can vary from instant to instant to reach the desired targets. In other words, this system is intended to balance the classical goals of removal of sodium and water excess (total body weight and equivalent conductivity targets) with the new goal of driving the BV reduction curve over time along a pre-set trajectory (relative BV change target). The equivalent conductivity value is defined as the conductivity value that, in standard HD with a constant dialysate conductivity, produces the same sodium mass balance as the BV-controlled HD, and it corresponds to the mean dialysate conductivity value throughout the BV-controlled session. The goal of this closed-loop bio-feedback software is to reach the best compromise, according to an error-based mathematical model, between the various targets, taking into account the fact that these targets sometimes may be in reciprocal conflict. The net result produced by this system is that the three target parameters (relating to water balance, sodium balance and desired BV reduction curve), decided by the operator at the beginning of the sessions, are smoothly driven, during the HD session, through a precise three-dimensional curve that represents the best compromise among the targets themselves. This operation is performed with a given range of tolerances for each parameter, decided by the operator as a safety feature.

In fact, the MIMO controller system acts as a BV controller that continuously modifies the instantaneous UF rate and dialysate conductivity, while guaranteeing sodium and water balance. The rationale of this system

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is to smooth out the acute and sudden reductions in BV that can appear during HD sessions, consequent to a transient imbalance in the patient’s vascular refilling capacity, in order to try to reduce the incidence of intra-HD hypotension episodes.

After preliminary studies indicating improved haemodynamic stability in BV-controlled HD in hypotension-prone patients [14,15], a randomized multi-centre controlled trial has been carried out to test this hypothesis formally [13]. Thirty-six hypotension-prone patients were selected and randomized in a crossover parallel-group design alternating 4 weeks of conventional (A) and BV-controlled (B) HD (sequence 1, ABAB; sequence 2, BABA). Before entering the allotted sequence, the patients underwent a 2 week run-in period to optimize the prescription of the dry body weight and to set the desired value of BV reduction in each patient. The operative variables of the treatments (dialyser membrane and surface, treatment time, blood and dialysate flow rate, and dialysate composition) were kept unchanged throughout the two alternating study periods. The two treatments were equivalent in terms of mean dialysate conductivity, so the only difference between treatment A and treatment B was that in the latter, both weight loss rate and dialysate conductivity were automatically and continuously adjusted throughout the treatment by the MIMO controller, in order to keep the BV changes within the desired time course. The pre-set weight loss and the actual weight loss were comparable between treatments A and B, as were sodium removal and the end-dialysis percentage reduction in BV. However, on treatment B, the patients experienced a significant reduction in the number of intra-HD hypotensive episodes, as compared with treatment A, which could not be explained by total percentage BV reduction, in accordance with the data of Andrulli et al. [11]. Interestingly, the higher the number of hypotensive episodes in the run-in period, the better was the response to BV-controlled HD. In other words, the most symptomatic patients were those who appeared to benefit most from the automatic BV control. Treatment B was also associated with a significant reduction in post-dialysis symptoms, such as asthenia, headache, nausea and vomiting. In conclusion, this randomized controlled trial showed that the BV-controlled HD treatments can significantly improve both intra-HD complications (number and intensity of hypotension episodes) and disturbing post-HD symptoms. However, the reasons for this improved outcome have still to be clarified. They may be related to the smooth and physiological reduction in the BV profile, which is also in accordance with the study by Andrulli et al. [11].

**Ionic dialysance monitoring**

Effective ionic dialysance can be defined as the dialysance of mobile electrolytes through the dialysis membrane corrected for recirculation and UF. Ionic dialysance can be measured on-line by a conductivity method, as first described by Petitclerc et al. [16] and Polashegg [17]. The principle of measurement of ionic dialysance involves the use of a temperature-compensated conductivity probe, which permits measurement of the conductivity at the dialysate inlet and outlet at regular intervals during HD. The calculation of ionic dialysance is based on observed differences in inlet and outlet conductivity values at two different steps of inlet dialysate conductivity. From a practical point of view, an automatic change of 1 mS/cm in the conductivity of the dialysis fluid entering the dialyser and lasting ~2 min is generated. The resulting change in conductivity at the dialyser outlet is measured and both the effective ionic dialysance and the patient’s plasma conductivity are automatically calculated. The advantages of ionic dialysance are that it is non-invasive (no need for blood sampling), inexpensive (no disposable cost) and fully automatically calculated at each HD session.

