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Automated Blood Volume Regulation During Hemodialysis

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1. Introduction

Intradialytic hypotension (IDH) is the most common complication of hemodialysis (HD), occurring in up to 20 to 33% of sessions (Daugirdas, 2001). IDH is responsible for various minor symptoms (nausea, vomiting, muscle cramps, dizziness, and fatigue) during dialysis, but is also associated with more severe adverse events such as myocardial infarction (Burton et al., 2009) and cerebral ischemia (Mizumasa et al., 2004). Moreover, as a result of frequent interruption of sessions and repetitive administration of intravenous fluids, underdialysis and inability to reach dry weight, with subsequent chronic overhydration, can follow.

Traditionally, HD prescriptions are based on clinical evaluation and laboratory measurements, and are re-evaluated periodically or when an adverse event, such as hypotension, commands it. The drawback of this prescription is that it relies on previous observations, with the assumption that the same will hold true for the next sessions. Hence, it implies discomfort for the patients, as the actions to remediate to IDH, for example, by stopping ultrafiltration (UF) or adjusting dry weight, are taken on an *a posteriori* basis (Locatelli et al., 2005).

In an attempt to prevent IDH, technological advances have made possible the detection of subclinical predictors of hemodynamic instability, for example relative blood volume variations. With repetitive measurement of such specific parameters during HD (Mercadal & Petitclerc, 2009), actions can be implemented to correct the monitored parameter toward a desired target, with the aim of preventing overt IDH. When this action is automatic and regulated by a closed feedback loop, it is called biofeedback.

In this chapter, we will review some of the physiological basis of IDH and blood volume reduction during HD, and we will examine the technical aspects of the various devices used to adjust blood volume during dialysis, with special emphasis on biofeedback systems. Finally, we will study the literature published on the effects of automated blood volume regulation devices on the occurrence of hypotensive episodes, volume overload control, hypertension management and quality of life in chronic HD patients.

2. Intradialytic hypotension

The causes of IDH are multifactorial. On one side, a number of patient-related conditions can promote blood pressure (BP) fall during HD: age, comorbidities such as diabetes and cardiomyopathy, anemia, large interdialytic weight gain (IDWG), use of anti-hypertensive

medication, etc. On the other hand, factors associated with the dialysis prescription itself can also contribute to hemodynamic instability: short HD sessions, high ultrafiltration rate, high dialysate temperature, low dialysate sodium concentration, inflammation caused by membrane activation, etc. As a consequence, various interventions aimed at modulating these parameters have been proposed to ameliorate the vascular tolerance to ultrafiltration (UF), but with variable efficacy and limited benefits.

On a physiological basis, IDH can be viewed as the inability of the cardio-vascular system to respond adequately to the reduction of blood volume. Cardio-vascular reactivity involves reflex activation of the sympathetic system, with appropriate tachycardia and arterial and venous vasoconstriction in response to cardiac underfilling and hypovolemia. These compensatory mechanisms are altered in some patients, which put them at risk of developing IDH. However, these are difficult to assess and to modify. Comprehensive study of blood volume regulation during HD can help understand IDH susceptibility of individual patients.

3. Blood volume regulation

3.1 Concept of plasma refilling

Blood volume is dependent on two main factors: plasma refilling capacity and UF rate. During HD, fluid is removed directly from the intravascular compartment. Total body water (TBW), which is about 60% of body weight (BW), is distributed in part in the intracellular (40% BW) and in part in the extracellular (20% BW) compartments. The latter is further subdivided in the interstitial (15% BW) and the intravascular (5% BW) spaces. Thus, only 8% of the TBW is readily available for UF. Therefore, in order to remove a substantial amount of fluid during a short period of time, the vascular compartment needs to be continuously refilled from the interstitial space.

Plasma refill is mostly driven by hydrostatic and oncotic forces. During the first part of a HD session, the vascular oncotic pressure raises and the hydrostatic pressure lessens as a result of progressive UF. Pressure gradients thus created drive the water back into the vascular space until a new equilibrium is reached. As UF and water withdrawal from the intravascular space continue, the new disequilibrium thereby generated has to be once again balanced, and so on until the end of the session (Santoro et al., 1996). Several factors can influence rate of plasma refilling by acting on these forces: hydration status, plasma osmolality, and plasma protein concentration. Patient's proper refilling capacity, which is not measurable as a parameter, also has an effect on the rate at which water moves back in the blood vessels. Overall, IDH is generated when the imbalance between UF rate and plasma refilling capacity cannot be surpassed by cardio-vascular compensatory reflexes.

3.2 Relative blood volume measurement

Cardio-vascular reactivity and plasma refilling capacity of each patient, albeit central in the pathogenesis of IDH development, are difficult to assess and therefore are not convenient as monitoring tools. Direct measurement of blood volume is feasible, classically using dilution of radioactively labelled blood elements (such as ^{131}I albumin or ^{51}Cr red blood cells), but it implies serial blood tests and radiation, and so is clearly impractical for the repetitive assessment of blood volume. One way to circumvent this problem is to measure blood volume change during HD which, as a surrogate marker of vascular refilling, can be estimated using bedside devices.

Relative blood volume (RBV) is the term used to describe « the blood volume at any time as a percentage of the blood volume at the commencement of treatment » (Nesrallah et al., 2008). Most of the non-invasive devices extrapolate the RBV change from the variation of the hemoconcentration of a blood element. The basic premise of this calculation is that if the blood component remains constant throughout the HD session (i.e., the numerator), the variation of its concentration is necessarily due to the change in the blood volume (i.e., the denominator). The various devices available vary in the blood element they measure (i.e., red blood cells, hematocrit, total protein concentration) and in the method used to measure it (i.e., optical absorbance, ultrasound, etc.).

One caveat of these techniques is that they are based on the assumption that uniform mixing of the measured blood element and plasma occurs throughout the whole circulation (Dasselaar et al., 2007a). Venous (or systemic) hematocrit (Hct_{sys}) is usually higher than whole-body hematocrit (Hct_w), due to the dynamic reduction of hematocrit in the microcirculation during blood flow through capillaries and venules. This is expressed as the F-cell ratio, Hct_w/Hct_{sys}. However, during UF, it was shown that the F-cell ratio rises as a result of the compliance of the microcirculation and fluid transfer to the macrocirculation. Therefore, the equations on which the inference of the blood volume change during HD is based may not be always valid (Mitra et al., 2004).

