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Identification of patients prone to hypotension during hemodialysis based on the analysis of cardiovascular signals

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ABSTRACT

Intradialytic hypotension (IDH) is a major complication during hemodialysis treatment, and therefore it is highly desirable to identify, at an early stage during treatment, whether the patient is prone to IDH. Heart rate variability (HRV), blood pressure variability (BPV) and baroreflex sensitivity (BRS) were analyzed during the first 30 min of treatment to assess information on the autonomic nervous system. Using the sequential floating forward selection method and linear classification, the set of features with the best discriminative power was selected, resulting in an accuracy of 92.1%. Using a classifier based on the HRV features only, thereby avoiding that continuous blood pressure has to be recorded, accuracy decreased to 90.2%. The results suggest that an HRV-based classifier is useful for determining whether a patient is prone to IDH at the beginning of the treatment.

1. Introduction

Hemodialysis is a well-established treatment for patients with severe kidney problems. A serious problem during treatment is intradialytic hypotension (IDH), which occur in about 20% of all sessions [1], causing symptoms such as dizziness and vertigo, and possibly also premature termination of the session [1,2]. The causes of hypotension are multifactorial, of which the primary factor is the decrease in blood volume that occurs during hemodialysis. This decrease results from fluid withdrawal of the vascular compartment during ultrafiltration and insufficient refilling of fluid from the interstitial compartment to the vascular compartment. Other factors include impaired peripheral vasoconstriction, autonomic dysfunction, arteriosclerosis, cardiovascular pathologies, hydration, and medication [3]. The occurrence of IDH not only leads to higher costs and increased need for medical service, but, more seriously, to increased mortality [4,5]. Therefore, it is desirable to determine, at an early stage of each treatment, whether a patient is prone or resistant to IDH.

Spectral analysis of heart rate variability (HRV) is a well-known technique for assessing information on the autonomic nervous system (ANS). The following two frequency bands are commonly studied [6]: high frequency (HF: 0.15 to 0.4 Hz) and low frequency (LF: 0.04 to 0.15 Hz). The HF power component mostly reflects parasympathetic activity, being influenced by respiration. The LF power component largely reflects sympathetic modulation when normalized with respect to LF and HF bands [6]. The ratio between the power of the LF and HF components is considered to be an index of sympathovagal balance [6]. Several studies have already investigated HRV information in hemodialysis patients, mainly the LF/HF ratio [4,7,8]. For example, it has been observed that the LF component tends to dominate during sessions without IDH in the sympathovagal balance when measuring the LF/HF ratio [9], and the power of this ratio drops markedly at the time of crisis in sessions with hypotension [10].

In terms of normal cardiovascular control, changes in the regulation of the heart rate produced by the ANS can be expected to affect blood pressure regulation as assessed by blood pressure variability (BPV). With respiration, arterial blood pressure typically falls on inspiration and rises on expiration, thus affecting the HF component of BPV. The LF component is related to variations in the sympathetic nervous system mediated through vasoconstriction, as well as to the interaction between vasoactive agents and hormones and the autoregulatory processes [11]. Usually, HRV and BPV exhibit high coherence so that baroreflex sensitivity (BRS) can be computed.

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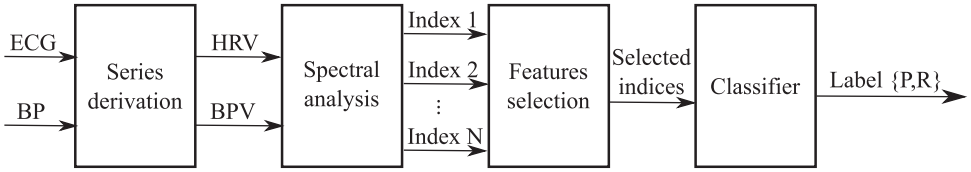

Fig. 1. Framework.

BRS indices characterize RR interval changes induced by changes in arterial pressure, and reflect impaired autonomic regulation [12]. BRS indices have been studied before in hemodialysis patients, the results suggesting that such indices cannot discriminate between IDH prone and resistant patients [13].