Given the linear correlation between the conductivity of a solution and its sodium content, conductivity values can be used instead of sodium concentration for both the dialysate and the patient’s plasma. Moreover, as sodium is by far the most represented electrolyte in the dialysate, ionic dialysance can be assumed to be equal to sodium dialysance with minimal imprecision.

**Ionic dialysance and assessment of delivered dialysis dose**

Effective ionic dialysance has been assumed to be equivalent to effective urea clearance because of the similar molecular weight and osmotic distribution volumes of sodium chloride and urea. This appeared immediately fascinating because of the possibility of calculating Kt/V by using the mean ionic dialysance throughout the session as the K value, the real duration of the session as the t value and the urea distribution volume as V, calculated either as 55% of the body weight or with anthropometric formulae. This hypothesis has been verified first by Petitclerc et al. both in vitro [18] and in vivo [19], comparing the effective urea clearance measured by collecting the whole spent dialysate with the mean of the ionic dialysance values determined throughout the sessions: the correlation coefficient was 0.94 and the 95% confidence interval of the difference was –8 to +4 ml/min. A subsequent study by Manzoni et al. [20] showed an important underestimation of Kt/V, determined by means of direct quantification, by Kt/V calculated using mean ionic dialysance and V determined either as 55% dry body weight (underestimation of 22%) or with anthropometric formulae (underestimation of 23%). The difference was explained both by the overestimation of the urea distribution volume (+17%) and by underestimation of effective urea clearance (–11%). Nonetheless, ionic dialysance and urea clearance proved to be closely correlated (r² = 0.89), so that effective urea clearance could be derived reliably from ionic dialysance. In the study by Di Filippo et al. [21], V was calculated
according to the single-pool variable volume (SPVV) three blood urea nitrogen method urea kinetic model using the mean dialysance (D) values, recorded during one HD session, instead of instantaneous effective urea clearance values. One month later, Kt/V was calculated as Dt/V, using actual D and t values and the pre-determined V values updated for final body weight. Kt/V was also calculated by means of the SPVV model and the Daugirdas and Smye formulae. The Kt/V values calculated by means of ionic dialysance (Dt/V) were equivalent to those calculated by the traditional methods requiring blood samples. This is due to the fact that, using ionic dialysance, the error in estimating the distribution volume is consensual to that in estimating the effective urea clearance, so the ratio Dt/V is correctly calculated. This is similar to what happens when the SPVV model is applied: the urea distribution volume is overestimated because of the urea rebound; at the same time, when post-dialysis urea rebound is present, effective dialytic urea clearance overestimates effective patient urea clearance. Nevertheless, the errors in clearance and volume cancel each other out in the ratio, and so the Kt/V is correctly estimated. The take-home message is that, as V is not expected to change drastically over a period of several months in clinically stable patients, one needs to determine pre- and post-HD equilibrated blood urea concentrations only every 6–12 months in order to determine V. Once the latter has been calculated, the mean ionic dialysance value can be used instead of the effective urea clearance to calculate Dt/V at each dialysis session. After it was shown by Di Filippo et al. that the underestimation of effective urea clearance by ionic dialysance depended on the modalities of changing the inlet dialysate conductivity for calculating ionic dialysance, and that cardiopulmonary recirculation was responsible for the differences between ionic dialysance and urea clearance [22], subsequent studies confirmed the excellent correlation between ionic dialysance and urea clearance, maintained over high urea clearance ranges (high-efficiency HD), and showed that, after taking into account or eliminating vascular access and cardiopulmonary recirculation, no difference between the two variables was present [23, 24].

In conclusion, ionic dialysance is equivalent to urea clearance, corrected for recirculation. It can permit the easy monitoring of dialysis efficiency session by session and during the same HD session, and the early detection of problems with the delivery of the prescribed dialysis dose. Given the widely documented relationship between dialysis dose and morbidity and mortality, one should expect substantial benefits and reduced complications from a continuous monitoring of the delivered dialysis dose.

**Ionic dialysance and sodium balance**

One major goal of dialysis treatment is to remove the exact amount of sodium that has accumulated in the inter-dialytic period in order to reach zero sodium balance. This is the cornerstone for maintaining normal BP values both in the inter-dialytic intervals (avoiding arterial hypertension and use of antihypertensive drugs) and during the HD sessions (avoiding intra-HD hypotensive episodes).

