Noninvasive Techniques for Prevention of Intradialytic Hypotension

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Methodological Review

***Abstract*—Episodes of hypotension during hemodialysis treatment constitutes an important clinical problem which has received considerable attention in recent years. Despite the fact that numerous approaches to reducing the frequency of intradialytic hypotension (IDH) have been proposed and evaluated, the problem has not yet found a definitive solution—an observation which, in particular, applies to episodes of acute, symptomatic hypotension. This overview covers recent advances in methodology for predicting and preventing IDH. Following a brief overview of well-established hypotension-related variables, including blood pressure, blood temperature, relative blood volume, and bioimpedance, special attention is given to electrocardiographic and photoplethysmographic (PPG) variables and their significance for IDH prediction. It is concluded that cardiovascular variables which reflect heart rate variability, heart rate turbulence, and baroreflex sensitivity are important to explore in feedback control hemodialysis systems so as to improve their performance. The analysis of hemodialysis-related changes in PPG pulse wave properties hold considerable promise for improving prediction.**

***Index Terms*—Cardiac information, ECG, feedback control, hemodialysis, intradialytic hypotension (IDH), photoplethysmography (PPG), prediction.**

I. INTRODUCTION

HEMODIALYSIS is since long a well-established treatment of patients with serious kidney problems. The treatment improves dramatically the living conditions for this group of patients, but it is also associated with episodes of intradialytic hypotension (IDH) which occur in approximately 25% of all sessions, thereby making IDH the most common complication during hemodialysis [1]. This percentage increases even further as the population grows older. The short-term consequence of such episodes is obviously decreased wellbeing for the patient, manifested by symptoms of fatigue, cramps, and vomiting. Since IDH can lead to premature termination of the session, the patient may end up with insufficient clearance of the blood. In the long-term perspective, IDH can cause permanent damage to the heart and intestines as well as occlusion of the arteriovenous fistula [2]. Repeated episodes of IDH have been established as a significant and independent risk factor for increased morbidity and mortality in hemodialysis patients [3], [4]. Hypotension which occurs at the onset of the hemodialysis session has been established as particularly serious [5]. Furthermore, it is well known that IDH can induce cardiac arrhythmias and predispose to myocardial ischemia, which in turn increases the risk for sudden cardiac death, being a common cause of death in dialysis patients [6].

The causes of hypotension are multifactorial. The primary factor is the decrease in blood volume that occurs during hemodialysis that results from fluid withdrawal of the vascular compartment during ultrafiltration and insufficient refilling of fluid from the interstitial compartment to the vascular compartment. The picture is further complicated by several, rather diverse factors, including impaired peripheral vasoconstriction, autonomic dysfunction, arteriosclerosis, cardiovascular pathologies such as left ventricular hypertrophy and dilated cardiomyopathy, hydration, and medication [7]. During a hemodialysis session, eating and changes in body position may also serve as triggers of a hypotensive episode.

The occurrence of IDH is found to be more frequent in the standard thrice-weekly hemodialysis treatment than in short daily or nocturnal treatment because the former type of treatment requires a higher dose of ultrafiltration. While short everyday treatment is not practically feasible when delivered in the hospital, the increasing dissemination of home-based hemodialysis may change this as future treatment paradigms are evolving.

In many hospitals, the clinical management of IDH remains synonymous to the placement of the patient in Trendelenburg position, i.e., supine body position with the feet held higher than the head [8]. This placement is accompanied with substantial slowing of the ultrafiltration rate (UFR) so that the reduction in blood volume due to fluid removal is slowed down. Another means is to infuse a hypertonic solution (low-volume saline or glucose) which increases the blood volume and accordingly the blood pressure; the solution facilitates osmotic shift of

Manuscript received February 03, 2012; revised May 13, 2012; accepted July 06, 2012. Date of publication July 24, 2012; date of current version December 06, 2012. This work was supported by the Swedish Research Council under Grant 2010-4772. The work of E. Gil in Lund was supported by the Ministerio de Ciencia y Tecnología (FEDER, TEC2010-21703-C03-02), Centro de Investigacíon Biomédica en Red de Bioingeniería, Biomateriales y Nanomedicina (CIBER-BBN), ARAID and Ibercaja (Programa de Apoyo A LA I+D+i), Grupo Consolidado GTC from DGA.

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Digital Object Identifier 10.1109/RBME.2012.2210036

fluid from the extravascular to the intravascular compartment [9]. These types of actions are invoked when the patient already exhibits symptoms, and therefore it is highly desirable to prevent episodes of IDH well in advance so that appropriate measures can be taken. A complicating factor is that the occurrence of IDH cannot always be observed through external signs. While most patients complain about dizziness or nausea when hypotension is about to occur, some patients do not display any precursory symptoms whatsoever [8].

The prevention of IDH has been the subject of intense research in recent years and has resulted in a range of techniques which aim at solving this issue. These techniques include improved assessment of the patient's "dry weight", cooler dialysate temperature, dialysate sodium concentration (DSC) profiling, and online blood volume monitoring. Interesting reviews have been published on this topic, all of them authored from a clinically oriented perspective [7], [10]–[12].

Considering that the problem of predicting IDH entails significant engineering challenges, it is quite remarkable that the problem has received so little attention among researchers in the biomedical engineering community; the vast majority of articles on this topic has been published in clinical journals. In fact, the significance of technology in hemodialysis is far from uncontroversial, and opinions diverge quite considerably. While many researchers are optimistic about its significance [10], [11], [13], others are much more skeptical since the major technological advances in dialysis have not yet been translated into longer patient survival [7], [12]. Irrespective of the opinion held on this issue, continuous monitoring of patient status during hemodialysis, based on lightweight, nonintrusive sensor technology, appears as inevitable if the goal is to ensure that the nephrologist has immediate access to relevant clinical information.

Hence, there is room for much more engineering research whose purpose is to develop methods which can dramatically reduce the frequency of IDH. This opinion is further underlined by a recent review which concluded that [13]: "What is badly needed in this area of clinical research are improved methods to reduce the frequency of intradialytic hypotension, thereby avoiding its untoward effects. Until progress is made in mitigating the incidence of intradialytic hypotension, standard thrice-weekly 3- to 4-h hemodialysis will continue to be episodically unpleasant".

The present paper takes more of an engineering perspective when reviewing and discussing noninvasive techniques developed for the prediction and prevention of IDH. Following a brief overview of well-studied hypotension-related variables in Section III, special attention is given to more recent techniques with which variables from electrocardiographic or photoplethysmographic signals are subject to analysis; see Sections IV and V, respectively. Feedback control in hemodialysis is discussed in Section VI, with reference to both fuzzy and model-based control. The paper is concluded with a discussion on future perspectives.

Definition of Intradialytic Hypotension

The clinical definition of IDH has not been universally agreed upon, but varies quite considerably among studies in the literature. Since blood pressure values can indicate hypotension in one patient, while they are judged as normal in another patient who suffers from chronic low blood pressure, a definition which only involves absolute blood pressure values is not meaningful. Rather, it is warranted to define criteria which account for relative reduction in blood pressure during a session as well as for episodes of acute symptomatic hypotension.

One recently proposed definition of IDH embraces the following three criteria [14] (see also [15]):

1) if predialysis systolic arterial pressure (SAP) is greater than 100 mmHg, then any episode with SAP less than 90 mmHg, even without complaints;
2) if predialysis SAP is less than 100 mmHg, then any SAP reduction by at least 10% associated with complaints;
3) any SAP reduction of 25% or more of the predialysis value with the typical symptoms requiring specific intervention.

