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Prediction of hypotension in hemodialysis patients

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Abstract

Intradialytic hypotension (IDH) is the most common adverse complication during hemodialysis. Its early prediction and prevention will dramatically improve the quality of life for patients with an end stage renal disease. In a recent study, changes in the normalized envelope of the test statistic of the photoplethysmograpic (PPG) signal were found to predict acute symptomatic IDH. In the present study, the PPG-based predictor is generalized to include a patient-dependent threshold which incorporates on-line information on heart rate variability and heart rate turbulence. From datasets with patients prone and resistant to IDH, the results show that symptomatic IDH could be correctly predicted in 9 out of 14 cases, while 5 out of 24 were falsely predicted. In a subset of the data containing only patients prone to IDH, acute symptomatic IDH could be correctly predicted in 5 out of 5 cases, with one false prediction out of 14. When testing the robustness of the predictor, no significant changes were observed in the test statistic when controlled changes occurred in dialysis fluid temperature, ultrafiltration rate and body position.

Keywords: ECG, PPG, intradialytic hypotension

(Some figures may appear in colour only in the online journal)

1. Introduction

Hemodialysis is a well-established treatment of patients with end stage renal disease. Unfortunately, episodes of intradialytic hypotension (IDH) occur in approximately 25%

of all treatment sessions which makes IDH the most common adverse complication during hemodialysis (Daugirdas 2001). Short-term consequences of IDH are symptoms of fatigue, cramps and vomiting, leading to premature termination of the session, whereas long-term consequences include permanent damage to the heart (Schreiber 2001). Frequent episodes of IDH represents a significant and independent risk factor for increased morbidity and mortality in hemodialysis patients (Tislér *et al* 2003, Shoji *et al* 2004). It is well-known that IDH can induce cardiac arrhythmias which increase the risk of sudden cardiac death (Selby and McIntyre 2007). The concept of predicting IDH can pave the way for wider applications, e.g. to study the physiology of hypotension proneness or orthostatic hypotension and the problem of fainting in the elderly population (Convertino *et al* 2005, Schwartz *et al* 2013).

The primary causes of IDH are decreased blood volume, occurring as a result of fluid withdrawal of the vascular compartment during ultrafiltration (UF) and insufficient refilling of fluid from the interstitial compartment to the vascular compartment. Other contributing factors include impaired peripheral vasoconstriction, autonomic dysfunction, arteriosclerosis and cardiovascular pathologies such as left ventricular hypertrophy and dilated cardiomyopathy (Davenport 2009).

Clinical management of IDH remains largely synonymous to placing the patient in the Trendelenburg position, i.e. supine body position with the feet held higher than the head, accompanied by substantial slowing of the UF rate so that the reduction in blood volume due to fluid removal is slowed down (Sherman *et al* 2007). Another means is to infuse a hypertonic solution which increases blood volume and, accordingly, blood pressure (Shimizu *et al* 2008). Since these types of actions are invoked when the patient already exhibits symptoms, it is highly desirable to predict the occurrence of IDH so that appropriate, early measures can be taken.

Short-term variability of oxygen saturation has been proposed as a predictor of IDH by Mancini *et al* (2008). It was hypothesized that increased variability in oxygen saturation precedes IDH, being a consequence of changes in cardiac output and tissue perfusion. In their study 17 out of 20 treatments with IDH were correctly predicted, whereas 18 out of 20 treatments without IDH were correctly predicted. Since information on the annotated occurrence time was considered when estimating the occurrence time, the performance of this method remains to be assessed.

Another approach to the prediction of acute symptomatic IDH is based on the assumption that peripheral vasoconstriction precedes acute symptomatic hypotension (Solem *et al* 2010). The magnitude of the normalized PPG envelope was used as input to a test statistic which, when dropping below a fixed threshold, produced a prediction. On a small dataset, the predictor performed accurately on all episodes of acute symptomatic IDH, without producing any false predictions.

Heart rate variability (HRV) has been extensively studied for the purpose of discriminating patients prone to IDH from resistant, although not considered in the context of real-time prediction (Sörnmo *et al* 2012). Most studies have concluded that the spectral power can be used for discrimination, e.g. the ratio between the low- and high-frequency power. Elevated values of this ratio in sessions without hypotension have been reported and reduced values at the time of crisis in sessions with hypotension (Pelosi *et al* 1999).

The frequent occurrence of ventricular premature beats (VPBs) in dialysis patients renders it possible to study heart rate turbulence (HRT), being a short-term fluctuation in heart rate triggered by a VPB (Sörnmo *et al* 2012). Blunted or missing HRT reflects autonomic dysfunction, where autonomic neuropathy in turn has been associated with a marked fall in blood pressure during hemodialysis (Calvo *et al* 2002). Consequently, HRT characterization has been put forward as a means to determine a patient's propensity to IDH (Solem *et al* 2006), see also Celik *et al* (2011).