According to the single-pool sodium kinetic model, zero sodium balance can be achieved by individualizing the dialysate sodium concentration for each dialysis session to result in a constant end-dialysis plasma water sodium concentration and applying a rate of UF equal to the inter-dialytic increase in body weight [25]. Using flame photometry to determine total sodium concentrations, this early analytical single-pool kinetic model showed a degree of imprecision of ±2.8 mEq/l in predicting end-dialysis plasma water sodium concentration. This means, for a final total body water volume of 401 (58% of a 70 kg body weight), there will be an imprecision of ±112 mEq in predicting sodium removal with dialysis. However, on the basis of Gotch’s theoretical premises, Di Filippo et al. [26] demonstrated more recently, using direct ionometry, a level of imprecision in predicting sodium balance of <34 mEq. Unfortunately, this model is unsuitable for routine clinical use because of the need for blood sampling and laboratory determinations at each dialysis session.

Given the linear correlation between the conductivity of dialysate and its sodium content, conductivity values can be used instead of sodium concentration values. The sodium kinetic model can therefore be changed into the conductivity kinetic model, that allows one to predict the final plasma water conductivity when the dialysate conductivity is known, and to determine the dialysate conductivity required to obtain a desired end-dialysis plasma water conductivity.

It has been shown that the conductivity kinetic model has a degree of imprecision in predicting end-dialysis plasma water conductivity of less than ±0.14 mS/cm, roughly equivalent to ±1.4 mEq/l in terms of ionized plasma water sodium concentration and to ±56 mEq in terms of sodium balance [27]. Paired filtration dialysis is a special version of haemodiafiltration in which convection and diffusion take place separately, allowing the on-line monitoring of ultrafiltrate conductivity. A multi-centre, prospective, controlled and randomized trial [28] demonstrated that the attainment of ‘constant’ end-dialysis ultrafiltrate conductivity values, by means of the application of a dedicated conductivity kinetic model [29], makes it possible to improve cardiovascular stability in HD patients prone to intra-HD hypotension. It is of note that the improvement in cardiovascular stability was obtained by simply reducing the variability of end-dialysis ultrafiltrate conductivity, mainly related to day-to-day variations in sodium intake. In fact, these results were obtained by simply modifying dialysate conductivity in order to reach an ultrafiltrate conductivity at the end of each session that was equal to the mean value determined in the same patient during the run-in period. This value was not different between the two treatment arms, but the variability
of end-dialysis ultrafiltrate conductivity was lower during the experimental treatment than during the conventional treatment.

On the basis of the patient’s plasma conductivity calculated from dialysate conductivity measurements [16], a bio-feedback control system has been developed which is able to change dialysate conductivity in order to obtain a predetermined plasma conductivity target at the end of each HD session. In other words, given the very strict correlation between conductivity and sodium content, the physiological controller computes the dialysate conductivity allowing the patient’s plasma sodium concentration to be changed from an unknown starting point to a prescribed end-of-session value. As a result, the patient’s post-dialysis sodium level becomes independent of the initial status. The initial prescriptions comprise the hourly UF rate, which is kept constant throughout the HD session, the prescribed end-dialysis body weight and the prescribed end-dialysis plasma sodium concentration, expressed as the patient’s plasma conductivity. The module assumes a monocompartmental distribution volume for sodium equal to the patient’s total body water and continuously updates the dialysate conductivity according to the comparison between the patient’s plasma conductivity calculated and that foreseen by the computer.

Restoring a stable sodium level at the end of each treatment is a way of ensuring that sodium removal equals the inter-dialysis sodium intake and should therefore lead to a significant improvement in intra-HD cardiovascular stability. However, large well-designed prospective trials investigating this equipment are still lacking, and the facility of sodium control certainly needs further investigation.