Simpler definitions of IDH have also been suggested. For example, only the last of the three criteria has been employed, replacing the 25% reduction in SAP with 20% as threshold value [16].

The time course of blood pressure can be involved in the definition of IDH as reflected by the duration of the reduction in blood pressure [17]. The reduction is then characterized by its rate in terms of mmHg/min, with a high rate categorized as acute IDH, whereas a low rate as nonacute IDH. An important reason for including rate in the definition is that the etiology of IDH may differ depending on duration and/or rate. Since changes and counteractions of the body relate to etiology, methods should likely differ in design depending on whether the target is to predict acute IDH or not.

The predominant problem treated in the literature is to predict prior to the dialysis session whether the patient will suffer from IDH or not ("offline prediction"). Since no temporal aspect is involved, the related design problem must be considered as being simpler than that associated with prediction of acute IDH since the latter type will have to involve online data processing.

II. WELL-STUDIED HYPOTENSION-RELATED VARIABLES

Over the years, numerous clinical studies have investigated the significance of variables that characterize the circulatory system in relation to IDH, notably blood temperature and blood volume. Bioimpedance is another well-established variable which may be continuously monitored for the purpose of assessing a patient's dry weight, i.e., the weight at the end of a session at which most excess body fluid has been removed, and below which the patient is likely to develop IDH [8]. Changes in "sensor" variables, such as blood temperature, blood volume, and bioimpedance, are analyzed and used to modify "actuator" variables, such as UFR, DSC, and dialysate temperature, so that the frequency of IDH may be reduced. The relationship between an actuator variable, in this case UFR, and the frequency of IDH, expressed as a percentage, is exemplified in Fig. 1. For many years, the settings of the dialysis machine were modified manually by the operator; however, such modifications have more recently been subjected to automation within the framework of feedback control; see Section VI. In this section follows a brief description of the variables blood pressure, blood temperature, relative blood volume, and bioimpedance.

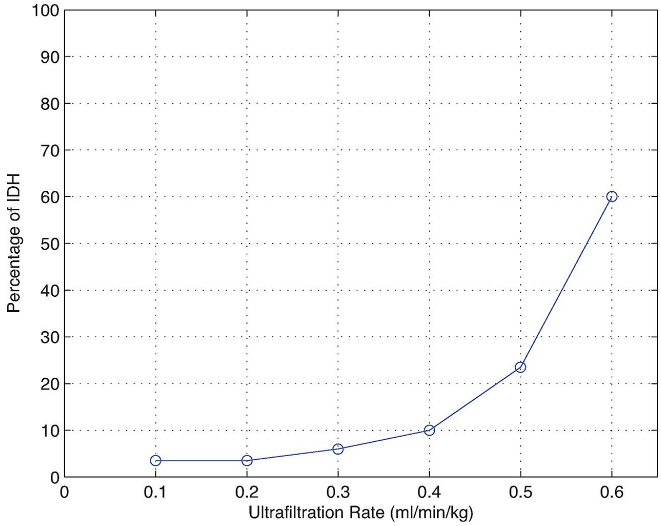

Fig. 1. Percentage of intradialytic hypotension as a function of ultrafiltration rate (adapted from [18]). Hypotension was defined as a drop in arterial blood pressure of more than 30 mmHg. It was concluded that the percentage of hypotension increases exponentially with ultrafiltration rate.

A. *Blood Pressure*

The arterial blood pressure may seem the natural starting point for developing an algorithm for online prediction and prevention of hypotension. However, such an approach is complicated by the fact that sensors for the measurement of continuous blood pressure, e.g., inflatable cuff-based devices, are highly inconvenient to wear throughout the entire hemodialysis session. Moreover, frequent cuff-based measurements have a direct influence on the blood pressure itself. On the other hand, indirect measurement of changes in SAP can be easily accomplished with the photoplethysmographic technique, involving a pulse oximeter attached to the finger and combined with temporal information derived from an ECG lead; see Section V.

B. *Blood Temperature*

It is well known that the patient's temperature tends to increase during hemodialysis for the conventional dialysate temperature of 37 °C. Hemodialysis increases the core body temperature since more blood, normally flowing to the body surface for heat dissipation, remains in the central circulation to preserve the core blood plasma volume which is reduced in response to ultrafiltration. Sympathetic activity is known to increase in response to ultrafiltration and leads to peripheral vasoconstriction which reduces heat dissipation. Although a certain amount of thermal energy is removed during hemodialysis through the extracorporeal blood circulation system, the net effect is still heat accumulation which tends to increase the core body temperature. When this increase in temperature overcomes peripheral vasoconstriction, the risk of IDH increases, especially in patients with low core body temperatures [11].

Cooling of the dialysate was already in the 1980s found to have a beneficial effect on cardiovascular stability and to reduce the frequency of IDH [19]; the reduction in temperature being from the standard 37 °C to about 35 °C. Several studies have since then reported a similar finding, many of which were compiled in a recent meta-analysis of 22 studies showing that a reduction in dialysate temperature is an effective intervention for reducing the frequency of IDH. Cool hemodialysis led to that IDH occurred 7.1 times less frequently than when standard hemodialysis was prescribed [20]. The results applied to different cooling profiles that spanned in complexity from a fixed, empirical reduction of the dialysate temperature to online monitoring of blood temperature and cooling based on feedback control, cf. Section VI. A disadvantage with blood cooling is the increased risk of shivering and cold sensation [21].

C. *Relative Blood Volume*

The loss in blood volume that occurs during hemodialysis constitutes an important cause of IDH [22], [23]. This loss is related to the ultrafiltration process during which fluid is withdrawn from the circulation. Since UFR is almost always higher than the plasma refilling rate, i.e., the rate at which fluid moves from the interstitial tissue into the circulation, the blood volume will decrease as fluid is withdrawn, and hypovolemia may develop. When the cardiovascular compensatory mechanisms that counteract hypovolemia are insufficient or impaired, hypotension may develop. Thus, the preservation of blood volume during hemodialysis represents an important target for preventing IDH.

Historically, blood volume has always been expressed as a relative measure that reflects changes in blood volume relative the time for onset of hemodialysis. Although it is preferable to measure absolute blood volume, there are many confounding factors which renders such a measurement difficult. A number of techniques are available for continuous, noninvasive measurement of relative blood volume which explore different types of blood constituent such as hemoglobin, hematocrit, or the concentration of total plasma proteins. Hemoglobin and hematocrit are measured by quantifying the absorption of monochromatic light in blood, whereas protein concentration is estimated from the velocity of sound waves in blood. Comparing the measurements produced by the different techniques, all of them could detect changes in relative blood volume during hemodialysis, although the resulting measurements differed appreciably between the techniques [24].

Several clinical studies have investigated the relationship between the reduction in relative blood volume and the development of ultrafiltration-induced IDH. However, as pointed out in, e.g., [7] and [25], most studies have been unable to establish a close relationship between these two factors: the reduction in relative blood volume at the time for symptomatic IDH did not differ significantly from what was observed in hypotension-free sessions. This finding suggests that IDH cannot be predicted by simply requiring the relative blood volume to drop below a certain fixed threshold level. Rather, the level is highly patient-dependent and, accordingly, much more difficult to determine. Improved prediction performance was achieved when the shape of the trend of relative blood volume was analyzed with respect to features such as decreased long-term variability [26], increased irregularity [27], or time for switch from an exponential to a linear decay [28].