In a study from Dasselaar et al. (2007a), the blood volume reduction estimated by three commonly used devices (Crit-line®, Hemoscan® and BVM®, see below) was compared to a standard laboratory-derived Hb relative blood volume measurement during two HD sessions. It was shown that all three devices systematically overestimate the RBV reduction at modest RBV change, and underestimate the real fall in blood volume at higher RBV decline.

In addition, RBV monitoring also assumes that red blood cell mass or plasma protein density remains constant throughout the length of the session, which may not be true if hemolysis or blood leak happens, or when a blood transfusion is given.

3.3 Relation between relative blood volume and intradialytic hypotension

While hypovolemia is clearly a major determinant in the pathogenesis of IDH, the link between blood volume reduction and appearance of arterial hypotension is still a matter of debate. Recent studies have been unable to find a linear relationship between RBV and blood pressure, and a specific threshold to which hypotension will certainly occur does not seem to exist, even in an individual patient. This is probably because of variations, for each treatment, in the patient's ability to activate cardio-vascular compensatory mechanisms, in order to offset BP reductions induced by a wide range of hypovolemic states.

In fact, in many trials where blood volume (BV) biofeedback was effective in reducing the occurrence of IDH, there was no difference in the final RBV reached by either the standard treatment or the BV-controlled treatment. According to some authors, it is possible that RBV reduction *per se* is not the main risk factor for development of IDH. Rather, the excessive fluctuations of BV and the form of the RBV slope during HD may contribute more to hemodynamic instability (Andrulli et al., 2002). Indeed, the slope of the RBV curve with BV regulation device is different from that produced by standard HD (Franssen et al, 2006). The initial phase is usually steeper (meaning higher UF rate), which is rendered possible and tolerable because of higher initial interstitial pressures and better plasma refilling rate. The second phase is characterized by a reduced UF rate, which in turn make the RBV more stable and the patient less prone to IDH in this vulnerable period.

4. Biofeedback system

While monitoring may help to understand how BV is regulated during UF in an individual patient, the HD prescription often remains empirical. The hemodynamic stability during the previous HD sessions dictates the delivered parameters of the next HD treatments. Dialytic parameters such as UF rate and dialysate sodium concentration are usually set at the start of the HD session, and remain fixed throughout the treatment, with the assumption that they continue to be adequate for the whole treatment duration. However, this is not taking into account that patients may undergo physiologic variations during HD, and that fixed parameters, creating labile gradients, may not always be appropriate and may promote IDH. In fact, the standard HD prescription lacks a rapid retroactive response in case of variation of the monitored parameter, as the action to bring it back towards the desired value are taken manually (by the operator, a nurse or physician) or semi-automatically (authorized by the operator) (Locatelli et al., 2005), thus implying a certain lag of time that may be deleterious if IDH is to be prevented.

The method used to traditionally prescribe HD parameters is far from how the kidneys really behave to maintain internal homeostasis, keeping biologic variables in very tight ranges through instantaneous adjustments in response to precise negative or positive feedback loops. To try to get closer to what would be called « physiological dialysis », technological advances of the last decades have conducted to the development of sophisticated softwares that allow automated biofeedback. The concept of biofeedback is based on repetitive on-line measurements of the patient's biochemical parameters with biosensors, which are then constantly analysed by an automatic controller as being within the target values pre-set by the operator, or not. If the measured parameter is within the desired values considered safe, the treatment continues unchanged. If not, an action to bring it back towards the aimed values is immediately and automatically undertaken through the effectors, in a closed-loop that insures the stability of the monitored parameter.

The theoretical advantage of such devices is that they not only rapidly detect physiological abnormalities which may predict hemodynamic instability (blood volume reduction for example), but they automatically adjust one or more dialytic parameters to correct the situation. This obviates the need to perform manual changes by the operator and, at the same time, avoids the time lag before the action is undertaken. By modulating on-line some of the delivered dialysis parameter, these devices also address the physiological variations occurring during HD (and the variability of the patient's parameters from session to session), and thus provide more physiological dialysis, which may be more suited to prevent IDH.

At the present time, biofeedback systems are available for different parameters: relative blood volume, thermal energy balance, plasmatic conductivity, to which arterial pressure feedback using fuzzy logic control can be added. These devices are described here, with emphasis on blood volume biofeedback.

5. Blood volume biofeedback

Currently, only two commercially blood volume biofeedback devices are available: the Hemocontrol® (Gambro) and the BVM® (Fresenius) systems. Although both monitor change in relative blood volume during HD, they use different technologies and different integration systems. They are reviewed here.

5.1 Hemocontrol® system

The Hemocontrol® blood volume management system was first designed by Santoro and colleagues (Santoro et al., 1994) and afterwards modified in collaboration with the Hospal-Gambro research group. It is available on the Integra® and Artis® machines (with a few updates on the latter).

This biofeedback system is based on an automatic multi-input multi-output controller (MIMO) capable of integrating a multitude of signals and to modulate controlled variables to force the blood volume reduction along a pre-defined trajectory towards a pre-defined target of blood volume reduction (Locatelli et al., 2005). This results in a smoother and more gradual decline of relative blood volume, limiting the irregularity of BV variation that was shown to be predictive of IDH (Andrulli et al., 2002).

Basically, the monitored parameters are the actual UF (or weight loss), the actual dialysate sodium (or conductivity) and the actual blood volume change. The differences between the target values of the same three parameters (that is: desired UF, desired dialysate sodium (or equivalent conductivity) and desired final blood volume change) and the actual parameters serve as inputs to the MIMO controller. At any moment, the actual BV curve is plotted against the pre-determined BV trajectory and, should it deviate the least, automatic modulation of the UF rate and dialysate sodium (or conductivity) allows smooth redirection to the « ideal » curve (figures 1 and 2).