**Ionic dialysance and vascular access monitoring**

Vascular access failure remains a major cause of morbidity for patients undergoing HD. The variation of vascular access blood flow rate (Qa) has been shown to be an important predictor of vascular access failure. Consequently, a simple, inexpensive and non-invasive method for routine measurement of Qa would be a useful tool. A new method was proposed recently to determine the Qa from measurements of ionic dialysance in normal and reversed positions of the blood lines. As the effective ionic dialysance takes into account the access recirculation, the difference between the two values of ionic dialysance in normal and reversed positions of the blood lines depends on the recirculation rate induced by the reversal of the blood lines. This recirculation rate is inversely proportional to Qa, and a simple relationship allows one to calculate the Qa from the two measurements of ionic dialysance [30, 31]. Clinical validation in HD patients showed a significant correlation with the ultrasound dilution method, taken as a reference [31,32]. A recent study evaluated the possibility of detecting vascular access stenosis by measurement of access blood flow from ionic dialysance [33]. Twenty-three patients had Qa evaluated by the ionic dialysance method and by the ultrasound dilution technique during the same dialysis session. In addition, they underwent ultrasonography of the fistula and, if a stenosis was detected, angiography was performed for confirmation. The Qa values measured by the ionic dialysance method were no different from those measured by ultrasound dilution. Qa measured by ionic dialysance was significantly lower in patients with a fistula stenosis than in those without (508±241 vs 1125±652 ml/min, P < 0.05). Among patients with a Qa <500 ml/min from ionic dialysance, five had a stenosis detected by ultrasonography (sensitivity 83%) and three had no stenoses. Of these three patients, two had a thrombotic event at 1 and 3 months, suggesting that Qa <500 ml/min from the ionic dialysance method is a better predictor of thromboses of HD vascular access than a stenosis detected by ultrasonography. In conclusion, by means of the ionic dialysance method, easy monitoring of vascular access function is possible with a device already operating in the dialysis monitor, i.e. without extra cost.

**Urea monitoring**

Based on urea kinetic modelling (UKM) analysis, dialysis quantification has proved to be a powerful tool to evaluate both dialysis dose delivery and dietary protein intake equivalent in HD patients. Despite the restricted value of urea as an uraemic toxin per se, it is recognized that dialysis dose and dietary protein intake are strong predictors of morbidity and mortality in HD patients. Urea-based dialysis quantification therefore represents a masterpiece in the evaluation of dialysis adequacy that is strongly recommended by the DOQI and European Best Practice guidelines [34,35]. Quantification of dialysis based on blood side methods (blood UKM) requires careful timing of post-dialysis blood sampling to avoid errors induced by post-dialysis rebound and access recirculation. It also requires the use of complex mathematical equations accounting for solute disequilibrium in the patient. Dialysate-based UKM used to solve technical and mathematical issues has been proposed as an alternative method. Direct dialysis quantification of urea removed during dialysis requires partial or total collection of the spent dialysate [36]. Collection of dialysate is cumbersome and does not permit a direct calculation of dialysis dose without estimating the urea volume [37].

On-line urea monitoring (Ol-UM) has been proposed to circumvent most of these technical and mathematical problems. The aim of these urea-sensing devices was to provide the clinician with automated real-time bedside tools assessing dialysis efficacy and the protein nutritional status of dialysis patients. Routine monitoring of dialysis efficacy by Ol-UM devices offers a permanent method capable of quantifying and assuring dialysis dose delivery and protein nutritional assessment of dialysis patients.
Haemodialysis with on-line monitoring equipment: tools or toys?

Urea monitoring devices

Several urea monitor devices were developed and marketed for HD. Two main approaches have been proposed, the first consisting of using the spent dialysate and the second of using the ultrafiltrate (equivalent to a blood kinetic) [38]. Both methods used a urea sensor device measuring urea concentrations (dialysate and/or ultrafiltrate) at frequent intervals during HD treatment coupled to a computer analysing urea kinetics according to specified models and providing a selected set of data in real time: urea mass removed, body clearance, normalized urea clearance (Kt/V), urea volume and protein catabolic rate (PCR). Urea concentrations were obtained by analysing the by-product result of urea degradation in the spent dialysate with urease (e.g. the ammoniac produced, measured using a sensitive probe) [39]. Ol-UM systems can be integrated into a dialysis monitor. For example, the ultrafiltrate produced via a two-chamber haemodiafilter is passed through a cartridge containing urease. The ultrafiltrate line is equipped with two conductivity cells up- and downstream of the urease cartridge. Conductivity changes induced by urease are then continuously measured and computerized into urea concentrations [40]. In both cases, algorithms were used to determine urea concentrations in the biological fluids.