The hypothesis of this study is that IDH is related to impaired autonomic regulation of the cardiovascular system. A novelty is that information from both the electrocardiogram (ECG) and the blood pressure (BP) signal is combined to assess ANS activity. As another novelty, only the first 30 min of the treatment are analyzed, when hypotensive events are unlikely to occur [14], for characterizing the ANS status in prone and resistant patients.

From the ECG and BP signals, HRV, BPV and BRS related indices are extracted and studied in terms of their power to discriminate between IDH prone and resistant patients, see Fig. 1. A multivariate classifier is designed which analyzes the signals at the beginning of the treatment, and which makes use of information on diabetes since ANS is usually impaired in diabetic patients. A simplified classifier is also studied which does not require information on blood pressure, as it is costly and cumbersome to record continuously.

2. Database

Two databases have been analyzed from patients with endstage renal failure on hemodialysis treatment thrice a week, each session lasting between 2 and 5 h. Both databases contain ECG and BP signals. The continuous arterial blood pressure signal was acquired with a Finapres (Finapres Medical Systems BV, Holland) and sampled at 200 Hz with a Biopac (BIOPAC Systems Inc., USA) data acquisition system. The ECG was recorded during dialysis using the standard 12-lead configuration, and sampled at a rate of 1000 Hz. Synchronization between the ECG and BP signals was performed manually, leading to a misalignment on the order of magnitude of a few ms, which has negligible significance in the present application.

The first database consists of 28 sessions from 15 patients (the number of sessions for each patient varies from 1 to 4, see Table 1) treated at Park Dialys, Lund, Sweden, and Helsingborg Hospital, Helsingborg, Sweden [7]. Each patient was classified by a nephrologist as either resistant (R) or prone (P) to IDH based on the clinical history, e.g., the number of hypotensive events per month. The second database consists of 29 sessions from 11 patients. These patients underwent hemodialysis treatment in Copenhagen, Denmark. Due to poor quality of the BP signal, 5 sessions had to be excluded so that only 24 sessions from 9 patients were used for BPV and BRS analysis. Based on clinical history, all patients in the second database were classified as prone to IDH. The databases were merged and a total of 52 sessions from 24 patients were analyzed of which 21 sessions belonged to 10 patients with diabetes, see Table 1.

Table 1
Study population characteristics.

Characteristic	Resistant	Prone
# Patients/# Sessions	7/11	17/41
# Ses. each patient	2,1,1,2,1,2,2	2,1,2,1,4,4,3,2,2,3,4,2,2,1,2,3,3
# Diabetic patients/# Ses.	3/4	7/17
Male/Female	6/1	9/8
Age (years)	59 ± 14	65 ± 11
Weight (kg)	87 ± 20	77 ± 20

3. Methods

3.1. Heart rate variability

The beat occurrence times t_k are obtained from the ECG using a multi-lead wavelet-based detector [15]. The heart rate signal is derived from t_k using a method based on the integral pulse frequency modulation model. This method assumes that ANS activity can be modeled as a modulating signal $m(t)$ which, together with a DC level, is integrated until it reaches a threshold T, when a beat occurs and the process is reset [16]. The threshold T represents the mean interval length between successive beats in the analyzed interval. From t_k, the instantaneous heart rate is obtained as [17]:

$$d_{\mathrm{HR}}(t) = \frac{1 + m(t)}{T} \tag{1}$$

where $1/T$ represents the mean heart rate and $m(t)/T$ represents the heart rate variability. The signal $d_{\mathrm{HR}}(t)$ is sampled with a rate of $F_s = 4$ Hz to produce the discrete signal $d_{\mathrm{HR}}(n) = d_{\mathrm{HR}}(t)|_{t=n\frac{1}{F_s}}$.

3.2. Blood pressure variability

The blood pressure signal is low-pass filtered with a cut-off frequency of 40 Hz (forward/backward filtering) to remove noise. The peaks of the low-pass filtered signal, $s(n_k)$ (discrete-time), are found by locating the zero crossings of the differentiated signal, implemented by the first order difference: $s'(n) = s(n) - s(n-1)$, where $s(n)$ is the low-pass filtered blood pressure signal. A protective rule is applied to the detected peaks, imposing a refractory period to make sure that a certain distance elapses between successive beat detections. The distance is set to 0.5 s.