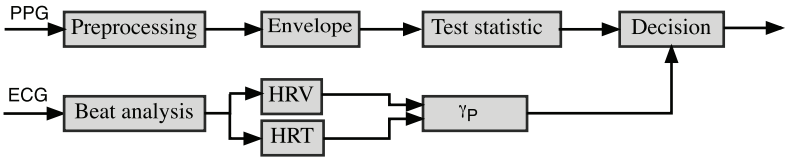

Figure 1. Block diagram of the IDH predictor. In the decision block, the test statistic is compared to a threshold composed of a fixed part (γ_f) and a patient-dependent part (γ_p), the latter being computed from the ECG.

The purpose of the present study is twofold: firstly, to generalize the predictor structure proposed in Solem *et al* (2010) to include a patient-dependent threshold which incorporates information on HRV and HRT. In doing so, the threshold can be adjusted to the patient's propensity to IDH. Secondly, the purpose is to evaluate the robustness of the resulting predictor with respect to disturbances commonly known to affect blood pressure that regularly occur during hemodialysis (changes in posture, dialysis fluid temperature and UF rate).

The paper is organized as follows. Section 2 details the datasets used for performance evaluation and provides a definition of IDH. Section 3 describes the signal model and the related predictor with the patient-dependent threshold. The results are presented in section 5 in terms of prediction performance and robustness, using the procedure described in section 4. The paper ends with a discussion of the results.

2. Materials

Two datasets are studied for performance evaluation, both recorded at Rigshospitalet in Copenhagen, Denmark. The first dataset ('D1') consists of 28 sessions from 11 hypotension-prone patients and was previously used in Solem *et al* (2010). The second dataset ('D2'), consisting of 20 sessions from 7 patients, was acquired with a protocol for investigating the robustness of the PPG-based predictor in a controlled, clinical study. The selection is based on patient available in the clinical routine, no exclusion criteria based on comorbidities were applied. Both studies were approved by the local ethics committee and written informed consent was obtained from each subject before enrolment into the study. D2 was acquired with the same device setup as for D1, but included both hypotension-prone ($n = 3$) and resistant ($n = 4$) patients.

Three different types of treatment sessions were performed for each patient, see figure 1: the first treatment ('reference treatment') was performed with standard settings, in the second the dialysate temperature was increased by 1 degree after 1.5 h and in the third treatment the UF rate was doubled after 1.5 h during 30 min. Three hours into all treatment sessions, the patient was instructed to perform a series of body position changes which lasted for 20 min (supine position, horizontal side position, supine position, raise non-access arm for 10 s, supine position, Trendelenburg position and upright position). Treatments were performed on the same day of consecutive weeks. The series of body position changes was always done prior to eating and drinking. One patient was unable to perform the third treatment.

Symptomatic IDH is defined according to the following criteria (Sörnmo *et al* 2012):

- if pre-dialysis systolic arterial pressure (SAP) was $\geqslant$100 mmHg: any event with SAP $\leqslant$90 mmHg, associated with complaints;
- if SAP was $\leqslant$100 mmHg: any SAP reduction by at least 10% associated with complaints;

Acute symptomatic IDH, being a subset of symptomatic IDH, is defined by a sudden drop in systolic blood pressure (30 mmHg per 10 min before hypotension).

Table 1. Summary of datasets. The sessions with acute symptomatic IDH constitute a subset of the sessions with symptomatic IDH.

	D1	D2
Patients	11	7
Diabetics	6	3
Age (years)	64.0 ± 12.3	63.1 ± 6.4
Weight (kg)	70.3 ± 20.0	82.3 ± 16.2
Time on dialysis (months)	38.0 ± 24.8	45.6 ± 40.6
Dialysis duration (min)	231.5 ± 28.7	243.3 ± 12.5
Ultrafiltration volume (l)	3.24 ± 0.89	3.65 ± 0.83
Ultrafiltration rate (l/h)	0.84 ± 0.20	0.90 ± 0.19
Total number of sessions	28	20
Sessions with symptomatic IDH	10	5
Sessions with acute symptomatic IDH	5	0

Table 1 summarizes the characteristics of D1 and D2 when the above criteria on acute symptomatic and symptomatic IDH are applied. Symptomatic IDH occurred in 5 hemodialysis sessions of D2; 1 hypotension-prone patient had symptomatic IDH in all 3 sessions and 2 patients (one which was classified as hypotension-resistant) had symptomatic IDH only during the session with temperature change. None of the cases of symptomatic IDH in D2 was classified as acute. Symptomatic IDH occurred in 10 hemodialysis sessions of D1; 5 of these cases were classified as acute.

Blood pressure, PPG and ECG were recorded using the Biopac MP150 data acquisition system (BIOPAC Systems Inc., USA) with a sampling rate of 1000 Hz. Signal acquisition was made in parallel with the conventional hemodialysis equipment. Continuous arterial blood pressure was acquired with the Portapres (Finapres Medical Systems BV, Holland), measured with two finger cuffs wrapped around the mid-phalanx of two different fingers on the hand of the access-free arm. Blood pressure was measured with one finger cuff at a time, i.e. 15 min on one cuff, then changed to the other cuff for 15 min and so on. Manual cuff-based blood pressure values was also measured at beginning and end of treatment as reference. The PPG was acquired continuously with a pulse oximeter (LifeSense, Medair AB, Sweden), using a finger sensor attached to the same hand as where the blood pressure was measured but to a cuff-free finger. The sensor was attached to the finger during the entire treatment. The PPG signal was tested with respect to signal quality in successive 5 min segments: whenever the maximum spectral peak was located outside the interval 0.8–2.3 Hz (48–138 BPM), the segment was excluded from further analysis as heart rate could not be detected. The ECG was acquired continuously throughout the hemodialysis session.