The blood volume change during dialysis is monitored using an optical sensor located in the arterial line that measures on-line hemoglobin (Hb) concentration by optical absorbance, according to Lambert-Beer law. The law states that Hb is a function of monochromatic light absorbance. Provided that the amount of Hb does not change, the blood volume variation from the start of the session can be inferred from the change in Hb concentration.
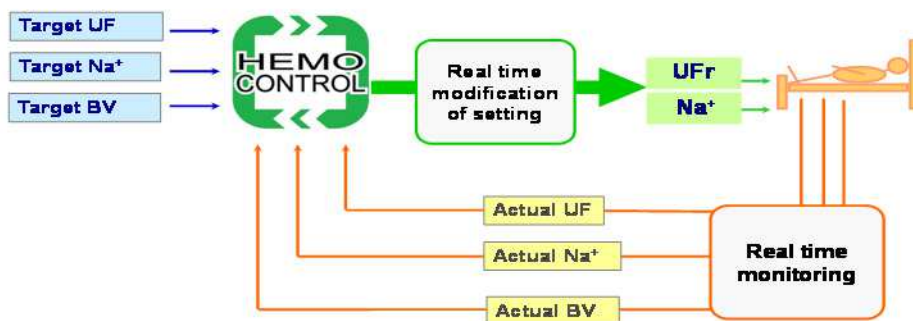

Fig. 1. Hemocontrol® biofeedback system (from Gambro).
The three targets prescribed by the physician (total UF, final dialysate sodium, and final BV reduction) are computed in the Hemocontrol® software and are compared to the actual same parameters (UF, dialysate sodium, and RBV) on a continuous basis during HD. The controller can modulate the UF rate and dialysate sodium in order to bring the actual parameters back on the pre-determined trajectory of the RBV curve.
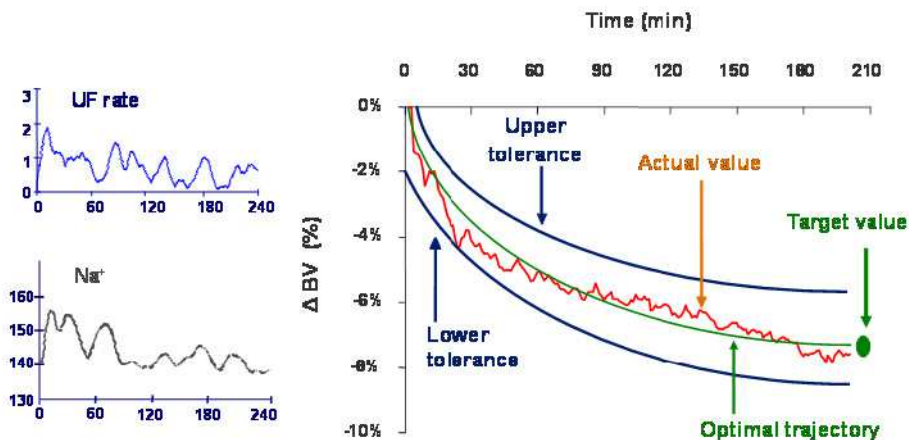
Fig. 2. Optimal trajectory of Relative blood volume (RBV) reduction during HD with Hemocontrol® (from Gambro).

The Hemocontrol® software designs the ideal RBV reduction curve, for each patient at each session, based on both initial and target parameters. Upper and lower tolerance limits are set to ensure safety. UF rate and dialysate sodium vary continuously during HD to keep the actual curve parallel to the optimal trajectory.

In practical terms, several parameters need to be set. Before the first use, data on the patient's sex, age, height and weight are needed to calculate total body water with any of the proposed formula. Treatment duration is also determined before the beginning of the treatment. Then, the three main targets need to be specified:

1. Total body weight loss or total UF (for water balance), based on clinical evaluation of dry weight;
2. Final sodium or equivalent dialysate conductivity. Conductivity refers to the electrical conducting property of the dialysis solution given by the dissociation of inorganic salts into charged ions. Since sodium is the principal ion in solution, conductivity is used as a surrogate for sodium concentration. For simplification purpose, conductivity was replaced by sodium concentration in the recent devices. Equivalent conductivity represents the dialysate conductivity that produces the same sodium balance at the end of a BV regulated session as a HD session with constant dialysate conductivity (Franssen et al., 2005);
3. Relative BV change to be reached at the end of HD which is individually determined for each patient on the basis of anterior sessions. A short observation period (approximately two weeks) is usually required to analyse each patient's BV curve morphology and to determine their respective BV/UF ratio. This ratio represents the %BV per each kilogram of UF fluid, and indirectly reflects the individual patient refilling plasma capacity. Depending on this ratio, and on the total UF prescribed for each dialysis, the final %BV can be adjusted.

Of note, these three targets may sometimes be in conflict with each other, for example when large UF is prescribed for a patient with low plasma refilling rate (i.e. a high BV/UF ratio). The closed feedback loop system has then to reach the best compromise between the various targets and produce the most appropriate BV curve for this patient during that specific session.

Because of safety concerns, limits (or tolerance range) concerning maximum UF rate and sodium/conductivity range are also pre-specified (figure 2). Of note, there is no specific probe for plasmatic sodium with Hemocontrol®, as it is the case for Diacontrol® (see below). The dialysate conductivity is modulated toward a mean final value, but not in an automatic feedback response to patient's plasmatic sodium.

Overall, the goal of the Hemocontrol® system is to reach the same sodium and water balance as would a traditional approach, while the hemodynamic tolerability is enhanced by the profiling of the UF rate and the dialysate conductivity. Indeed, when the blood volume approaches the lower acceptable value for a given patient, UF is diminished or ceased while the dialysate conductivity is raised. Conversely, UF rate can be increased and/or dialysate conductivity decreased when blood volume is higher than expected on the pre-defined BV trajectory.

5.2 BVM® Fresenius

The Blood Volume Management (BVM®) module designed by Fresenius is available on the 4008 and 5008 HD machines. This system also has relative blood volume as the core feature of the feedback loop, but rather deals with the « critical relative blood volume (cRBV) » concept instead of tracking an optimal curve to reach a final BV.

The BV monitor is based on the measurement of total protein concentration (which includes plasma protein and Hb) by on-line ultrasound technology. Initially described by Schneditz (Schneditz et al., 1990), this method uses a probe in the arterial line that continuously measures the speed at which the ultrasounds travel through a specially designed cuvette. Since the sound speed is positively correlated to blood density, and, once again, assuming that the total content of blood does not change during UF, blood volume variations can be calculated from the changes in sound transmission velocity.