Signal segments lost due to calibration of the blood pressure device need to be detected and removed from further analysis. An amplitude threshold is used in successive 5-min segments, where a "gap" is found if there is more than 5 s without any valid peak above the threshold. The pairs $(n_k, s(n_k))$ are interpolated using cubic splines to generate the systolic blood pressure signal $d_{\mathrm{BP}}(n)$ sampled at a rate of 4 Hz. If the segment contains a gap, $d_{\mathrm{BP}}(n)$ is obtained using a shorter segment which does not contain that gap, as long as it exceeds 3 and a half minute. If shorter, the segment is removed for further analysis.

3.3. Spectral indices

Classification of resistant and prone patients is based on a set of spectral parameters determined during the first 30 min of the treatment session. The minimum variance distortionless response (MVDR) method [18,19] is applied for estimation of power spectral densities since, in general, it offers higher spectral resolution than does the classical periodogram. The respective spectra of $d_{\mathrm{HR}}(n)$ and $d_{\mathrm{BP}}(n)$ are computed in successive 5-min segments, using a resolution

of 2048 frequency bins and a window length of 300 samples, and followed by computation of the powers of the LF and HF bands [20]. Also, the median of the power estimates from the first six 5-min segments is computed for each band and signal type to produce robust estimates of spectral indices in the presence of outliers. The median absolute deviation (MAD) is computed as a measure of dispersion.

The following spectral indices of HRV and BPV are considered: P_{HR}^{LF}, P_{HR}^{HF}, P_{BP}^{LF} and P_{BP}^{HF}, which are the spectral band power in LF and HF bands. Also for HRV, the spectral ratio

$$R_{HR} = \frac{P_{HR}^{LF}}{P_{HR}^{HF}} \tag{2}$$

and the normalized spectral ratio

$$R_{HR}^{n} = \frac{P_{HR}^{LF}}{P_{HR}^{LF} + P_{HR}^{HF}} \tag{3}$$

are obtained.

The BRS indices are defined from the spectral power in the LF and HF bands:

$$\alpha^{LF} = \sqrt{\frac{P_{HR}^{LF}}{P_{BP}^{LF}}}, \quad \alpha^{HF} = \sqrt{\frac{P_{HR}^{HF}}{P_{BP}^{HF}}} \tag{4}$$

The MVDR method is also employed for computing the magnitude squared coherence function. The indices α^{LF} and α^{HF} are computed only when $d_{HR}(n)$ and $d_{BP}(n)$ are linearly related within the corresponding frequency bands. We assume that $d_{HR}(n)$ and $d_{BP}(n)$ are linearly related at a given frequency when the value of spectral coherence between $d_{HR}(n)$ and $d_{BP}(n)$ exceeds a threshold ρ, determined as follows: the spectral coherence between two segments of white noise, assumed to be uncorrelated, is first computed and then, after 1000 repetitions, the maximum coherence in each repetition is obtained and sorted [21]. The 99th percentile is taken as the threshold value ($\rho = 0.7$).

3.4. Statistical analysis

Statistical analysis is performed to determine whether the indices differ between prone and resistant patients. The Mann–Whitney analysis is used to test equality of population medians among groups. Two groups are considered to be significantly different when $p < 0.05$.

3.5. Classifier design and evaluation

The sequential floating forward selection (SFFS) method is considered for selecting the most discriminative features for use in a linear discriminant classifier [22]. This method combines forward and backward feature selection by removing less informative features and reevaluating features previously removed. The method performs a forward step followed by several conditional backward steps as long as the accuracy of the classification decreases. For the selected features, the linear classifier providing the best separation between the classes was determined.

A rule of thumb for determining the number of features K in the classifier is to use no more than $\sqrt{n_f}$ features, where n_f denotes the number of observations which belong to the smallest group [23]. As mentioned in Section 2, the database consists of 17 prone patients, and 7 resistant patients. Hence, since the resistant group is the smaller one, the number of features should be $K = 2$.

Leave-one-out method was applied to feature selection: it was performed for all sessions of all patients except for one patient whose sessions were left out. This process was then repeated for all patients, which lead to 24 different sets of features. The 2 most repeated features were selected. For classifier training, the leave-one–out method uses all patients to train the classifier but one, which is used for evaluation, and process is repeated such that each patient in the database is used once as the validation data.