Two types of machine were used: one type for patients undergoing hemodialysis (Gambro AK 200) and another for hemodiafiltration (Gambro AK 200 S), both manufactured by Gambro Lundia AB, Sweden.

3. Methods

An overview of the IDH predictor is provided by the block diagram in figure 1. The upper branch transforms the PPG signal into a test statistic which is computed in a sliding window. Since the PPG preprocessing is identical to that described in Solem *et al* (2010), section 3.1 describes the novel aspects of the predictor structure. Section 3.2 details the lower branch of the block diagram where the ECG-based parameters are computed, providing information on HRV and HRT for incorporation in the patient-dependent threshold.

3.1. Prediction with a patient-dependent threshold

The predictor, also referred to as the detector, is based on the hypothesis that a decrease in the normalized PPG envelope $x[n]$ reflects peripheral vasoconstriction and decreased cardiac output which precede IDH (the normalized envelope is produced by the preprocessor) (Solem *et al* 2010). This hypothesis is translated to the problem of detecting a change in the level of $x[n]$ in a window that slides as new data becomes available. The level detection problem is first treated for a fixed window, indexed by m and then modified to involve a sliding window.

The detection problem is modeled as one of choosing between hypothesis $\mathcal{H}_0$, in which no change has occurred, i.e. the level of the normalized envelope is $A = 1$ and hypothesis $\mathcal{H}_1$, when the level drops to $A = 1 - \Delta A$ due to an approaching IDH:

$$\mathcal{H}_0\colon x[m] = 1 + w[m], \quad m = 0, 1, \ldots, N-1, \tag{1}$$

$$\mathcal{H}_1\colon x[m] = 1 - \Delta A + w[m], \quad m = 0, 1, \ldots, N-1, \tag{2}$$

where N is the number of samples contained in the window and ΔA ($0 < \Delta A \leqslant 1$) is the unknown drop in level. The Laplacian model is employed since it better characterizes the noise than does the Gaussian model (Solem *et al* 2010); $w[m]$ is assumed to be independent and identically distributed, zero-mean with known variance σ^2.

The generalized likelihood ratio test (GLRT) is employed in which ΔA is first estimated using maximum likelihood (ML) estimation; thus, the GLRT decides $\mathcal{H}_1$ if

$$L_G(\mathbf{x}) = \frac{p\left(\mathbf{x}; \hat{A}, \mathcal{H}_1\right)}{p(\mathbf{x}; \mathcal{H}_0)} > \frac{p(\mathcal{H}_0|\boldsymbol{\theta})}{p(\mathcal{H}_1|\boldsymbol{\theta})}\gamma' \tag{3}$$

where $\mathbf{x}$ is a vector with the observations $x[0], x[1], \ldots, x[N-1]$, $p(\mathbf{x}; \mathcal{H}_0)$ denotes the probability density function (PDF) of $\mathbf{x}$ under $\mathcal{H}_0$, $p\left(\mathbf{x}; \hat{A}, \mathcal{H}_1\right)$ denotes the PDF of $\mathcal{H}_1$ when the unknown parameter A is replaced by its maximum likelihood estimate and γ' is a fixed threshold. The prior probability $p(\mathcal{H}_1|\boldsymbol{\theta})$ is chosen such that it reflects a patient's propensity to IDH, conditioned on the parameter vector $\boldsymbol{\theta}$ which reflects the patient's clinical history. Alternatively, $p(\mathcal{H}_1|\boldsymbol{\theta})$ can be based on information which characterize ongoing cardiac activity such as HRV and HRT—an approach which is adopted in the present study. The extension to include prior probability in the GLRT is novel to this work.

When $\mathcal{H}_1$ is true, the ML estimate of $A = 1 - \Delta A$, denoted by $\hat{A}$, is given by the median of the observations for Laplacian noise. Taking the constraint $0 < \Delta A \leqslant 1$ into account, the ML estimator is given by

$$\hat{A} = \min\left(1, \text{median}\{x[0], x[1], \ldots, x[N-1]\}\right). \tag{4}$$

The two PDFs in (3) are given by

$$p\left(\mathbf{x}; \hat{A}, \mathcal{H}_1\right) = \frac{1}{(2\sigma^2)^{N/2}} \exp\left(-\sqrt{\frac{2}{\sigma^2}} \sum_{m=0}^{N-1} |x[m] - \hat{A}|\right), \tag{5}$$

and

$$p(\mathbf{x}; \mathcal{H}_0) = \frac{1}{(2\sigma^2)^{N/2}} \exp\left(-\sqrt{\frac{2}{\sigma^2}} \sum_{m=0}^{N-1} |x[m] - 1|\right). \tag{6}$$