Clinical studies performed with Ol-UM devices

Despite the initial enthusiasm created by Ol-UM, it is interesting to note that few studies have been published. Those reported in the literature cover four main aspects: scientific validation of the urea sensor; cross-sectional studies on a small cohort of patients; short-term surveys on a limited number of HD patients; and the use of Ol-UM as a tool for examining urea kinetics in HD patients. Unfortunately, there currently are no studies proving the clinical benefits of the Ol-UM tool in the routine management of HD patients. No long-term longitudinal studies have been performed to explore the role of these Ol-UM devices in the early detection and correction of treatment failure or to evaluate their potential role in improving the morbidity and mortality of HD patients. Accordingly, it is currently difficult to ascertain that the use of Ol-UM devices will positively affect outcomes for HD patients.

Validation studies. Clinical validation of the Ol-UM devices has been confirmed in several studies. The most convincing evidence has been produced by studies comparing dialysis quantification based on Ol-UM with direct dialysis quantification based on a total or partial dialysate collection [39] or compared with ionic dialysance [23]. The reproducibility of the Ol-UM data has also been confirmed in short-term studies with repeated measurements in the same patients.

Cross-sectional studies with Ol-UM. Ol-UM was used to assess dialysis performances in cross-sectional studies in which small cohorts of dialysis patients were examined. However, these studies are interesting since they serve to illustrate the heterogeneity of results achieved in a group of patients treated in a similar way with the same follow-up [41]. This is particularly obvious when analysing dialysis dose delivered (Kt/V) or protein nutritional status in a group of stable patients. In all cases, the distribution of the patients’ values is largely spread around the mean value. Dialysis dose delivery as Kt/V can be used to illustrate this point. For a mean 1.2 Kt/V target value aimed at in a dialysis facility, it is easy to show that >20% of the dialysis population is below this value. The use of Ol-UM would be beneficial in this case by identifying patients not reaching the Kt/V targeted value and by facilitating the correction of the treatment schedule to achieve the optimal dialysis dose.

In some studies using the ultrafiltrate-based Ol-UM device, it was possible to explore urea kinetics during the intra- and immediate post-dialytic period. Mathematical analysis of these kinetics have confirmed that urea fitted a multi-compartmental model. Intra-corporeal urea body clearance is a personal characteristic with large inter-patient variation that determines the urea concentration disequilibrium during the dialysis. The volume accessible to clearance represents one-third of the urea distribution volume.

Short-term survey with Ol-UM. Permanent dialysis quantification monitoring with Ol-UM has been performed in HD patients over a period of several weeks [42]. Despite the small number of patients explored, it is interesting to note that the dialysis dose delivered remained relatively constant over a 1–3 month period, whilst the PCR fluctuated around the mean value with a variation averaging 18%. Such physiological variations in PCR observed in stable HD patients suggest that dialysis quantification must be performed frequently to be clinically meaningful. Moreover, time behaviour changes of dialysis dose delivered and PCR are clinically more interesting than the absolute value of the computed parameters.

Ol-UM as a tool for examining urea kinetics in HD patients. The use of UM devices has also contributed to our better understanding of the complex kinetics of urea in the body and to validate a simplified calculation approach [43,44].

Future of Ol-UM in dialysis

Ol-UM devices must be considered as ideal tools to ensure the delivery of quality dialysis on a routine basis. Ol-UM permits simple, reliable and permanent control of dialysis efficacy (dialysis dose). At the same time, it gives direct insight into the protein nutritional status of the patients.

However, these devices currently are not in widespread use because they can be time consuming and costly, because of the disposable materials required. In order to be usable in routine HD, Ol-UM must be adapted to this function. Integration of an Ol-UM device into the dialysis monitor is obviously required.
Clinical use must be simplified, automated and coupled to the dialysis monitor function. Disposable materials required to carry out Ol-UM (e.g. urease) must be simple and available at low cost. Analysis must be performed automatically and results provided at the end of the dialysis session.

With respect to on-line dialysis dose determination, it is worth noting that a new device has been developed, based on the continuous monitoring of solutes in the spent dialysate using ultraviolet (UV) absorbance determined by a double-beam spectrophotometer [45]. Kt/V is calculated as the slope of the logarithmic on-line UV absorbance measurements vs time, replacing the slope of blood and dialysate urea concentrations. In the study by Uhlin et al. [45], the Kt/V values from on-line UV absorbance measurements were similar to those obtained from blood urea and dialysate urea measurements and from an Ol-UM device. Therefore, on-line monitoring of solute removal by dialysis via an optical UV absorbance-based device represents a valid alternative to the classical and, to date, expensive Ol-UM devices.