The performance of the classifier is measured in terms of sensitivity (*Se*), specificity (*Sp*) and accuracy (*Acc*), defined as:

$$Se = \frac{N_{TP}}{N_{TP} + N_{FN}},$$

$$Sp = \frac{N_{TN}}{N_{TN} + N_{FP}},$$

$$Acc = \frac{N_{TP} + N_{TN}}{N_{TP} + N_{TN} + N_{FP} + N_{FN}}$$

where N_{TP}, N_{TN}, N_{FP} and N_{FN} denote the number of true positives, true negatives, false positives and false negatives, respectively. Prone patients are classified as positive, while resistant patients are classified as negative.

When taking information on diabetes into account, feature selection and classifier training are not done on the whole database, but on the diabetic and nondiabetic subgroups. In each subgroup, feature selection is first performed and then the classifiers are trained and evaluated. Although two different classifiers are designed, they can be viewed as a decision tree where information on diabetes decides which branch to activate. Hence, the two classifiers can be treated as one classifier with a global *Se*, *Sp* and *Acc*.

Table 2
Median ± MAD of HRV (s^{-2}), BPV ($mmHg^2$) and BRS (s^{-1}/mmHg) indices for prone and resistant patients. The symbols {∗, †, ‡} represent *p*-values less than {0.05, 0.01, 0.001}, respectively.

Variable	Prone	Resistant
P_{HR}^{LF}	0.0028 ± 0.008	0.0034 ± 0.005
P_{HR}^{HF}	0.0012 ± 0.002	0.0021 ± 0.004
R_{HR}^{n}	0.46 ± 0.23 ‡	0.76 ± 0.17 ‡
R_{HR}	1.39 ± 1.44‡	6.12 ± 5.05 ‡
P_{BP}^{LF}	0.0012 ± 0.002	0.0009 ± 0.002
P_{BP}^{HF}	0.0008 ± 0.001 †	0.0006 ± 0.001 †
α^{LF}	1.05 ± 1.63 ∗	1.84 ± 2.32 ∗
α^{HF}	0.85 ± 1.07	2.08 ± 3.91

4. Results

4.1. Statistical analysis

Table 2 shows that the indices R_{HR}^{n} and R_{HR} are the ones which exhibit the most significant differences between prone and resistant patients. For the BPV indices, P_{BP}^{HF} is the one that exhibits differences in both groups. For BRS indices, α^{LF} exhibits a *p*-value below 0.05.

4.2. Classification of prone and resistant patients

When classification is performed without any account for diabetes information, R_{HR}^{n} and R_{HR} are the best to differentiate prone and resistant patients, see Table 3. While the accuracy is 88.2%, the specificity is very low, see Table 4.

When diabetes information is taken into account, the database is split into 2 subgroups, i.e., 10 diabetic patients (of which 7 are prone) and 14 non-diabetic patients (of which 10 are prone), and a subgroup-specific classifier is determined.

Table 3 also shows the features selected for diabetic and non-diabetic patients. For the diabetic group, the selected features are P_{HR}^{LF} and R_{HR}^{n}, while for the non-diabetic group the features are R_{HR}^{n} and α^{LF}. The global performance is shown in Table 4, with an accuracy

Table 3
Selected features using either all indices or only the HRV indices.

	Features selected	
	All indices	HRV indices
All patients	R^{n}_{HR}, R_{HR}	R^{n}_{HR}, R_{HR}
Diabetic	R^{n}_{HR}, P^{LF}_{HR}	R^{n}_{HR}, P^{LF}_{HR}
Non–diabetic	R^{n}_{HR}, α^{LF}	R^{n}_{HR}, R_{HR}

Table 4
Classifier perfomance using all indices and HRV indices only.

	All indices			HRV indices		
	Se	Sp	Acc	Se	Sp	Acc
All patients	97.5	54.5	88.2	97.5	54.5	88.2
Using diabetes information	97.5	72.7	92.1	95	72.7	90.2

of 92.1%. Both sensitivity and specificity improve considerably when information on diabetes is included.

Although the BPV indices exhibit differences between prone and resistant patients, cf. Table 2, none of them were selected.