Thus, the GLRT becomes

$$L_G(\mathbf{x}) = \frac{\exp\left(-\sqrt{\frac{2}{\sigma^2}}\sum_{m=0}^{N-1}|x[m]-\hat{A}|\right)}{\exp\left(-\sqrt{\frac{2}{\sigma^2}}\sum_{m=0}^{N-1}|x[m]-1|\right)} > \frac{p(\mathcal{H}_0|\boldsymbol{\theta})}{p(\mathcal{H}_1|\boldsymbol{\theta})}\gamma', \tag{7}$$

or, equivalently, after taking the logarithm,

$$\sqrt{\frac{\sigma^2}{2}}\ln L_G(\mathbf{x}) = -\sum_{m=0}^{N-1}(|x[m]-\hat{A}|-|x[m]-1|) > \sqrt{\frac{\sigma^2}{2}}\ln\left(\frac{p(\mathcal{H}_0|\boldsymbol{\theta})}{p(\mathcal{H}_1|\boldsymbol{\theta})}\gamma'\right). \tag{8}$$

Simplifying this expression, $\mathcal{H}_1$ is decided if the test statistic $G(\mathbf{x})$ fulfils

$$G(\mathbf{x}) = 1 + \frac{1}{N}\sum_{m=0}^{N-1}(|x[m]-\hat{A}|-|x[m]-1|) < 1 - \frac{1}{N}\sqrt{\frac{\sigma^2}{2}}\ln\left(\frac{p(\mathcal{H}_0|\boldsymbol{\theta})}{p(\mathcal{H}_1|\boldsymbol{\theta})}\gamma'\right). \tag{9}$$

It is obvious from (9) that the optimal GLRT detector computes the difference between the mean absolute deviation from $\hat{A}$ and the mean absolute deviation from 1 and compares it to a threshold which depends on N, σ^2, γ', as well as on the prior probabilities $p(\mathcal{H}_0|\boldsymbol{\theta})$ and $p(\mathcal{H}_1|\boldsymbol{\theta})$. The test statistic is made time-varying, then denoted $G(\mathbf{x}[n])$, by computing it in a sliding window with the samples $x(n)$, $x(n+1)$, … $x(n+N-1)$.

Since $p(\mathcal{H}_1|\boldsymbol{\theta})$ is the probability of IDH, the threshold in (9) can be viewed as being composed of a fixed part γ_f and a patient-dependent part γ_p,

$$\gamma = \gamma_f + \gamma_p, \tag{10}$$

where

$$\gamma_f = 1 - \frac{1}{N}\sqrt{\frac{\sigma^2}{2}}\ln(\gamma'), \tag{11}$$

$$\gamma_p = -\frac{1}{N}\sqrt{\frac{\sigma^2}{2}}\ln\left(\frac{1-p(\mathcal{H}_1|\boldsymbol{\theta})}{p(\mathcal{H}_1|\boldsymbol{\theta})}\right). \tag{12}$$

It is noted that γ_f is identical to the fixed threshold applied in Solem *et al* (2010), whereas γ_p is the novel part. In the present study, $p(\mathcal{H}_1|\boldsymbol{\theta})$ is conditioned on two random variables θ_1 and θ_2 which both convey information on cardiac rhythm. Hence, the patient-dependent part of γ is given by

$$\gamma_p = -\frac{1}{N}\sqrt{\frac{\sigma^2}{2}}\ln\left(\frac{1-p(\mathcal{H}_1|\theta_1,\theta_2)}{p(\mathcal{H}_1|\theta_1,\theta_2)}\right). \tag{13}$$

Using Bayes' rule, the conditional probability of IDH can be expressed as

$$p(\mathcal{H}_1|\theta_1,\theta_2) = \frac{p(\theta_1|\mathcal{H}_1)p(\theta_2|\mathcal{H}_1)p(\mathcal{H}_1)}{p(\theta_1|\mathcal{H}_0)p(\theta_2|\mathcal{H}_0)p(\mathcal{H}_0)+p(\theta_2|\mathcal{H}_1)p(\theta_1|\mathcal{H}_1)p(\mathcal{H}_1)}. \tag{14}$$

3.2. HRV- and HRT-dependent threshold

Spectral analysis of HRV is commonly used to assess changes in the autonomic nervous system by measuring the power of the low frequency (LF) and the high frequency (HF) bands, defined by the passbands [0.04, 0.15] Hz and [0.15, 0.4] Hz, respectively. The ratio between

LF and HF power is considered to be a measure of sympathovagal balance. Since the LF/HF ratio has been related to propensity of IDH (cf Introduction), the LF/HF ratio defines θ_1. Using the method in Hernando *et al* (2011), the ratio is computed from the first 30 min of the session when hypotensive events are unlikely to occur.

Turbulence onset (TO) and turbulence slope (TS) are the most popular parameters for characterizing heart rate turbulence (Schmidt *et al* 1999). In the present study, TS is studied since it was found to be significantly different between patients being prone and resistant to IDH (Solem *et al* 2006), while not so for TO; thus, TS defines θ_2. Similar to θ_1, θ_2 is computed during the initial 30 min of the session. For both θ_1 and θ_2, smaller values suggest that the patient is more prone to IDH.