Relative blood volume can be monitored for the purpose of controlling UFR and DSC in response to changes in relative blood volume, cf. Section VI. Sodium concentration is an important determinant of plasma conductivity [29] and has an indirect influence on relative blood volume as it modifies plasma osmolarity which controls the plasma refilling process. Thus, DSC serves as an actuator variable on relative blood volume, and is increased during hemodialysis in order to reduce the frequency of IDH. The role of sodium profiling for reducing this frequency is not fully concordant. One study concluded that the frequency can be reduced with about 15% [30], whereas another study found no difference between hemodialysis with either fixed or profiled sodium concentration [31].

D. Bioimpedance

The measurement of bioelectrical impedance is a well established, noninvasive technique for assessing the hydration status of the body [32], [33]. Impedance is decomposed into resistance, being the opposition to the flow of a current passing through both intra- and extra-cellular fluid, and reactance, being the capacitative component of cellular membranes. Changes in whole-body fluid volume can be assessed by measuring changes in impedance, with increased impedance corresponding to decreased fluid volume. The contribution of the trunk and limbs to whole-body impedance is about 10% and 90%, respectively [34]. The impedance is measured by injecting an alternating current, traditionally with a single frequency of 50 kHz, using electrodes placed on the hand and foot. Before being analyzed, the impedance measurement is usually normalized with the subject's height as it approximates the length of the human conductor. The impedance measurements are highly site-dependent, and consequently one cannot compare measurements from different sites. In general, measurements made from the legs should be more profoundly influenced by ultrafiltration than are central measurements.

In hemodialysis, the impedance measurement has been explored for the purpose of estimating dry weight [35], [36]. While the use of impedance-based techniques has been claimed to offer "the benefits of avoiding deliberate search of hypotension" [35], very few studies have actually considered such techniques for the prediction of IDH. In an early study, it was found that impedance is associated with both a very low positive predictive value (42%) and poor sensitivity (66%) when employed for the prediction of IDH [37]. It was concluded that the investigated impedance-based technique was unsuitable for predicting hypotensive episodes.

More recently, the prediction of IDH was suggested as a possible application of a method for bioelectrical impedance vector analysis, however, the method's potential was not further explored for this purpose [38], [39]. The method analyzes impedance values in the complex plane, spanned by height-normalized resistance and reactance, by comparing the values to a reference population characterized by the equidensity contours of a bivariate Gaussian probability density function. A value is judged to reflect tissue dehydration when it falls outside an ellipsoid-shaped tolerance zone so that both resistance and reactance exceed their respective mean values. The trajectory resulting from repeated measurements thus indicates how hydration changes during hemodialysis treatment. From their results, the authors concluded that a trajectory pattern of dehydration is consistent with hypovolemia as a cause of hypotension, whereas a pattern of hyperhydration would indicate other causes [38].

Multifrequency bioelectrical impedance offers the advantage of providing measurements on both intra- and extra-cellular volumes. Such an approach has been investigated as a means to improve the poor performance of single frequency measurements [40]. The study showed though that the intradialytic time course of multifrequency measurements could not serve as a predictor of hypotension in the individual patient. In another study, it was concluded that monitoring of relative segmental changes in extracellular volumes using multifrequency bioimpedance may help to prevent IDH [41]; no quantitative results were, however, presented to further support this conclusion.

Impedance cardiography is, just like bioelectrical impedance, a special form of impedance plethysmography, but designed to characterize variations in blood flow during the cardiac cycle, in particular the estimation of stroke volume (cardiac output) [42]. The measurement setup typically involves four electrodes, two symmetrically positioned on both sides of the neck and two on both sides of the chest. The resulting impedance cardiographic signal can be used to derive hemodynamic information which characterize, e.g., thoracic fluid content, blood pressure (systolic, diastolic, and mean value), systemic vascular resistance, and heart rate. This type of information was investigated in a study with the aim to monitor impedance-related parameters so that significant hemodynamic instability could be identified. Out of 35 patients, five experienced instability but none of them could be correctly identified [43]. Impedance cardiographic monitoring was found to be more promising in a study involving 48 patients prone to IDH [16]. Out of the 18 patients with a fall in SAP of 20% or more relative to the baseline value at the onset of hemodialysis, 11 exhibited a decrease in cardiac output, and seven exhibited a significant fall in peripheral resistance. No information was presented on whether changes in cardiac output or peripheral resistance were predictive of IDH episodes.

Whether impedance measurements are whole body, segmental, or cardiographic in nature, they have, to date, only found an indirect importance for the prediction of IDH as reliable information on dry weight may help to reduce the frequency of IDH. This type of measurement has a number of advantages such as being noninvasive, low-cost, and safe. Its rather poor reproducibility has been improved over the years [44], [45]. However, modern systems for impedance measurements require the use of a multiple electrode configuration, making them less suitable for adoption in clinical routine.

Thoracic admittance, which is the reciprocal to thoracic impedance, has also been studied as a predictor of IDH since it is considered to reflect thoracic fluid content (and thus central blood volume) [46]. It was found that the mean absolute value of the admittance differed significantly in patients which were prone and resistant to IDH, suggesting that patients with a large central blood volume are unlikely to experience an IDH, and vice versa.

III. Electrocardiographic Variables

Cardiac function has been studied extensively in hemodialysis patients owing to the fact that cardiovascular diseases cause almost 50% of all deaths [47]—a figure which is dramatically higher than in the general population. Sudden cardiac death, ischemic heart disease, and heart failure are the most common causes of mortality. Some of this disease burden is unfortunately caused by the prevailing clinical opinion on what the prescribed dose of hemodialysis should be [48]. It has been established that ventricular premature beats (VPBs) and complex ventricular arrhythmias are both more common during hemodialysis than after, especially during the last hour of the session [49]. Moreover, myocardial ischemia may be induced during hemodialysis in its silent manifestation, usually reflected by ST-segment depression, and has been found to occur in a substantial number of patients. Better understanding of these types of cardiac events are important for improved patient management as it may lead to modifications of the hemodialysis prescription and reduced disease burden.

Although the ECG signal has been recorded during hemodialysis for analysis purposes in numerous cardionephrological studies, it has not yet become part of clinical routine, most likely due to the inconvenience of having to attach and wear electrodes. As a consequence, information on, e.g., the occurrence of paroxysmal arrhythmias or ischemic episodes, is not readily available to the clinical staff. Even if such cardiac information would be available, it remains largely unclear how it should be integrated in the dialysis procedure so that more appropriate treatment parameters can be selected for prevention of IDH.

A. Heart Rate

The maintenance of blood pressure is a result of compensatory actions mediated by the baroreflex, of which one action is a modest increase in heart rate which is usually observed during hemodialysis. However, no study has so far been able to translate information on heart rate into a useful predictor of IDH. Several studies have concluded that the change in heart rate during hemodialysis does not differ significantly between patients which are prone and resistant to hypotension; see, e.g., [17] and [50]–[53].