The critical relative blood volume (cRBV) is individually determined for each patient. It is the threshold at which a particular patient would be at risk of IDH, based on the anterior sessions. The monitored parameter is the blood volume reduction, and a defined algorithm modulates the UF rate according to the relation of the actual BV to the cRBV. The algorithm is designed to allow the maximal UF rate at the beginning of the session, where the plasma refilling capacity is generally at its best, with a gradual decrease afterwards to avoid reaching the cRBV:

$$\text{Actual UF rate} = \text{initial UF rate} \times \text{factor} \qquad (1)$$

$$\text{Initial UF rate} = 2 \times (\text{remaining UF/remaining time}) \qquad (2)$$

The actual UF rate is the delivered UF rate and the initial UF rate is two times the ratio between the remaining UF and the remaining time (remaining UF/remaining time). The factor is a coefficient between 0 and 1 determined according to the current RBV. When the cRBV is reached, the factor is 0 and so the UF is transitorily suspended until the RBV rises again. When the relative blood volume is more than halfway the distance between the cRBV and 100%, the factor is 1 and maximal UF is allowed. Finally, when the RBV is more than halfway towards the cRBV, the factor is between 0 and 1 and decreases in a linear fashion (figure 3). This automatic feedback loop thus constantly adjust the UF rate to ensure, on one hand, that RBV stays over the predefined threshold and, on the other hand, that the UF rate is maximal at the beginning of the session and minimal at the end, where hypovolemia is
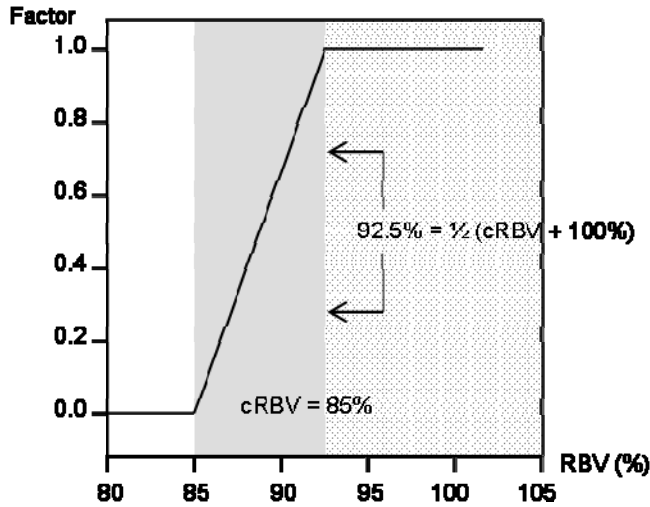
Fig. 3. BVM® algorithm (from Fresenius).
This figure illustrates an example where the cRBV is set at 85%. When the actual RBV is 85% or less (white area), factor is 0 and UF stops. When RBV is greater than halfway between cRBV and 100% (here, halfway between 85% and 100% is 92,5%), the factor is 1,0 and UF is maximal (shaded area). In between (gray area), factor is between 0 and 1, and UF is not maximal.
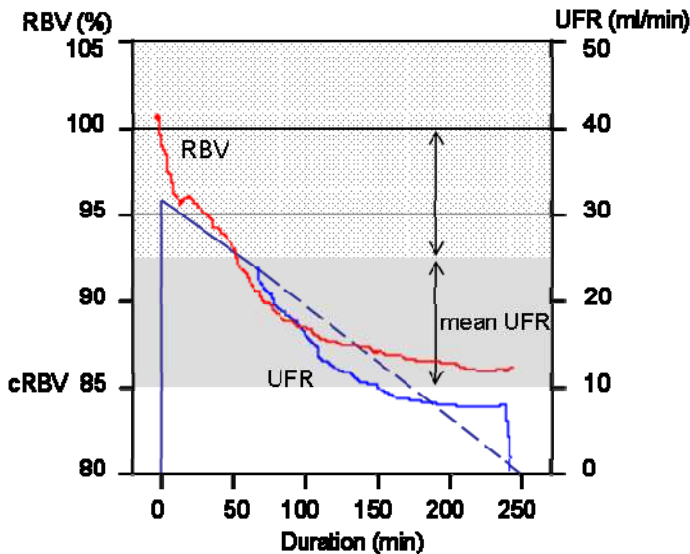

Fig. 4. UF rate in relation to RBV with the use of BVM® algorithm (from Fresenius).
This figure illustrates the changes in UF rate (UFR) and RBV during HD given a cRBV set at 85% (same as Figure 3). The UFR is initially higher and progressively declines following reduction of RBV.

more likely to happen (figure 4). Of note, the dialysate conductivity is not an effector in this system and, unless a specific sodium profile is prescribed, remains unchanged.

5.3 Impact of blood volume biofeedback systems

The two biofeedback systems described above are designed differently but share the same goal: stabilizing blood volume reduction to avoid IDH and, ideally, its related complications. Many studies have been published on the ability of these devices to reduce vascular instability, mostly with the Hemocontrol® system, but few studies assessed other outcomes. Table 1 summarizes published trials that evaluated the impact of blood volume biofeedback systems.

5.3.1 Reduction of intradialytic hypotension and nursing interventions

Definition of IDH in the literature is not standardized and so differs between studies. Some authors use a strict definition based on an absolute or relative reduction of arterial pressure, while others report IDH as a drop in BP accompanied by symptoms and/or requiring nursing intervention (such as stopping or slowing UF, saline infusion or Trendelenburg's position). Regardless of the definition used, the great majority of published trials, conclude that blood volume biofeedback systems are valuable in reducing IDH compared to standard hemodialysis (cf. table 1). Reduction of the proportion of HD sessions with at least one IDH episode ranges from 10 to 60%. However, it must be emphasized that most of these studies recruited patients who were already prone to hemodynamic instability, at varying degrees. As a general rule, the more severe and/or frequent the hemodynamic instability, the greater the benefits are from the automatic volume regulation.