For simplicity, all four conditional PDFs that characterize θ_1 and θ_2 in (14) are assumed to be Gaussian, i.e.

$$p\left(\theta_j|\mathcal{H}_i\right) = \mathcal{N}\left(\overline{\theta}_{j|\mathcal{H}_i}, \sigma_{j|\mathcal{H}_i}\right) \quad i = 0, 1, j = 1, 2. \tag{15}$$

Due to the limited data available, a leave-one-out cross-validation strategy was employed to determine estimates of the mean $\overline{\theta}_{j|\mathcal{H}_i}$ and the standard deviation $\sigma_{j|\mathcal{H}_i}$; when computing $p(\mathcal{H}_1|\theta_1, \theta_2)$ for one recording, the remaining ones were used for estimation.

4. Evaluation procedure

4.1. Prediction of IDH

Two different issues were investigated with respect to IDH prediction. Whereas the main target application of the present method is prediction of symptomatic (acute and non-acute) IDH in the general population, prediction of acute symptomatic IDH in hypotension prone patients was evaluated to allow for comparison with previously presented work (Solem *et al* 2010). Hence, prediction of acute symptomatic IDH was evaluated on D1. The dataset D1 was formed into two groups: patients with acute symptomatic IDH and patients without symptomatic IDH; patients with non-acute symptomatic IDH were excluded. After exclusion of 4 PPG recordings with poor signal quality (at least 20% of the analyzed 5 min segment in the recording did not reflect heart rate, according to the criteria described in Materials section), the two groups contained 5 and 14 sessions. Secondly, prediction of symptomatic IDH (both acute and non-acute) was evaluated by combining D1 and D2 and then dividing the resulting dataset into two groups: patients with and without symptomatic IDH. After exclusion of 4 (all without IDH) and 6 (5 without IDH) PPG recordings with poor signal quality from D1 and D2, respectively, the two groups contained 14 and 24 sessions. Hence, prediction of symptomatic and acute symptomatic IDH was evaluated using 38 and 19 sessions, respectively.

The following parameter values were used for performance evaluation (see Discussion for more details): $\sigma^2 = 0.2$ and $p(\mathcal{H}_0) = p(\mathcal{H}_1) = 0.5$; the prior probabilities were identical to those used in Solem *et al* (2010). The length of the sliding window was set to 5 min.

4.2. Robustness

Predictor robustness to changes in body position was evaluated by comparing the mean, the standard deviation and the number of excluded values of the test statistic G ($\mathbf{x}[n]$), computed in 20 min intervals before and during body movements, see figures 2(*a*)–(*c*). Out of the 20 sessions in D2, 11 could be analyzed since there were notes on other types of interference, e.g. dropped sensors, during the 20 min interval of scheduled movement in 9 sessions. The robustness to a change in temperature/UF rate was evaluated in the same way, except that 30 min

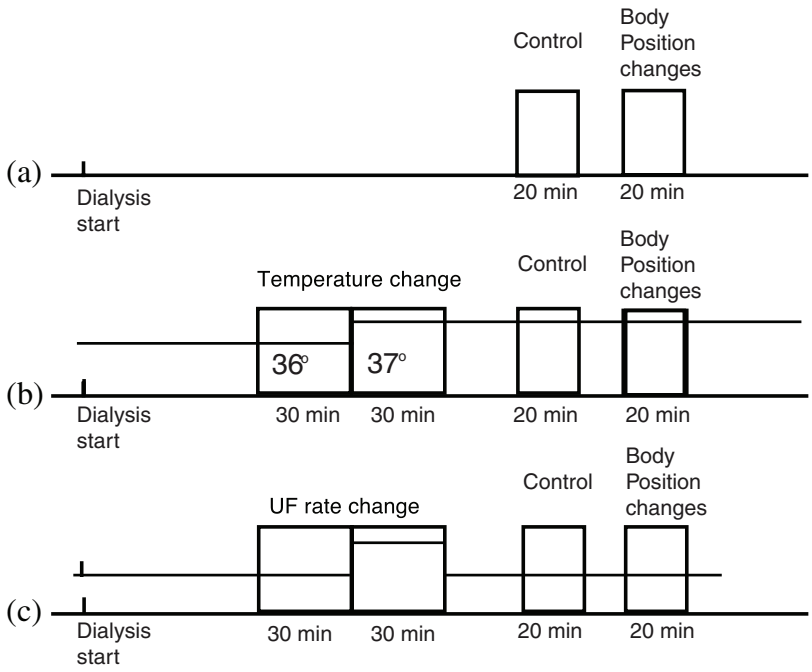

Figure 2. Segments compared for testing predictor robustness to changes in (*a*)–(*c*) body position, (*b*) dialysis fluid temperature and (*c*) UF rate. The changes in body position took place after 3 h, whereas the changes in temperature and UF rate took place after 1.5 h.

Table 2. Summary of dataset used for evaluating predictor robustness.

	#Patients	#Sessions
Body position changes	7	11
Temperature changes	7	7
UF rate changes	6	6

intervals were analyzed before and after the change, see figures 2(*b*) and (*c*), respectively. The comparison of a change in temperature/UF rate was based on 7/6 sessions, respectively. The dataset used for evaluating predictor robustness is summarized in table 2. In all comparisons, the paired student's *t*-test was employed to determine whether a change in G ($\mathbf{x}[n]$) was significant.