B. Heart Rate Variability

The analysis of heart rate variability (HRV) has proven to be a powerful noninvasive tool for quantifying the neural regulatory mechanisms that control the cardiovascular system. Heart rate variability has been investigated with reference to countless pathologies, including myocardial infarction, congestive heart failure, and diabetic neuropathy [54], [55]. The dynamics of HRV are usually characterized by time domain analysis, e.g., the standard deviation of the RR intervals between normal sinus beats, or frequency domain analysis where the resulting power spectrum, by convention, is divided into a low frequency (LF) band (0.04–0.15 Hz) and a high frequency (HF) band (0.15–0.40 Hz). These two bands are predominantly related to the activities of the sympathetic and parasympathetic branches of the autonomic nervous system, respectively, and therefore the LF/HF power ratio is a commonly studied spectral parameter reflecting autonomic balance.

TABLE I
HRV LF/HF Power Ratio in Patients Being Resistant and Prone to Intradialytic Hypotension. Asterisk Indicates a Statistically Significant Difference. See Text for Further Comments on Results

Study	#Patients resistant/prone	IDH-resistant	IDH-prone
Cavalcanti et al. [50]	15/15	3.8 ± 0.6	$0.9 \pm 0.4^*$
Pelosi et al. [52]	6/6	8.0 ± 3.5	$0.6 \pm 0.2^*$
Barnas et al. [51]	11/8	1.7 ± 0.4	1.1 ± 0.3
Rubinger et al. [53]	27/29	5.9 ± 7.0	$2.3 \pm 2.2^*$
Solem et al. [17]	7/9	1.4 ± 1.6	$0.6 \pm 0.2^*$

Heart rate variability has been extensively studied in dialysis patients with respect to hemodynamic instability; see, e.g., [17] and [50]–[53]. At an early stage, it was pointed out that the LF component plays a dominant role since it is representative of an autonomically mediated compensatory response [50]. With insufficient cardiovascular compensatory mechanisms to counteract a reduction in blood volume during hemodialysis, the cardiopulmonary and arterial baroreceptor reflex leads to excitation of the sympathetic activity and inhibition of the parasympathetic activity. As a consequence of this reflex, the LF component tends to dominate the oscillations that constitute HRV during sessions without IDH.

Studies on HRV have focused on uremic patients which are prone or resistant to hypotension, almost unanimously concluding that the spectral power parameters can discriminate between these two patient groups, using either the LF power separately or the LF/HF power ratio. It has been reported on elevated values of the LF/HF power ratio in sessions without hypotension, whereas the ratio dropped markedly at the time of crisis in hemodialysis sessions with hypotension [52]. Table I presents the results from five HRV studies of which four found statistical significant differences between patients being resistant and prone to IDH. It should be noted that the comparison of LF/HF power ratio between studies is rendered somewhat difficult since the computation of this variable differs slightly from study to study.

Some of the above-mentioned studies have performed spectral analysis in short successive segments during dialysis, thus making it possible to monitor the evolution of computed parameters in real time. The obvious idea to let changes in the spectral parameters predict an approaching IDH has so far not been explored at greater length. While spectral HRV parameters may not be powerful enough to alone predict IDH with a clinically acceptable accuracy, they are likely a part of the set of physiological parameters which would be embraced in an online predictor.

Although frequency domain analysis appears to be the predominant approach to characterizing HRV, nonlinear time domain analysis represents another powerful approach which typically relies on entropy-based measures [56]–[58]. One of the few dialysis-related studies pursuing a nonlinear approach was the one which investigated Shannon entropy of RR intervals occurring just prior to performing dialysis in patients with chronic renal failure [59]. This measure of complexity is computed by integrating the logarithm of the HRV power spectrum over all frequency bands. The results showed that the Shannon entropy is strongly correlated to a change in SAP during a hemodialysis session, making the authors conclude that the entropy measure may serve as a predictor of a patient's proneness to IDH.

C. Ventricular Premature Beats and Heart Rate Turbulence

It is well known that VPBs are frequent in dialysis patients [60], [61] and that they increase in number during hemodialysis when excess potassium is removed [62]. Ventricular arrhythmias in hemodialysis patients has recently been studied in long-term, ambulatory ECG recordings. The results showed that VPBs occurred much more frequently during hemodialysis than they did during the postdialysis period [49]. Patients with regional wall motion abnormalities, ischemic heart disease, and left ventricular hypertrophy all had a higher frequency of VPBs during hemodialysis than those without.

Given these findings, it is somewhat surprising that so few studies on HRV in dialysis patients disclose information on the handling of VPBs as well as other ectopic beats. One study which actually provided such information showed that HRV analysis could only be performed in 18 out of 30 sessions when the exclusion criterion required the number of VPBs to be less than 4% [17]. Since the presence of VPBs perturbs the impulse pattern initiated by the sinoatrial node, RR intervals neighboring to a VPB cannot be analyzed. The presence of occasional VPBs can be adequately handled prior to HRV analysis using correction techniques [63], [64]. If correction is not performed, the resulting power spectrum will exhibit fictitious frequency components, manifested as a "white noise" level [65]. Signal segments with too many ectopic beats should be completely excluded from further analysis.

The frequent occurrence of VPBs in dialysis patients makes it possible to compute parameters which characterize heart rate turbulence (HRT). This phenomenon refers to a short-term fluctuation in heart rate, triggered by a single VPB [66], [67]. Such turbulence is considered to be a blood-pressure-regulating mechanism which, in normal subjects, compensates the VPB-induced hypotension by an accelerated sinus rate. The heart rate then decelerates to its baseline level and the blood pressure returns to its pre-extrasystolic level. The magnitude of the HRT depends on the preceding heart rate such that higher heart rates are coupled to lower magnitudes, and vice versa. Blunted or missing turbulence reflects autonomic dysfunction and is associated with various conditions. Several studies have established HRT as one of the most powerful risk predictors of mortality and sudden cardiac death following acute myocardial infarction [68].

For hemodialysis patients, there are good reasons to believe that HRT conveys clinically significant information since autonomic neuropathy is known to be associated with a marked fall in blood pressure during hemodialysis [69]. To date, only one study has addressed the issue whether higher propensity to IDH is reflected in HRT parameters [17]. The results showed that the acceleration in heart rate that follows a VPB is significantly lower in patients which are prone to IDH than in patients which are resistant; both groups exhibited blunted HRT according to the standard criterion [67]. The significance of the "local" hypotension which immediately follows a VPB was explored in [70]. This study concluded that HRT is physiologically modulated by the duration of the local hypotension. It remains to be established if a relationship exists between the degree of local hypotension and the prevalence of IDH.

The parameters conventionally used to characterize HRT, i.e., turbulence onset and turbulence slope [67], were developed for use in long-term, ambulatory recordings, based on the assumption that the poor signal-to-noise ratio (SNR) of single HRTs could be improved by averaging of the VPB series. For hemodialysis sessions with a duration of 3–4 h, a much lower number of VPBs is expected and therefore novel HRT parameters are needed which perform better at lower SNRs than do the conventional parameters. The ultimate goal would, of course, be to analyze single HRTs, without having to resort to averaging, so that the possible existence of HRT dynamics can be monitored over time [71].

Model-based detection and characterization of HRT was recently proposed as a step toward this goal [72]–[74]. The employed signal model is an extended version of the well-known integral pulse frequency modulation model which also accounts for the presence of VPBs and HRT. Based on a set of Karhunen–Loève basis functions which characterize turbulence shape, the generalized likelihood ratio test statistic was employed for HRT detection. Using a small dataset from hemodialysis patients, the model-based parameters achieved better separation between patients being prone and resistent to IDH than what could be achieved by the conventional parameters [72]. The model-based HRT parameters, computed from an average of 10 VPBs, performed similarly to the conventional parameters but computed from an average of 50 VPBs [74]. Interestingly, it was shown in the same study that the model-based HRT parameters, but not the conventional parameters, remained predictive of cardiac death in a population of patients with ischemic cardiomyopathy and congestive heart failure when computed from 4-h instead of 24-h ECG recordings.