The largest randomized controlled trial assessing the impact of biofeedback regulation on IDH occurrence was published by Santoro in 2002. Thirty-two hypotension-prone patients recruited in ten Italian nephrology centers were analysed in a cross-over, parallel group study of 4 months duration, comparing conventional HD to automatic BV-controlled HD. Although UF rate, pre and post-dialysis BP, and end-dialysis BV were the same with both treatments, a 30% reduction in dialysis sessions complicated by acute hypotension (systolic blood pressure ≤ 90 mm Hg or a ≥ 25 mm Hg decrease with symptoms) was observed with the use of automatic biofeedback. An additional aim of this trial was to identify which patient's parameters influence individual response to biofeedback. Clinical characteristics, dialysis prescriptions and plasma sodium values did not differ between the two treatment arms. However, two parameters appeared to be linked to responsiveness to BV-regulated feedback. First, good responders had higher final BV reduction and higher BV/UF ratio, suggesting a certain plasma refilling impairment. Second, poor responders had lower mean arterial pressure at the start of the HD sessions, and smaller increase in heart rate when standing from the lying position. Overall, these results indicate that IDH secondary to decreased plasma refilling capacity responds better to BV regulation than IDH due to impaired cardio-vascular reactivity. Of note, most studies that reported beneficial effects of biofeedback systems found similar results with regard to RBV changes during HD suggesting that reduction of IDH might not be exclusively explained by RBV preservation. As postulated by several authors, it is possible that treatment with BV automatic feedback exerts its favourable hemodynamic effect by preventing rapid RBV fluctuations (Santoro et al., 1994).

To evaluate whether BP stabilisation obtained per-dialysis with Hemocontrol® in IDH-prone patients was also sustained in the post-HD period, Franssen et al. (2005) used 24h BP

monitoring in a small prospective study. Following Hemocontrol®-driven HD, systolic blood pressure was significantly higher in the first 16 hours following HD, but this difference disappeared on the next morning. There was no difference in diastolic blood pressure. The authors concluded that the higher post HD systolic BP may explain the improvement of inter-HD symptoms observed in other studies (see below), although their study did not specifically evaluate interdialytic symptoms.

Only one randomized controlled trial did not restrict patient selection on the basis of previous hemodynamic instability or fluid overload (Déziel et al. 2007). This study included 57 patients (55% of them hypotension-prone) who were randomized to either standard HD or Hemocontrol®-driven HD. At 6 months, there was a 43% reduction in the number of sessions that required nursing interventions for IDH in the Hemocontrol® group (35% to 19%), compared with a 36% increase in nursing interventions in the control group (23% to 32%, p=0,04 for changes between groups). These results are in accordance with those reported by Ronco et al. (2000), who also demonstrated a significant decrease in the number of nursing interventions in a population prone to IDH when treated with BV biofeedback.

Finally, two non-randomized, short-term prospective studies specifically assessed the value of BV-regulated HD among non hypotensive-prone patients (Wolkotte et al., 2002 and McIntyre et al., 2003). Both found a statistically significant improvement in dialysis tolerance in terms of reduction of IDH.

Randomized trials							
Author	Study design	Patients	Intervention (control)	Duration	Main endpoint(s)	Results (treatment vs. control)	
Ronco (2000)	RCT Cross-over	12 patients IDH-prone	AFB + HC vs. AFB	4 weeks	Sessions with IDH (%)	33 vs. 82	p<0,001
					Equilibrated Kt/V	1,13 vs. 1,03	p<0,001
Santoro (2002)	RCT Cross-over Multicenter	32 patients IDH-prone	Std HD+HC vs. Std HD	4 months	Sessions with IDH (%)	24 vs. 34	p=0,004
					Mean no. of interdialytic symptoms	2,7 vs. 3,1	p<0,001
Moret (2006)	RCT Cross-over	10 patients IDH-prone	Std HD+HC vs. Std HD	4 months	Post-HD plasm. conduct.	14,11 vs. 14,11	NS
					Ionic mass removal (mmol)	432 vs. 383	NS
					IDH (%)	16 vs. 8	NS
Selby (2006)	RCT Cross-over	8 patients IDH-prone LVH	Std HD+HC vs. Std HD	4 weeks	No. of regional wall motion abnormalities	23 vs. 42	OR 1,8; 95%CI, 1,1-3,0
					No. of IDH	12 vs. 24	OR 2,0; 95%CI, 1,0-4,4

Randomized trials							
Déziel (2007)	RCT	57 patients Unselected	Std HD+HC vs. Std HD	6 months	Home SBP change (mm Hg)	142 to 135 vs. 148 to 140	NS between groups
					Nursing interventions (% change)	-16 vs. +9	p=0,04
					Kidney burden score (change in score)	-6 vs. +5	p=0,004
Dasselaar (2007)	RCT	28 patients with hypertension and volume overload	Std HD+HC vs. Std HD	16 weeks	Pre-HD weight reduction (kg)	0,2 vs. 0,1	NS
					Pre-HD SBP reduction (mm Hg)	-23 vs. +3	p<0,01
					Pre-HD DBP reduction (mm Hg)	-8 vs. +1	p<0,05
Garzoni (2007)	RCT Cross-over Multi-center	56 patients IDH-prone	Std HD+BVM vs. Std HD	6 weeks	Sessions with IME requiring intervention (%)	43 vs. 46	NS
					Subgroup of high IDH incidence	57 vs. 65	p=0,016
Nesrallah (2008)	RCT	60 patients with volume overload	Std HD+BVM vs. Std HD	6 months	Change in ECFV (%)	1,8 vs. 0,87	NS
					Frequency of IDH	0,11 vs. 0,19	p<0,01
Gabrielli (2009)	RCT Cross-over Multi-center	26 patients IDH-prone	Std HD+BVM vs. Std HD	12 weeks	Sessions with IME requiring intervention (%)	32 vs. 40	p=0,02
					Mean no. of IME/session	0,42 vs. 0,53	p=0,04
					Equilibrated Kt/V	1,17 vs. 1,12	NS
Non-randomized trials							
Santoro (1998)	Prospective Cross-over	8 patients IDH-prone	Std HD + HC vs. Std HD	3 months	% of IDH	26 vs. 44 (A_1) and 27(A_2)	NS
					% of severe IDH	3 vs. 27 (A_1) vs. 17(A_2)	p<0,01