5. Results

5.1. Prediction of IDH

The prediction of IDH is illustrated for two patients: one without symptomatic IDH and another with acute symptomatic IDH, see figure 3. It is noted that the two investigated thresholds γ ($=\gamma_f + \gamma_p$) and γ_f are virtually identical for the patient with acute symptomatic IDH, see figure 3(*b*), whereas γ is lower than γ_f for the patient without symptomatic IDH, see figure 3(*a*).

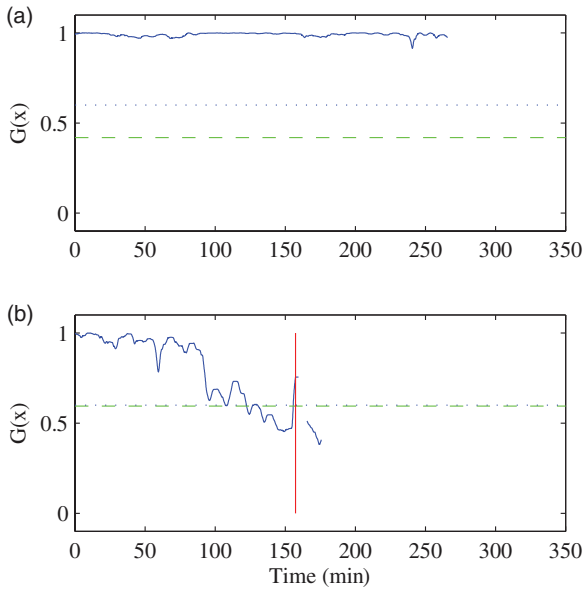

Figure 3. The test statistic $G(\boldsymbol{x}[n])$ (blue line) displayed for patients with (*a*) no symptomatic IDH and (*b*) acute symptomatic IDH, using the fixed threshold $\gamma_f = 0.6$ (dotted blue line) or the patient-dependent threshold γ (dashed green line). The vertical red line indicates the occurrence time of acute symptomatic IDH. Note that γ_f and γ coincide in (*b*).

The reason for a lower γ in the latter case is that, based on LF/HF and TS, the patient is less prone to IDH.

The receiver operating characteristics (ROCs) for predicting acute symptomatic IDH and symptomatic IDH are displayed in figure 4 for different values of γ_f. The area under the curves, 0.93 (95% confidence interval 0.61–1.0) and 0.71 (95% confidence interval 0.56–0.80), respectively, are significantly different from 0.5 according to the Mann-Whitney U-test. The confidence intervals were computed by bootstrapping.

Setting the fixed threshold γ_f to 0.6, acute symptomatic IDH was correctly predicted in 5 out of 5 sessions and falsely in 1 out of 14 sessions, see table 3. Symptomatic IDH was correctly predicted in 9 out of 14 sessions and falsely in 5 out of 24 sessions, see table 4. In most cases, the results obtained with γ were virtually identical to those obtained with γ_f so that the two curves cannot be discerned from each other in figure 4.

To shed light on these results, θ_1 and θ_2 are compared when computed for sessions with acute symptomatic IDH and for sessions without symptomatic IDH, see table 5. Both θ_1 and θ_2 exhibited lower values in sessions with acute symptomatic IDH, although the differences were not statistically significant. HRT computation was feasible in 5 out of 5 sessions with acute symptomatic IDH and in 9 out of 14 sessions without symptomatic IDH. For the present datasets, the results suggest that information on LF/HF and TS do not improve prediction.

However, comparing θ_1 and θ_2 in patients classified as hypotension prone and hypotension resistant significant differences are found, see table 6.

5.2. Robustness

Figure 5(*a*) displays the mean and standard deviation of the non-excluded values of $G(\mathbf{x}[n])$ in the 20 min segment with scheduled movement and the preceding 20 min segment, respectively,

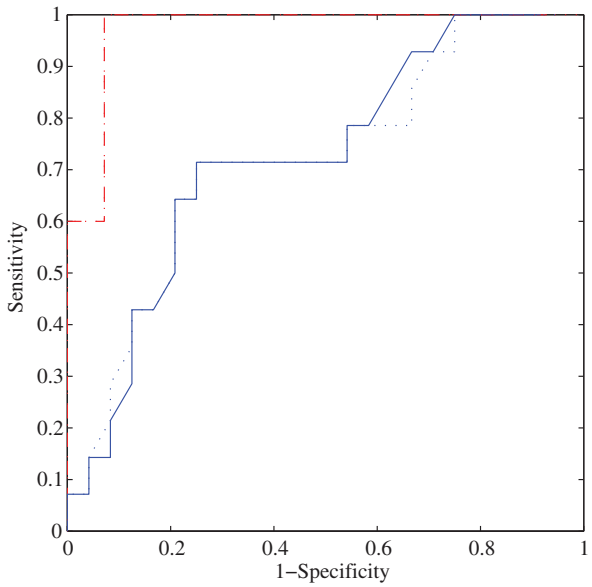

Figure 4. ROC for prediction of acute symptomatic IDH (dashed line) and symptomatic IDH (solid line) using $\gamma = \gamma_f + \gamma_p$ with different values of γ_f. The corresponding results obtained using γ_f (dotted line) are almost identical; the ROC curves coincide for acute symptomatic IDH.