Based on 48-h ambulatory recordings or longer, changes in the conventional HRT parameters were studied before and after, but not during, hemodialysis [75]. The dataset consisted of 71 patients with end-stage renal disease, but only 31 of these had VPBs which qualified for HRT analysis. The parameters were found to be significantly blunted in all patients, but were not altered by hemodialysis. This latter finding may suggest that HRT is not a phenomenon which exhibit considerable variation over time.

D. Baroreflex Sensitivity

Arterial–cardiac baroreceptor reflex sensitivity (BRS) is usually assessed with the sequences technique which relies on noninvasive measurements on cardiac activity as well as SAP [76]–[78]. With this technique, the slope of the regression line between SAP measurements and RR intervals is computed in each of the baroreflex sequences, after which the resulting slopes of all sequences are averaged in order to produce an estimate of BRS. A sequence is delimited in the beat-to-beat series of SAP measurements and RR intervals whenever both types of samples increase or decrease. Impaired BRS is characterized by smaller slope values.

The assessment of spontaneous BRS in patients prone to IDH is of particular interest since the baroreflex arc is under autonomic control and regulates the short-term dynamics of blood pressure. Two recent studies have shed light on the role of BRS in this group of patients. Using a variant of the sequences technique, the first study showed that cool dialysate reduces asymptomatic IDH (cf. Section III-B); however, absolute BRS values did not change significantly by lowering the dialysate temperature [79]. Increased variability in BRS during cool hemodialysis was observed which may suggest improved hemodynamic stability. In that study, it was concluded that early identification of patients with reduced BRS variability may reduce the prevalence of IDH by individualizing the therapy. The other study investigated the contribution of impaired BRS to the pathophysiology of IDH [80]. The major finding was that BRS, measured at rest immediately prior to the onset of hemodialysis, is extremely heterogenous and, therefore, no individual patterns of hemodynamic response could be identified, not even in patients prone to IDH.

It is well known that the above-mentioned sequences technique sometimes fails to produce an estimate in patients with impaired BRS, and dialysis patients are obviously among those where the technique will fail. To address this serious shortcoming, a novel method was recently developed which employs a different definition of baroreflex sequences and which introduces global/total slope estimators, as replacements of the local slope estimator, in order to ensure more robust estimation [81]. The results showed that the method could always produce a BRS estimate, also in those cases where baroreflex sequences could not be identified.

Baroreflex sensitivity can also be assessed at different frequencies, relying on a measure of spectral coherence between the variability which is present in heart rate and systolic blood pressure [82]. Using the LF and HF bands, defined in the same way as for the HRV analysis mentioned earlier, the BRS was found to differ significantly in the HF band in patients prone and resistant to IDH [83]. In contrast to the results reported in [80], this result suggests that failure of the baroreflex function is likely to be one of the factors which is responsible for IDH.

IV. PHOTOPLETHYSMOGRAPHIC VARIABLES

The pulse oximeter is an optical technique, based on photoplethysmography (PPG), for measuring blood volume changes in the microvascular bed of the tissue. This device is clinically attractive since it offers noninvasive, continuous monitoring relying on existing, low-cost technology. Photoplethysmography has gained widespread clinical use because it can provide information on diverse physiological variables such as arterial oxygen saturation, respiration, heart rate, vasoconstriction, blood pressure, and autonomic function [84]. The interaction of light with arterial blood generates a pulsatile response due to changes in blood volume with each heartbeat, while the interaction with skin, bone, and venous blood is more constant. As a result, the PPG signal comprises a pulsatile component, synchronized to each heartbeat, which is superimposed on a slowly varying baseline related to the average blood volume and tissue properties. The baseline varies slowly due to the influence of respiration, sympathetic activity, and thermoregulation.

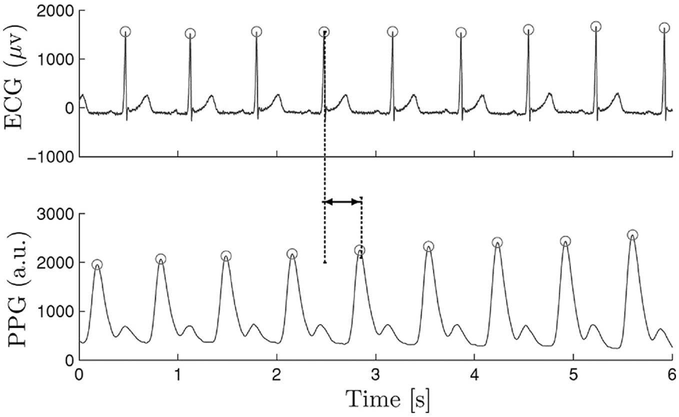

Fig. 2. Pulse wave transit time estimated from ECG and PPG signals.

Different characteristics of the finger PPG signal have been explored for continuous monitoring of hemodynamic stability during hemodialysis [85]–[87], though none of these studies have devised an algorithm for prediction of IDH. Depending on the underlying hypothesis on hemodynamic information in the PPG signal, basic pulse wave characteristics such as amplitude, occurrence time, and area are subjected to analysis and can be trended for display.

A. IDH and Pulse Transit Time

The pulse wave transit time (PTT) is related to the time required for transit of the pulse wave to the periphery and can be used to monitor changes in systolic blood pressure [85], [88]. The pulse transit time can be estimated by the time interval between the peak location of the R wave, determined from the ECG signal, and the PPG pulse onset; see Fig. 2. The PTT provides an indirect estimate of blood pressure changes since arterial compliance is reduced when blood pressure increases which makes the pulse wave travel faster, and vice versa. The manifestation of hypotension in PTT measurements was simulated by placing healthy subjects in an airtight box in which a lower body negative pressure was induced [85].

The measurement of PTT was also central to a study which evaluated the "harmonized alert sensing technology" (HASTE) device, developed especially for dialysis monitoring [87], [89]. Besides PPG and ECG sensors, this device includes a cuff placed on the arm for arterial pressure whose purpose is to make intermittent control measurements and to exclude outliers. The SAP was estimated as being linearly proportional to PTT, with coefficients adjusted during hemodialysis. Using data from 18 patients, the performance of the HASTE device was evaluated by comparing the PTT-based estimates of systolic arterial pressure to invasive SAP taken as [87].