Non-randomized trials							
Basile (2001)	Prospective Cross-over	19 patients IDH-prone	Std HD + HC vs. Std HD	20 – 36 months	% sessions with IDH Post-HD asthenia score	21 vs. 32 6,2 vs. 4,3	p<0,0001 p<0,0001
Bégin (2002)	Prospective Cross-over	7 patients IDH-prone	Std HD + HC vs. Std HD	12 weeks	% of event-free sessions (sessions without intervention for IDH)	51 vs. 29	p<0,01
Wolkotte (2002)	Prospective Cross-over	16 patients Non IDH-prone	Std HD + HC vs. Std HD	9 weeks	% of IDH % of minor symptoms	6 vs. 16 11 vs. 18	p<0,05 p<0,05
McIntyre (2003)	Prospective Cross-over	15 patients Non IDH-prone	Std HD + HC vs. Std HD	8 weeks	% sessions with IDH	3,5 vs. 7	p<0,001
Franssen (2005)	Prospective	12 patients IDH-prone	Std HD + HC vs. Std HD	12 weeks	% sessions with IDH Post-HD SBP o 24h recording (mm Hg) Dry weight reduction (kg)	28 vs. 64 Same at 24h 2,1 vs. 2,0	p<0,01 NS NS
Winkler (2008)	Observational Cohort	18 patients IDH-prone with diabetes	Std HD + HC vs. baseline	48 weeks	No. of IDH per session Dry weight reduction (kg) % Cardiac ejection fraction	1 vs. 9 -1,7 vs. 0 53 vs. 43	p<0,01 NS NS

Trials are subdivided in randomized or non-randomized studies and listed by year of publication. AFB: acetate-free biofiltration, BVM: blood volume monitor (Fresenius), DBP: diastolic blood pressure, ECVF: extracellular fluid volume, IDH: intradialytic, hypotension, IME: intradialytic morbid events, HC: Hemocontrol® (Gambro), HD: hemodialysis, LVH: left ventricular hypertrophy, NS: non-significant, RCT: randomized controlled trial, SBP: systolic blood pressure, Std HD: standard bicarbonate-based hemodialysis

Table 1. Trials on the use of blood volume biofeedback control system in chronic hemodialysis

5.3.2 Reduction of intra- and inter- dialytic symptoms and improvement in quality of life

Regarding improvement of patient's symptoms during HD, some data are available in the literature but they are mostly based on secondary outcome analysis and show only limited evidence of benefit. Basile et al. (2001) prospectively followed patients for up to 36 months with BV-regulated HD during which period nurses and patients had to fill a symptoms questionnaire for each HD session. A reduction of muscle cramps during HD and an improvement in the post-HD asthenia score were found to be significantly associated with biofeedback system. However, self-evaluation of other intra- and inter- HD symptoms (notably, thirst) was not significantly different between the two treatment arms.

Ronco et al. (2000) found a significant reduction of the proportion of sessions with self-reported intradialytic symptoms following treatment with BV-controlled UF (21% vs. 76%, p<0,001). In addition, Santoro et al. (2002) also showed a 10% decrease of interdialytic symptoms following treatment with BV-controlled HD.

In a study by Déziel et al. (2007), the Kidney Disease and Quality of Life questionnaire (KDQOL) was used to evaluate quality of life at baseline and after 6 months of treatment with either Hemocontrol® or standard HD. Among the 20 items related to physical and mental health, only one parameter, burden of kidney disease, was significantly improved in the Hemocontrol® group versus the control group. Finally, in a randomized controlled trial of 60 patients, Nesrallah et al. (2008) did not find any significant difference with regard to dialysis-related symptoms and quality of life between the two treatment groups (Hemocontrol® versus standard HD) despite the fact that a reduction of IDH could be observed.

5.3.3 Hypertension and volume control

Three RCT specifically assessed the utility of BV regulation devices in improving fluid status and/or BP control in chronic hemodialysis patients. First, Dasselaar et al. (2007b) studied 12 hypertensive and mild volume-overloaded patients managed with either standard HD or BV tracking, where dry weight reduction was gradually undertaken by nephrologists according to clinical judgement. At 12 weeks, patients treated with BV regulation had a significantly lower pre- and post- HD systolic and diastolic blood pressure. Patients achieved larger UF volume without any change in RBV and showed reduction in extracellular water (determined by bioimpedance analysis). Despite these improvements in surrogate markers of volume status, no difference in mean weight from baseline could be observed. Authors concluded that this observation could result from increase in lean body mass; however, other specific nutritional parameters were not measured.

Second, in a trial published by Nesrallah et al. in 2008, volume-overloaded patients were included if bioimpedance displayed an extracellular fluid volume (ECFV) of at least 45%. In the treatment group, dry weight was adjusted by an algorithm guided by the Hemocontrol® biofeedback software based on plasma-refilling characteristics. At 6 months, there was no statistically significant difference between the two groups in the primary endpoint (change in ECFV) nor were there any significant differences in systolic blood pressure, total UF and interdialytic weight gain.

Finally, in a trial by Déziel et al. (2007), change in home blood pressure was evaluated following treatment with BV device versus standard HD. Patients were not selected on the basis of prior hypertension or volume overload history. While the use of Hemocontrol® effectively reduced home systolic BP, the clinical-based decision algorithm to manage BP in

the standard group was as effective, and the overall difference between the groups was not significant.

In summary, no randomized trial has clearly demonstrated that the use of biofeedback devices is superior to standard HD and clinical judgement in reducing dry weight in volume expanded patients. Biofeedback devices may be of value in reducing blood pressure in hypertensive patients, although a systematic and clinical treatment algorithm may be as useful.

5.3.4 Reduction of left ventricular dysfunction

Cardiovascular morbidity and mortality are extremely high among chronic HD patients. Aside from the conventional risk factors for atherosclerosis, it was proposed that recurrent subclinical myocardial ischemia occurring during HD, as a result of silent decrease in myocardial perfusion, may contribute to the excessive cardio-vascular burden. In support of this hypothesis, Selby et al. (2006) demonstrated that reversible regional wall motion abnormalities which develop in a majority of hypotension-prone patients during HD, were substantially reduced with biofeedback dialysis. However, the observation period in this study was only 4 weeks, and it is unknown at the present time whether biofeedback HD provides any benefit on long-term cardiac dysfunction.

5.3.5 Improvement of dialysis delivery

Hemodialysis and UF may cause vasoconstriction of peripheral vascular beds, thus reducing peripheral tissue perfusion. This phenomenon may cause sequestration of urea, as only a central vascular loop of blood remains to be dialyzed. When hypotension occurs, this phenomenon may be aggravated leading to enhanced urea compartmentalization and reduced HD efficiency. Hence, it was proposed that improved hemodynamic stability during dialysis may improve urea removal and increase Kt/V.