Table 3. Confusion matrix for prediction of acute symptomatic IDH in D1 using the patient dependent threshold $\gamma = \gamma_f + \gamma_p$, when setting $\gamma_f = 0.6$.

		Predicted		
		Acute sympomatic IDH	No symptomatic IDH	Total
Actual	Acute symptomatic IDH	5	0	5
	No symptomatic IDH	1	13	14
	Total	6	13	19

Table 4. Confusion matrix for prediction of symptomatic IDH in D1 and D2 combined using the patient dependent threshold $\gamma = \gamma_f + \gamma_p$, when setting $\gamma_f = 0.6$.

		Predicted		
		Symptomatic IDH	No symptomatic IDH	Total
Actual	Symptomatic IDH	9	5	14
	No symptomatic IDH	5	19	24
	Total	14	24	38

for each of the sessions. In two sessions, all values of G ($\mathbf{x}[n]$) in the 20 min segment with scheduled movement were excluded from analysis due to poor signal quality (at least 20% of a 5 min segment not reflecting heart rate). Hence, the comparison of mean value and standard deviation (std) of G ($\mathbf{x}[n]$) was based on 9 sessions. There were no significant differences in mean value, std or reliable values of G ($\mathbf{x}[n]$) between the segments with scheduled movement and the preceding segments.

Table 5. Statistics of the HRV and HRT parameters in sessions with acute symptomatic IDH and without symptomatic IDH in D1, based on *n* sessions. A two-sample Kolmogorov–Smirnov test was employed to determine whether the differences were significant.

Parameter	Acute Symptomatic IDH	Without Symptomatic IDH	*p*-value
θ_1 (LF/HF)	1.11 ± 1.00 ($n = 5$)	2.87 ± 3.67 ($n = 14$)	N.S.
θ_2 (TS)	1.48 ± 1.42 ($n = 5$)	2.06 ± 1.89 ($n = 9$)	N.S.

Table 6. Statistics of the HRV and HRT parameters in sessions from patients classified as hypotension prone and hypotension resistant in D1 and D2 combined, based on *n* sessions. A two-sample Kolmogorov–Smirnov test was employed to determine whether the differences were significant.

Parameter	Hypotension Prone	Hypotension Resistant	*p*-value
θ_1 (LF/HF)	1.29 ± 1.60 ($n = 32$)	0.01 ± 0.01 ($n = 6$)	<0.01
θ_2 (TS)	2.16 ± 2.47 ($n = 22$)	4.81 ± 1.45 ($n = 4$)	<0.01

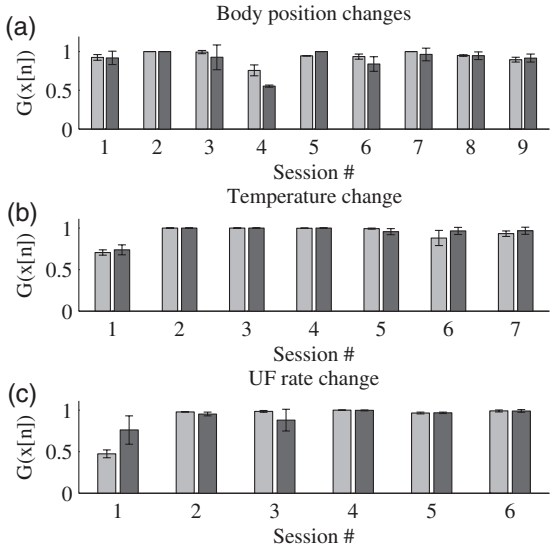

Figure 5. (*a*) Mean ± std of $G(x[n])$ before (gray) and during changes in body position (black). (*b*) Mean ± std of $G(x[n])$ before (gray) and after (black) a change in dialysate temperature. (*c*) Mean ± std of $G(x[n])$ before (gray) and after (black) a change in UF rate. Details of the evaluation procedure are given in section 4.2.

Figures 5(*b*) and (*c*) display the mean of G ($\mathbf{x}[n]$) in the 30 min segment preceding and following a change in temperature and UF rate, respectively. No significant differences were found, neither between the mean value, std and reliable values of G ($\mathbf{x}[n]$) of the segments preceding and following a change, nor for changes in temperature or UF rate. Exclusion of the sessions with symptomatic IDH did not alter the results of the comparison between sessions with different protocols; no significant differences were found.

6. Discussion

The present work generalizes the fixed-threshold approach earlier taken to prediction (Solem *et al* 2010), to here become a threshold adjusted according to the prior probability of IDH. The main motivation for this generalization is the wish to account for a patient's propensity to IDH—hence, the introduction of a patient-dependent detection threshold.