Interestingly, the results reported in the two above-mentioned PTT-based studies were almost identical, despite the fact that the investigated datasets were completely different. The correlation r^2 between PTT and a cuff-based reference measurement on SAP was 0.66 in [85], whereas it was 0.65 between

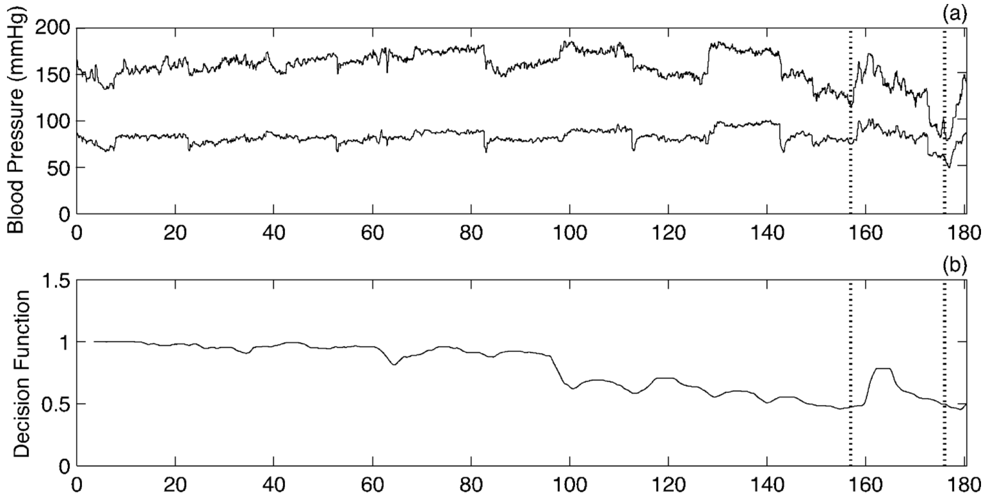

Fig. 3. Arterial and diastolic blood pressure (upper panel) and preprocessed PPG signal (lower panel) during a hemodialysis session with two hypotension episodes occurring at time instants indicated by vertical, dotted lines.

PTT-based estimates of SAP and invasive SAP [87]. No quantitative results were presented on the agreement between measurements in terms of temporal dynamics, and thus no conclusions can be drawn on the methods' suitability for prediction of IDH.

While recent results suggest that PTT is unsuitable as a surrogate marker of systolic blood pressure [90], PTT can still be useful for assessing variability in blood pressure as observed, e.g., during hemodialysis.

B. IDH and Pulse Wave Amplitude/Morphology

As mentioned in Section III-B, sympathetic activity increases in response to ultrafiltration and leads to peripheral vasoconstriction. As a result of vasoconstriction, the core body temperature tends to increase since heat dissipation is impaired. When combined with the increase in central heat production that accompanies dialysis, increased core body temperature can overcome peripheral vasoconstriction and accelerate the occurrence of acute hypotension [11]. In the PPG signal, peripheral vasoconstriction is manifested as a decrease in pulse wave amplitude when measured in the finger [91].

This pulse wave amplitude was further explored through the development of a PPG-based method for the prediction of IDH [92]. The method takes the envelope of the PPG signal as its starting point since the envelope was considered to reflect changes in relative blood volume of the capillaries. Using a sliding window approach, statistical hypothesis testing is performed in each window in order to determine if the amplitude of the envelope has dropped or not, using a window length of 5 min. Thus, the method does not explore the amplitude of individual pulse waves but long-term changes in amplitude. With good accuracy, the noise was found to be characterized by a Laplacian probability density function. Using leave-one-out cross validation, the results showed that the method could predict six out of seven hypotensive events, whereas it only produced one false prediction out of 17 possible. The mean time of prediction was found to be 38 min. The method is illustrated by the example presented in Fig. 3. While these results are promising, they were obtained on a rather small dataset and therefore need to be established on a more comprehensive dataset before more far-reaching conclusions can be drawn.

The variability of the pulse wave amplitude series has been investigated with reference to the reduction in blood volume during hemodialysis [93]. The proposed analysis closely resembles that performed in the frequency domain of HRV, but with the crucial difference that pulse wave amplitude instead of rhythm is investigated. As a consequence, the physiological interpretation of PPG variability differs from that of HRV: the PPG-LF band mostly reflects sympathetic-related vascular activity with minimal direct vagal influence, whereas the PPG-HF band is governed by the mechanical effect of respiration on venous return. For fluid overloaded patients, both PPG-LF power and PPG-HF power were found to increase significantly due to a progressive reduction in relative blood volume during hemodialysis, but not so for nonfluid overloaded patients. Early findings published in the literature showed from the analysis of intraneural recordings that IDH is related to acute withdrawal of sympathetic vasoconstrictor drive [22]. With the PPG-based method described in [93], changes in peripheral autonomic control can be monitored and, possibly, detect this type of sympathetic withdrawal.

Monitoring of pulse wave morphology in the PPG signal has been proposed as a means to quantifying intermittent hemodynamic instability [86]. In that study, the authors introduced a "reflective index," defined as an average of the samples that make up the dicrotic notch of the diastolic component of each pulse wave. An increase in this index is associated with increased peripheral pulse wave reflection due to, e.g., vasoconstriction. In 15 out of 20 patients with end-stage renal failure, the index was found to increase during hemodialysis, suggesting increased systemic vasoconstriction. While the reflective index was continuously trended during the session, its temporal dynamics was not explored for various purposes such as the prediction of IDH; only the change in index value from onset to end of the hemodialysis session was studied in statistical terms. When the dicrotic notch is absent, which is often the case in patients prone to hypotension, the reflective index is no longer defined, and thus the resulting trend will contain gaps.

C. IDH and Oxygen Saturation

Short-term variability of oxygen saturation has been proposed as a "warning parameter" of IDH [94]. Although measurements of oxygen saturation were acquired from blood entering the dialyzer, similar information is provided by a PPG finger sensor since both types of measurements are made on arterial blood. Short-term variability was quantified by the standard deviation of the samples in a sliding window of 4-min length. It was hypothesized that increased variability precedes hypotension and is a consequence of changes in cardiac output and tissue perfusion. The results were promising since 17 out of 20 treatments with hypotension were correctly predicted, and no prediction was made in 18 out of 20 treatments without hypotension. The mean time of prediction was 14 min. Unfortunately, the significance of these results cannot be easily assessed since information on the annotated occurrence time of hypotension was made use of when determining the estimated occurrence time. Hence, it is difficult to compare these results with those presented in [92], although this would be highly interesting since the two methods are the only ones published to date which address the problem of real-time IDH prediction.

D. Hypovolemia in Other Applications

The withdrawal of blood volume can be monitored using the PPG signal for the purpose of detecting progressive hypovolemia. The significance of such monitoring has been thoroughly investigated within the contexts of intensive care and anesthesia, but not so for hemodialysis despite the fact that withdrawal of blood volume is an important cause of IDH. In the following, recent advances in methodology for detecting hypovolemia are briefly reviewed.

Several studies have established that respiratory-induced amplitude changes in the PPG signal can serve as a parameter for detecting progressive hypovolemia; see, e.g., [95] and [96] for some early results. The changes are commonly quantified by first determining the pulse wave amplitude, i.e., the difference in amplitude between the peak and the preceding trough, and the respiratory amplitude, i.e., the maximal and minimal pulse wave amplitudes within a respiratory cycle. A "hypovolemic" parameter can be defined as the difference between these two amplitudes and normalized by their mean value. Since this parameter requires peak-picking, which is known to be vulnerable to noise, recent efforts have aimed at robustifying the peak-picking procedure [97], [98]. The significance of respiration-induced variability in the PPG signal was evaluated in 33 anesthesized patients by withdrawing blood in steps of 2% of estimated circulating blood volume, up to 20% [99]. Using the hypovolemic parameter, it was found that the PPG signal is useful for detecting hypovolemia for reductions in blood volume of 6% or more.

Similar results were obtained from 18 healthy subjects who underwent a progressive reduction in central blood volume induced by lower body negative pressure [100]. In that study, the amplitude, width, and area of each individual pulse wave were analyzed and averaged over minute-long segments. Changes in these features were found to be strongly correlated with progressive reduction in stroke volume during lower body negative pressure; subsequent restoration of the central blood volume was reflected by a return of the parameter values to their respective baseline levels. It was concluded that PPG analysis is suitable for detection of clinically significant hypovolemia before the onset of cardiovascular decompensation in spontaneously breathing patients.