Ronco et al. (2000) conducted a multi-center, cross-over randomized trial of 12 IDH-prone patients treated for two weeks with acetate-free biofiltration (AFB, schedule A) and for two weeks with AFB plus Hemocontrol® (schedule B). Parameters of urea kinetics were significantly improved when patients were on schedule B, with higher equilibrated Kt/V (1,12 vs. 1,03, p<0,001), and lower urea rebound at 30 minutes post-HD (6,4 vs. 14,2 g, p<0,001), despite similar predialysis urea concentration, HD prescriptions and treatment time.

However, a larger randomized trial of 26 patients followed for 12 weeks and treated with standard HD or BVM-controlled HD in a cross-over fashion did not find any significant improvement of equilibrated Kt/V in the treatment group (1,17 vs. 1,12, p=0,156) in spite of a slightly but significant higher treatment time and a 20% reduction of intradialytic morbid events (Gabrielli et al., 2009).

5.3.6 Morbidity and mortality

With improved hemodynamic tolerance, reduction of left ventricular wall dysfunction, and superior dialysis delivery, it would be reasonable to assume that the use of biofeedback systems would improve morbidity and mortality in chronic dialysis patients. Unfortunately, no trial to date has examined this issue and the question remains open.

Nevertheless, one large trial published in 2005 assessed the effect on morbidity of a BV-monitor based algorithm of UF control versus conventional management of volemia. The CLIMB (Crit-Line® Intradialytic Monitoring Benefit) study (Reddan et al., 2005) was a

multi-centered, randomized, controlled trial of 443 chronic HD patients followed for 6 months during which ultrafiltration was either managed according to Crit-Line® values of RBV reduction, or by usual clinical strategies. Patients were not selected on a basis of prior IDH history, and the algorithm of the treatment group was only proposed and not mandatory. During the follow-up period, there were no statistically significant differences between the two groups regarding the number of IDH, the occurrence of intradialytic symptoms and the control of BP. Surprisingly, the risk ratios for both non-access and access-related hospitalizations were higher in the Crit-Line® group (adjusted RR 1,61 and 1,52; p-value 0,01 and 0.04, respectively). Mortality was 8.7% in the treatment group and 3.3% in the control group (p=0.021). The authors concluded that the availability of Crit-Line® may alter clinicians' behaviour and may cause a risk for patients, although these results have to be interpreted cautiously since the control group had an atypically low hospitalization and mortality rate.

5.4 Blood volume biofeedback and sodium overload
One of the potential risks of automated BV regulation using sodium (Na) or conductivity modulation is alteration in sodium removal, with consequent Na overload and increased thirst, which can theoretically lead to increased interdialytic weight gain and worsening hypertension. Most of the studies described above did not find a significant change in pre and post HD sodium concentration (Santoro et al., 2002; Wolkotte et al., 2002; Dasselaar et al., 2007b, etc.), although plasma Na is a poor surrogate of real sodium balance.
Moret et al. (2006) assessed the effect of such devices on sodium transfer during hemodialysis. In a cross-over randomized trial of 10 patients with frequent hypotension, plasma conductivity (PC) and ionic mass balance (IMB) were compared in four different HD modalities: standard HD with fixed Na concentration (140 mmol/L), linear Na profiling (150 to 140 mmol/L), BV-controlled feedback with Hemocontrol® (mean dialysate conductivity (DC) 14,0 mS/cm) and plasma-conductivity (PC)-controlled feedback with Diacontrol® (see below) (post-dialytic PC target of 14,0 mS/cm). Mean pre- and post-dialytic PC were statistically higher during Na-profiled HD, and post-dialytic PC was lower in PC-controlled feedback, compared to the other three modalities. The effects of BV-regulated HD on PC and IMB did not differ from those of standard HD, and thus it seems that BV-regulated HD can be prescribed without any safety concern regarding sodium loading.

6. Other biofeedback systems

Three other biofeedback systems were designed to reduce the occurrence of hypotensive episodes during HD. Rather than focusing on BV changes during HD, these devices use other targets (e.g. arterial BP) or other means of action (e.g. thermal balance, plasma conductivity). They are reviewed here briefly.

6.1 Arterial pressure biofeedback
Arterial pressure biofeedback aimed at stabilizing BP during HD uses repetitive measurement of arterial blood pressure as the monitored parameter and a fuzzy-logic system as the controller of fluid removal. Created by B. Braun and implemented on the Dialog Advanced machines, the APBS® (Automatic Blood Pressure Stabilization system) puts blood pressure itself as the main input to the automatic fuzzy controller rather than a surrogate marker (e.g. blood volume). Fuzzy logic is a problem-solving system, rather than

a mathematical model, and is reported to be better suited to analyse and compute non-linear data systems. It mimics how a person would make a decision, based on judgments such as: « if X, then Y», according to the rules pre-set by the operator. In a practical manner, the operator has to set two parameters for each patient: the BP set point and the maximal UF rate. The set-point is the critical BP level at which the patient experiences symptomatic hypotension, or simply the BP threshold at which the nurse or the physician would consider stopping the UF in that particular patient. The maximal UF rate is defined as the maximal rate of fluid removal that can be applied at any time, since this system is designed to maximise UF rate at the start of the HD session and to minimize it towards the end. With a specialized arm cuff that takes BP measurements every five minutes, three variables are calculated (Mancini et al., 2007): 1) Relative difference between actual systolic BP and the pre-adjusted set point; 2) Short-term pressure trend (15 min); 3) Long-term pressure trend (25 min). These input data are then computed by the fuzzy controller through several steps that involve probabilistic reasoning according to specific rule bases, and ultimately result in modulation of the UF rate, in a closed feedback loop (figure 5). This system allows gradual and continuous variations of the UF rate, as it varies proportionally to the changes of the BP trends.
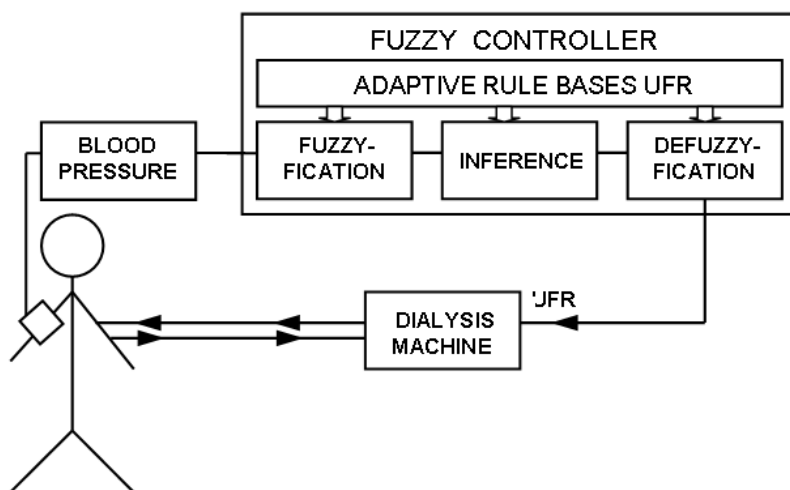