**Monitoring of thermal energy balance**

Since the first reports, many studies have confirmed that if dialysate temperature is adjusted to the range of 34–35.5°C, cardiovascular stability during HD treatment is better than if dialysate temperature is set to 37°C [46–48]. This is because, as the dialyser also works as an efficient heat exchanger, the use of warmer dialysate is associated with an increase in core body temperature, shown to interfere with the appropriate haemodynamic response to UF, consisting of systemic vasoconstriction (increasing the peripheral vascular resistance), thus favouring the onset of hypotensive episodes in predisposed patients. Instead of using a constant dialysate temperature, thermal balance can be modulated by modifying the dialysate temperature by means of a blood temperature monitor integrated into standard HD machines [49]. This device can be used to measure blood temperature non-invasively in the arterial and venous lines of extra-corporeal blood circulation. On the basis of these data and of blood flow rate measurements, with correction for blood heat capacity, the monitor can calculate thermal energy flow to the patient. Arterial blood temperature corrected for recirculation approximately reflects the core body temperature. Through the feedback loop connecting the arterial and the venous blood temperature sensors with the thermostat in the machine, the device can modulate the dialysate temperature to maintain unchanged body temperature (so-called isothermic HD) or energy flow rate across the extra-corporeal circuit (so-called thermoneutral HD). In a randomized controlled trial by Maggiore et al. [50], the isothermic procedure was associated with significantly improved cardiovascular stability in comparison with the thermoneutral treatment. The explanation is that the feedback system, by modulating dialysate temperature, allowed the removal of extra heat accumulated during HD, thus improving the vascular reactivity in response to relative hypovolaemia.

The body temperature monitor is also capable of measuring non-invasively total recirculation (i.e. vascular access + cardiopulmonary recirculation) by applying a thermodilution measurement technique. The dialysate temperature is changed by 3°C for ~3 min and the resulting temperature change in both the venous and arterial blood lines is measured. The recirculation is calculated from these temperatures. This method has been validated in comparison with an ultrasound velocity dilution technique [51]. Recirculation above 10% is highly suggestive of problems with the vascular access, which in the majority of cases are due to a stenosis. Therefore, the body temperature monitor can be used as a non-invasive screening procedure to identify patients whose vascular access needs further study. This can be performed easily at no extra cost.

**Online monitoring: toys or tools?**

In order to address this issue correctly, it is useful to revise the definitions of toys and tools. A toy is a thing meant to play with; a tool is any instrument for doing a special job.

Many of today’s indispensable dialysis technology tools initially were considered to be toys by the nephrology community. For some time, on-line monitoring devices had also been considered mere toys for advanced research rather than real tools for routine clinical application. Today, several of these new devices are increasingly displaying their clinical utility, as shown by the clinical trials implementing the on-line monitoring and bio-feedback systems. The implementation of conductivity monitoring appears particularly promising, considering its versatility. The same system can be used to: (i) monitor the sodium balance on-line, the delivered dialysis dose and the vascular access blood flow; and (ii) guarantee an improved cardiovascular stability in hypotension-prone patients by reaching a zero sodium balance session by session (i.e. by removing during dialysis treatment the exact amount of sodium that has accumulated in the inter-dialytic interval). BV monitoring and modelling is another promising tool, although less versatile than conductivity monitoring. It has been proven to be effective in improving cardiovascular stability by controlling the shape of intra-HD BV change via continuous changes in UF rate and dialysate conductivity, while seeming not to affect the sodium balance negatively.

The present dialysis panorama has been characterized by the development of technological toys that have undergone clinical experimentation for feasibility, clinical testing, refinement and validation. While the experimentation phase needs to be expanded further, many of these HD machine-incorporated devices have already been marketed on the basis of the results of the
previous clinical trials. It is now time for nephrologists to become familiar with these devices in order to start using these tools in their clinical practice and to improve the quality of dialysis care. The issue of cost is a real one, considering that current dialysis techniques cost ~50,000 Euros per year per patient and the public health providers do not intend to increase budgets for health care. However, the advances in technology will make sophisticated on-line accessories more affordable from the mere economics perspective. It seems, therefore, that a new generation of dialysis machines will incorporate different sensors and on-line monitoring devices. The next step is the generation of 'intelligent' dialysis machines able to mimic what happens in nature, where rapid feedback occurs in response to many physiological signals. Of course, it is necessary that these instruments become a real part of everyday clinical practice to develop a favourable cost-effectiveness profile to justify the investment. As shrewdly pointed out by Tattersall: ‘Nephrologists have an ethical responsibility not to lose interest in developing new technology’ [52].