Rather than relying on time domain features of individual pulse waves for detecting hypovolemia, more detailed information can be obtained by spectrally decomposing the PPG signal into different components which, e.g., reflect respiratory activity. A recent method explores modulation of the PPG signal by heart rate and respiratory rate [101]. Such modulation is considered to be related to changes in arterial and venous pulsations. An advanced demodulation technique was developed for multicomponent narrowband signals whose center frequencies can be time varying [102]. At every time instant, the largest value of the respiration spectral band is determined, forming a sample of the signal which represents the time-varying amplitude modulation due to respiration; the heart rate related modulation signal is determined in an analogous way. From the PPG signals recorded from 11 healthy subjects exposed to lower body negative pressure, it was found that a reduction in amplitude modulation of the respiration rate, as well as in amplitude modulation of the heart rate, serve as markers for early detection of blood volume reduction.

E. Cardiac Rhythm

Although it is well known that heart rate can be accurately estimated from the PPG signal [103], it is only until recently that pulse rate variability, determined from the PPG signal, has been investigated as a possible surrogate for HRV [104], [105]. When analyzing data from healthy subjects, it has been shown that neither time domain nor frequency domain parameters differ significantly when determined from the ECG or the PPG. However, this finding remains to be established for different groups of patients before the PPG can be employed as a definitive surrogate signal. An important difference between ECG- and PPG-based signal analysis is that the latter is confounded by the influence of PTT which fluctuates on a beat-to-beat basis. Although the fluctuations introduce an error component to the analysis, its influence appears to be quite negligible, both for HRV determined at rest and during nonstationary conditions. Since PTT is related to blood pressure, its influence on the HRV spectrum is largely confined to the LF region.

The analysis of HRT has also been performed on rhythm information derived from the PPG signal, the outcome suggesting that this may be a feasible approach [106]. To make such analysis meaningful, it is crucial that VPBs can be determined from the pulse wave characteristics. This requirement applies to the analysis of pulse rate variability as well as to the situation where the occurrence of VPBs must be dealt with.

F. Signal Quality

To ensure that PPG-based methods are robust enough for clinical use, the influence of motion artifacts caused by the patient moving his/her arm to communicate, drink, or eat is essential to minimize. For example, patient movement can compromise the accuracy of the analysis based on the PPG sensor in the non-fistula arm [87]. Over the years, considerable research has been directed toward reducing the influence of motion artifacts on PPG measurements: see, e.g., [107] and [108]. With more sophisticated PPG applications being developed, it has become increasingly important to devise algorithms which improve the SNR. At the same time, it is essential that such algorithms do not remove those frequency components which are constituent, e.g., to PPG variability, and, therefore, their design should be evaluated in terms which are relevant for the target analysis.

A broad range of signal processing techniques have recently been proposed for improving the SNR. While a review of those techniques is outside the scope of this paper, some interesting studies are still listed here. Accelerometers were used to detect the presence of motion artifacts so that an adaptive filter could be employed to reduce the influence of such artifacts [109]. Based on a model derived from photon diffusion analysis, a method was proposed for motion-resistant measurement of blood oxygen saturation [110]. Statistical model-based approaches to signal estimation in noise have been pursued which rely on basis functions including sinusoids [111], [112], see also [113]. Such an approach was, for example, found to provide accurate monitoring even in signals with abrupt changes in heart rate or respiration rate [112].

V. FEEDBACK CONTROL IN HEMODIALYSIS

Traditionally, hemodialysis has been performed with parameter settings of the dialysis machine which remain fixed throughout the session. As more information on the patient's clinical history unfolds, suitable changes in the parameter settings can be introduced at the onset of subsequent sessions in order to adjust the treatment to the patient's need. For example, the patient's history of hypotension is a factor which should exert influence on how to choose a suitable UFR profile. Nonetheless, the use of session-fixed parameters stands out as rather crude when contrasted with the body's continuous regulation of the normal kidney which ensures that a stable internal environment can be maintained (homeostasis). Consequently, it is not surprising that recent research interest has been directed toward the design and implementation of feedback control[1] in the hemodialysis machine in order to prevent hemodynamic instability [115], [116]. Feedback control represents an important step toward individualized treatment and should, ideally, lead to improved efficacy of hemodialysis and reduced frequency of IDH, especially when combined with information on patient history.

Feedback control is today implemented in clinical systems whose aim is to control one target variable, reflecting either blood temperature or relative blood volume.[2] When blood temperature is subject to control, the dialysate temperature is continuously adjusted to ensure that the required amount of thermal energy is removed by cooling of the extracorporeal circulation system [117]. The controller performs this adjustment based on the information provided by different sensors which measure arterial and venous line blood temperatures as well as blood flow.

When, instead, relative blood volume is subject to control, UFR and DSC serve as actuators for stabilizing the hemodynamic response during hemodialysis. These two actuators are known to have a major influence on the volume of blood circulating in the body. Information on the status of relative blood volume is provided by sensors which measure different types of blood constituent such as hemoglobin, hematocrit, or the concentration of total plasma proteins; see Section III-C.

Javed *et al.* [118] have just recently published an excellent review of feedback control of hemodynamic variables during hemodialysis. The reader is referred to that review for a more detailed perspective on feedback techniques than offered as follows.

A. Fuzzy Control

Since the relationship between process (output) and actuator (input) variables is nonlinear, time varying, and patient dependent, the design of a controller is far from straightforward. Some early attempts explored the use of the proportional integral derivative (PID) controller in the hemodialysis context [29]; however, the use of fuzzy logic has since long become the predominant principle for controller design since it can have nonlinear characteristics [119], [120]. The knowledge from designing a PID controller can nonetheless serve as a starting point since a linear fuzzy controller can be designed to have performance identical to a PID controller. The resulting linear fuzzy controller can then be made nonlinear through a trial and error procedure so that more complicated input–output relationships can be handled.

Under stable hemodynamic conditions, as reflected by normal values of the process variables, UFR and DSC are adjusted to its maximum and minimum value, respectively. When the relative blood volume is decreasing, possibly reflecting an approaching IDH, the fuzzy rules should ensure that UFR is decreased and DSC increased in relation to the deviation of the process variables from their normal values [119], [120]. In a fuzzy controller, these relations are translated into a set of *if–then* statements, which thus may include many input and output variables and logical operators, in order to mimic heuristic reasoning.

An alternative approach is to formulate the *if–then* statements of the fuzzy controller based on the analysis of different scenarios which can be simulated with a physiological model of IDH. For example, a model was developed for simulation of systemic arterial pressure, heart rate, total systemic resistance, and cardiac output during hemodialysis [121]; see also [122]. A set of differential equations defines the dynamics of the cardiovascular system, the solute and water kinetics, and the exchange of water between body compartments. This simulation model has served as the basis for the design of a fuzzy controller which adjusts the DSC and UFR profiles based on the prescribed decrease in body weight and sodium content [15]; the controller performance regarding reduced frequency of IDH is discussed

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[1] In the literature, feedback control in hemodialysis has, somewhat misleading, been referred to as "biofeedback" though it is widely accepted that this terms refers to a process that enables an individual to learn how to change physiological activity for the purposes of improving health and performance; see, e.g., [114].