Fig. 5. Fuzzy control of the UF rate.
Technical scheme of the closed-loop system for the fuzzy control of the UF rate. (Adapted from Mancini et al., 2007)
Literature on the use of fuzzy logic control in preventing IDH is still scarce, but a prospective multi-center study published in 2007 (Mancini et al., 2007) showed a significant decrease of 25% in IDH incidence in 55 hypotension-prone patients. The authors emphasized the need to introduce correct critical BP for each patient for the fuzzy controller to perform adequately (Mancini et al., 2007).

6.2 Thermal balance system
During HD, body temperature usually rises due in part to an increased production of heat secondary to inflammatory reactions induced by imperfect dialysate water and bio-

compatibility of membranes, and in part by decreased blood flow to the skin, with subsequent heat retention. This phenomenon can contribute to hemodynamic instability. Cooler dialysate, by inducing vasoconstriction, is known to enhance vascular stability, but poor tolerance due to chills and discomfort is a major drawback to its use.

Blood temperature control (BTC®, Fresenius) is a biofeedback system aimed at keeping body temperature stable throughout the session, with progressive decline of dialysate temperature in response to progressive increased in heat production, resulting in « isothermic dialysis » (Mercadal & Petitclerc, 2009). Designed by Fresenius, the blood temperature monitor (BTM) is composed of sensors in the arterial and venous lines and monitors blood temperature change by a thermodilution technique. Thermal balance can be maintained through the automatic modulation of the dialysate temperature (the output) by the BTC® software (the controller) in response to BTM measurements compared to the set target temperature (the input).

A systematic review, published in 2006, reviewed the most pertinent publications on the clinical effects of cool dialysate (Selby & McIntyre, 2006). Six of them, which were all cross-over studies of relatively short duration, evaluated the use of BTM compared to various control groups. Overall, there was a significant decrease in IDH frequency with reduction in dialysate temperature using BTM, with a rate of IDH 2.0 (95% CI, 1.9-2.1) times less than control group.

6.3 Plasma conductivity biofeedback system

This biofeedback system was designed to allow variation in the dialysate sodium (Na) concentration to better suit the patient's initial plasmatic value and parallel the changes in plasma Na concentration occurring during dialysis. Instead of a fixed dialysate Na concentration, a target final plasma conductivity (as a surrogate for Na) is rather prescribed, and thus the patient's post-dialysis sodium concentration is independent of the initial status. The goal of this system is to maximise sodium removal individually for each session, but avoiding large gap between plasmatic and dialysate sodium, which can produce patient's discomfort, hypotension and cramps (if dialysate Na is lower) or sodium loading, thirst and worsening hypertension (if dialysate Na is higher).

The Diascan® (Gambro) module monitors the patient's plasma conductivity every 15 minutes through conductivity probes located at the dialysate inlet and outlet. The software Diacontrol® (Gambro) computes this information and softly and gradually modulates the dialysate conductivity in order to reach the prespecified target plasmatic conductivity at the end of the session. The curve of the conductivity trajectory is pre-defined and minimizes large variations to avoid rapid shift of plasmatic osmolality and disequilibrium syndrome.

Again, large randomized trials are lacking to evaluate the utility of this feedback system, and results of two small prospective studies published recently are conflicting. Both compared Diacontrol® to standard dialysis in stable patients to assess whether gradual decrease in target conductivity, and consequent increased ionic mass balance (meaning increased sodium removal) could be achieved. Manlucu and colleagues (2010) found a significant reduction in end plasmatic conductivity and in ionic mass balance, with consequent reduction in IDWG and BP. On the contrary, Selby and al. (2007) found a lower final conductivity with fixed dialysate conductivity, and no difference in BP, IDH frequency or dialysis tolerability. Hence, demonstration of a Diacontrol® beneficial effect remains to be proven.

8. Conclusions

IDH is the most frequent complication of dialysis, and is associated with significant patient morbidity. Although pathogenesis is multifactorial, blood volume reduction appears to be central in the development of such events, especially when cardio-vascular compensatory mechanisms are impaired. In an attempt to reduce hypotensive episodes, blood volume biofeedback devices have been developed. The underlying premise of such devices is to automatically adjust dialysis parameters such as UF rate and dialysate conductivity, in response to variations of monitored patient's characteristics, in order to make dialysis sessions more physiological and to prevent IDH by acting on subclinical signs of hemodynamic instability. Evidence supports BV biofeedback in hypotensive prone patients to reduce occurrence of IDH, nursing interventions, and probably intra- and inter- dialytic symptoms, although no large scale randomized trial has been published to date. BV biofeedback may also be helpful to enhance vascular tolerance in stable patients, but literature is limited. Data concerning improvement of hypertension and volume overload, as well as improvement of dialysis delivery, is conflicting. Finally, there is no large randomized trial that assessed the impact of automatic BV control on morbidity and mortality. Data suggesting that Crit-line® based algorithm of hypertension management is associated with higher hospitalisation and mortality rates are of concern. Larger and long-term randomized trials comparing BV biofeedback devices to standard HD are needed to better define the impact of these novel technologies on patient outcomes.

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Hemodialysis (HD) represents the first successful long-term substitutive therapy with an artificial organ for severe failure of a vital organ. Because HD was started many decades ago, a book on HD may not appear to be up-to-date. Indeed, HD covers many basic and clinical aspects and this book reflects the rapid expansion of new and controversial aspects either in the biotechnological or in the clinical field. This book revises new technologies and therapeutic options to improve dialysis treatment of uremic patients. This book consists of three parts: modeling, methods and technique, prognosis and complications.

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