The prior probability of IDH was estimated from two ECG-derived parameters characterizing HRV and HRT. However, other parameters can be incorporated into the threshold that may convey information on IDH, e.g. baroreflex sensitivity (Hernando *et al* 2011), thoracic admittance (Cordtz *et al* 2008) and relative blood volume (Andrulli *et al* 2002). It should be noted that parameters can remain constant throughout treatment, as is the case with the present parameters, or dynamic, then leading to a time-varying detection threshold.

Performance was evaluated under the assumption of identical noise variance σ^2 in all sessions. While this assumption may seem very restrictive, the same results were obtained for a wide range of values of σ^2, suggesting that performance is not critically dependent on σ^2; therefore, a value was chosen which was typical for the database. Since ML estimation of σ^2 (in Laplacian noise) is not needed, the computational demands associated with the detector are very low.

The assumption of prior probability of IDH $p(H_1) = 0.5$ in the performance evaluation may seem high compared to the overall incidence of IDH in dialysis sessions (25%) (Daugirdas 2001). However, it should be noted that the patients of D1 were selected since they were prone to IDH and the incidence of IDH is therefore expected to be higher than for the general population.

In this study the indexes LF/HF and TS were employed to quantify HRV and HRT, respectively, as they are well-known from numerous studies. In addition, it has been shown that there are significant differences in LF/HF between hypotension prone and hypotension resistant patients (Sörnmo *et al* 2012).

When comparing θ_1 and θ_2 relative propensity of IDH in the present dataset, see table 6, significant differences were found. Surprisingly, θ_1 was larger for patients prone than for patients resistant to IDH. These results are not in accordance with the LF/HF ratios previously reported for patients being prone and resistant to IDH: 0.9 ± 0.4 versus 3.8 ± 0.46 (Cavalcanti *et al* 1998), 1.1 ± 0.3 versus 1.7 ± 0.4 (Barnas *et al* 1999), 2.3 ± 2.2 versus 5.9 ± 7.0 (Rubinger *et al* 2004), 0.6 ± 0.2 versus 1.4 ± 1.6 (Solem *et al* 2006) and 0.77 ± 0.05 versus 3.99 ± 0.71 (Hernando *et al* 2011). Whereas comparison of the numerical values is difficult since the definition of the LF/HF ratio may vary between studies, previous studies unanimously report smaller values for patients prone to IDH. The limited size of the dataset in the present study may be one reason for the deviating result.

The use of a patient-dependent threshold did not produce results better than those obtained with a fixed threshold. The main explanation to this rather disappointing result are the statistical properties of θ_1 and θ_2; the results in table 5 show that these parameters do not differ significantly in sessions with acutely symptomatic IDH and without symptomatic IDH, although the former type of sessions exhibit smaller mean values.

The results show that prediction of acute symptomatic IDH is more reliable than prediction of symptomatic IDH. This result may be explained by the different etiologies of acute and non-acute IDH and, consequently, that the mechanisms preceding IDH may be quite different. The hypothesis behind the proposed PPG-based test statistic $G(x[n])$, i.e. that peripheral vasoconstriction often precedes acute symptomatic IDH (Solem *et al* 2010), may not be equally applicable to non-acute symptomatic IDH.

The results shows that $G(x[n])$ is neither influenced by changes in UF rate and dialysis fluid temperature, nor by postural changes. Although G ($\mathbf{x}[n]$) proved to be robust to the scheduled movements, the percentage of G ($\mathbf{x}[n]$) that had to be excluded due to poor signal quality was much higher in D2 than in D1. This is due to that D1 was acquired with frequent manual supervision, whereas D2 was acquired during ordinary hemodialysis conditions. While the patients of D1 were instructed to keep the hand with the PPG sensor close to the heart, no such instructions were given to the patients of D2. Hence, more noise as well as alterations in PPG signal magnitude are expected to be present in D2.

It deserves to be mentioned that the recent development of feedback systems represent a major leap forward in hemodialysis technology (Colì *et al* 2011, Javed *et al* 2011), offering the potential to improve the treatment of patients with end stage renal disease with respect to the incidence of IDH. While cardiac activity, e.g. reflected by HRV and HRT, has not been much explored in such systems, such information may nonetheless help to improve performance.

The main limitation of the present study is the small dataset, with results on prediction of acute symptomatic IDH based on only 5 sessions. Some of the data was used in a previous study (Solem *et al* 2010). Hence, it is highly desirable to analyze a larger dataset. The collection of a larger database is our next step in this work. The analysis of a larger dataset may indicate that the use of a patient-dependent threshold is advantageous. The data selection is based on patients available in the clinical routine. Some patients suffering from distal ischemia or low blood perfusion in the extremities (VanHoek *et al* 2010) may have been excluded based on the quality of the PPG signal.

7. Conclusions

The present paper generalizes the PPG-based method for predicting IDH (Solem *et al* 2010) by not only taking the magnitude of the PPG signal into account but also the prior probability of a patient to develop IDH during a session. Information on HRV and HRT was estimated from the ECG in each session and used to determine the prior probabilities. Prediction performance seems promising since all episodes of acute symptomatic IDH were correctly predicted. The potential improvement from using a patient-dependent threshold remains, however, to be established on a larger database. The predictor proved to be robust to changes in dialysis fluid temperature and UF rate as well as to changes of body position.

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