[2] Arterial blood pressure has also been treated as a target variable for control, together with measurements on the arterial blood pressure itself as sensor information [14]. The overall purpose of the system was to prevent IDH. However, no information was disclosed on the employed sensor principle.

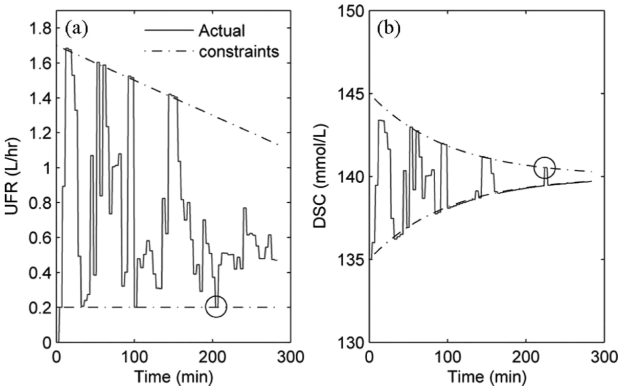

Fig. 4. (a) Ultrafiltration rate and (b) dialysate sodium concentration subjected to feedback control for an asymptomatic hypotensive patient. Time instant at which systolic blood pressure dropped to the lower constraint is circled. (Reprinted from [123] with permission.)

as follows. Unfortunately, the technical details of this controller, as well as other fuzzy controllers employed in clinical studies, are poorly disclosed since their design is proprietary and implemented in commercial products, thereby limiting their significance for the engineering research community.

B. Model-Based Control

Model-based control was recently investigated for the purpose of maintaining hemodynamic stability during hemodialysis and represents a novel, promising approach to feedback control in hemodialysis [123]; see also the precursor study in [124]. The model, assumed to be linear and time varying, embraces variables similar to the ones of fuzzy control, i.e., UFR and DSC as actuator variables, and relative blood volume, systolic blood pressure, and change in heart rate as process variables. The matrices of the system state equation are defined by several time-varying parameters, identified in individual patients using a multistage estimation technique. Hemodialysis sessions profiled with respect to UFR and DSC, either being constant, linearly decreasing, step decreasing, or square changing, are crucial to the identification procedure as the model response of an individual patient can then be fine-tuned. The average goodness of fit between the measured and the estimated process variables, expressed in terms of r^2, was found to be approximately 0.7 for all variables. Changes in heart rate were more difficult to model which, according to the authors, could be explained by the presence of HRV. However, it can be questioned whether heart rate should be modeled at all considering that a change in heart rate does not differ significantly between IDH prone and resistant patients, cf. Section IV-A.

The controller design aims at regulating relative blood volume and heart rate by varying UFR and DSC while, at the same time, maintaining a stable systolic blood pressure. Model-based predictive controller design was explored for this purpose as it can, among other things, easily account for constraints which must be fulfilled so that the controlled variables remain within safety margins. The behavior of this type of controller is illustrated in Fig. 4.

Preliminary results were obtained from a dataset with 12 patients who underwent profiled hemodialysis treatment. The results suggest that the proposed feedback control system can maintain the systolic blood pressure within certain bounds and avoid the occurrence of sudden changes in relative blood volume and heart rate. In contrast to fuzzy controllers, the model-based controller has the scientific advantage of being described in considerable detail. It remains to be established whether this approach to feedback control can reduce the frequency of IDH.

C. Clinical Results

The use of feedback control based on relative blood volume has in several studies been found to reduce the frequency of IDH—a result which may be attributed to the fact that the feedback control helps to avoid rapid fluctuations in relative blood volume [25], [29], [125]–[127]. In an early study, 12 hypotension-prone patients were treated with both standard (manual) UFR control and feedback control of UFR and DSC [128]. The latter type of control was associated with considerably fewer hypotensive episodes: the number of sessions with hypotensive episodes dropped from 59 to 24 out of a total of 72 sessions. In a more recent study, involving 26 hypotension-prone patients, the percentage of sessions with symptomatic IDH was found to decrease from 32% in standard hemodialysis to 24% when using feedback control of UFR [129]. A similar reduction ratio was reported in [14], where the percentage of sessions with severe IDH decreased from 13.8% to 8.3%.

Among the most impressive results presented to date are those of a multicenter study which involved 55 patients, all having had IDH during at least one session per week in the 6 months preceding hemodialysis treatment [15]. Employing the above-mentioned model-based fuzzy controller, labelled "automatic adaptive system dialysis (AASD)," more stable intradialytic blood pressure and lower heart rate were found when compared to standard treatment. The number of sessions complicated by hypotension decreased from 58.7% to as low as 0.9%. While differences in results can be explained to some extent by different datasets, the methodology adopted for feedback control of UFR and DSC is likely to be the main explanation.

The outcome of clinical studies may be partially biased by a patient's knowledge on whether hypotension-preventive measure are taken or not during the hemodialysis session. It is well known that such knowledge can, by itself, act to reduce the frequency of IDH.

Despite the fact that feedback control in hemodialysis has produced promising results in terms of reducing the frequency of IDH, not all nephrologists are equally convinced about the overall value of this technology. The use of feedback control may be time consuming for the clinical staff and may therefore represent a barrier to widespread deployment. Furthermore, it is felt that the technological advances in hemodialysis treatment have yet to be translated into longer patient survival [12]; a similar view has been expressed in [7] and [130]. It is, however, essential to contrast such pessimistic views with the fact that patients who undergo hemodialysis treatment today are much older and have more serious medical problems than had patients who were treated some 20 years ago.

VI. FUTURE PERSPECTIVES

Since cardiovascular problems remain the most common intradialytic complication [131], it is remarkable that so scarce information on cardiovascular status is provided to the clinical staff during hemodialysis. This lack can partially be explained by the need to use additional sensors for recording such activity, which may cause discomfort to the patient. Moreover, it is clinically undesirable to be forced to spend time on attaching ECG electrodes and cables for every session. The finger-based pulse oximeter represents a more comfortable sensor alternative and is resistant to electrical interference and loosening of electrodes. Ultimately, however, the clinical goal would be to develop techniques which make it possible to extract cardiac information without having to introduce additional sensors.

An interesting concept, recently proposed, is the "patient deterioration index" which is designed to reflect the risk of a patient to develop IDH [132]. This index is inspired by previous work on a patient monitoring system which involved data fusion [133], [134]. Based on a probabilistic model of normality, the main idea is to identify abnormalities in hypotension-related variables of a patient, where the statistics characterizing normality are first learned from data collected from a representative group of IDH-resistant patients. Prediction of IDH is then accomplished in real-time by searching for substantial deviations from the model. While this approach does not replace feedback control, it can provide the clinical staff with valuable information on patient status as well as to enrich the information which serves as input to the feedback controller.

Feedback systems represent a great leap forward in hemodialysis technology and offer the potential to improve the treatment of patients with end stage renal disease. To date, their implementation has largely been confined to the analysis of "wet" variables such as relative blood volume, UFR, and DSC. Besides requiring additional sensors, a technical reason to why information on cardiac activity has not been much explored for feedback control may be that variables reflecting HRV and HRT are irregularly sampled in time. Indeed, certain cardiac variables are represented by just a single value for the entire hemodialysis session, thus serving as an indicator of the patient's proneness to IDH for the entire session. Consequently, research is needed on how to design a feedback controller which not only processes dynamic, regularly sampled data, but also sparsely and irregularly sampled data so as to improve the overall interpretation of the data.

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