Final accord

After intensive discussion, the panel reached consensus on the following key points.

**BV monitoring and modelling**

- Relative intra-HD BV reduction can be monitored via specific devices, integrated into the HD monitors, which detect the variation in haemoglobin/haematocrit concentration. BV change is the result of an equilibrium between UF and vascular refilling capacity.
- No critical threshold of BV reduction at which hypotension predictively occurs has ever been identified. Although UF plays a central role in the determination of intra-HD hypotension, total relative intra-HD BV reduction is not a predictor of hypotension.
- Clinical variables that independently predict intra-HD hypotensive episodes are: plasma–dialysate sodium gradient, relative BV reduction from 20 to 40 min of HD, irregularity of the relative BV reduction over time and heart rate decrease from the start to the 20th minute of HD.
- The pathogenesis of intra-HD hypotensive episodes is multifactorial and certainly involves mechanisms beyond BV reduction, primarily cardiovascular compensatory mechanisms. While relative BV reduction from 20 to 40 min of HD has a sensitivity of only 30% in predicting hypotensive episodes, the multivariate model including other clinical variables increases the predictive power to a sensitivity of 82%, a specificity of 73% and an accuracy of 80%.
- A bio-feedback system has been developed that is able to control the relative BV reduction according to a pre-set trajectory by continuously modulating the UF rate and dialysate conductivity, while ensuring the achievement of the prescribed total weight loss and mean dialysate conductivity, in order to guarantee the efficient removal of the sodium/water excess.
- Such a device has been associated with significantly improved intra-HD cardiovascular stability in hypotension-prone patients.

**Ionic dialysance**

- Effective ionic dialysance can be calculated automatically from dialysate conductivity measurements carried out by electrodes integrated into HD machines.
- Ionic dialysance is equivalent to urea clearance corrected for recirculation. Therefore, it is a valuable tool to monitor dialysis efficiency within a single HD session and from session to session, without the need for blood or dialysate sampling and at no extra cost.
- The implementation of the conductivity kinetic model, replacing the previous sodium kinetic model that was unsuitable for routine application because it required blood sampling, permits the achievement of a zero sodium balance at each HD session.
- It has been demonstrated that the conductivity kinetic model can significantly improve intra-HD cardiovascular stability.
- A bio-feedback system has been built which, from the calculation of the patient’s plasma conductivity, is able to modulate the conductivity of the dialysate continuously in order to achieve a desired end-dialysis plasma conductivity, corresponding to the desired end-dialysis plasma sodium concentration.
- Ionic dialysance is also useful for the determination of the vascular access blood flow, therefore also providing a tool for surveillance of vascular access function.

**Urea monitoring**

- Urea kinetic monitoring is carried out by probes capable of detecting the products of urea degradation by urease.
- OI-UM is able to provide an abundance of information in real time: urea mass removed, body clearance, normalized urea clearance (Kt/V), urea volume and PCR.
- OI-UM has provided a useful tool for better understanding of complex urea kinetics. However, studies concerning the clinical utility of these devices are limited to date.
- OI-UM is not suitable for routine clinical use during each dialysis session, because the urease cartridge or the solutions for calibration are expensive and these methods are time consuming.
Thermal energy balance monitoring and bio-feedback

- As the dialyser also works as an efficient heat exchanger, the temperature of the blood returning to the patient is influenced by that of the dialysate.
- The blood temperature monitor allows the non-invasive measurement of blood temperature in both the arterial and venous lines using two independent and highly precise temperature sensors.
- A bio-feedback system has been developed which, by continuously modifying the dialysate temperature, is able to control the core body temperature of the patient (isothermic HD).
- The implementation of this device is proven to be associated with significantly improved intra-HD cardiovascular stability.
- By applying a thermodilution measurement technique, this device permits the calculation of total recirculation, thus providing a tool to monitor factors determining decreased dialysis efficiency.

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