4.3. Classification based on HRV indices only

The results in the previous subsection shows that HRV indices carry most of the information for discriminating IDH prone and resistant patients, and therefore we constrain the analysis to only HRV indices, with diabetes information included. In this scenario, we also included the 2 patients (both diabetic and prone) which were removed due to poor quality in the blood pressure signal (see Section 2), since blood pressure information is not used in this case, increasing the study population size. The selected features are shown in Table 3, being P^{LF}_{HR} and R^{n}_{HR} for diabetic patients, and R^{n}_{HR} and R_{HR} for non-diabetic patients. These results are very similar to the ones involving all types of indices where three out of four selected features were HRV-related. The performance of the HRV-based classifier is shown in Table 4: a slight decrease in accuracy (Acc = 90.2%) is observed.

5. Discussion

Hypotensive events represent a major complication during hemodialysis treatment. Since such events are associated with autonomic dysfunction, several ANS-related indices have been studied with respect to their ability to determine whether a patient is prone to IDH. In this work, information based on HRV and BPV was extracted from ECG and blood pressure signals from the initial 30 min of the session to allow for early prediction of hypotensive events.

The HRV indices have been thoroughly studied in the past, especially the ratio R_{HR} since it assesses cardiovascular autonomic regulation and reflects the activity of the sympathetic versus the parasympathetic branch [8]. It has been shown that patients prone to IDH exhibit a much lower ratio than do resistant patients [24]. Similar information is conveyed by R^{n}_{HR}, since it represents the normalized value of the power in the LF band relative to the sum of the LF and HF bands. Since this index also conveys information about the balance between the two ANS branches, it is expected to exhibit significant differences between the two patient groups.

Regarding BRS, α^{LF} is significantly different between the two groups, implying impaired regulation of the heart rate in prone patients when a sudden drop in blood pressure occurs, i.e., at IDH. However, other studies have obtained conflicting results, claiming that the baroreflex mechanism is preserved and adequately activated during intradialytic hypotension [25]. An hypothesis is that even though the vessels have reduced parasympathetic innervation, potentially not affecting BPV, it still can exist a secondary modulation given by the HRV that implies variability in the blood volume at the ventricles leading to variability in the BP. Precisely on one BP parameter used in BRS, P^{HF}_{BP}, there are significant differences between prone and resistant patients (Table 2), reflecting that the blood pressure in prone patients is more unstable.

Robust assessment of BRS indices requires that a linear relationship between HRV and BPV exists. Two signals are assumed to be linearly related at a given frequency when the value of spectral coherence at that frequency exceeds a certain threshold, which commonly is set to 0.5. However, the estimated spectral coherence of two realizations of white noise differs from zero and depends on the estimator used to compute auto- and cross-spectra, and may exhibit values above 0.5 [26]. In this work, a statistical analysis of our spectral coherence estimates has been conducted to determine the threshold above which two signals can be considered linearly related with an error of 1%.

The preferred classification framework is to have two disjunct groups: one for selecting the features and training the classifier, and another for evaluating the classifier. However, when only sparse data is available, feature selection and classifier training can be overfitted to the training data. This may not be representative enough, and thus the classifier would not work properly for the evaluation data. Using all data for training and evaluation leads to optimistically biased results, and thus we decided to use the k-fold crossvalidation method [27]. A value of $k = 1$ patient leave-one-out crossvalidation was adopted for both feature selection and classifier training.

It should be noted that the standard leave-one-out method is not appropriate to use on the present database. This method involves "observations" which in this study translates to "patients". A patient can have 1, 2, 3 or even 4 different sessions, corresponding to different days. Different sessions from the same patient should not be treated as independent measurements. Due to this, the leave-one-out method analyzes patients instead of sessions in the present study.

Regarding classifier performance, the obtained specificity is lower than the sensitivity, influenced by the unequal numbers of prone and resistant patients. When taking information on diabetes into account, the specificity increases, and the overall accuracy improves. This result agrees with the hypothesis that the ANS of diabetic patients is dysfunctional. Furthermore, this result means that information on diabetes should be treated as another feature when training the classifier.

Since almost all of the selected indices are HRV related, it was natural to investigate classification performance solely based on HRV indices. Such a restriction is of interest since it has been shown that HRV can be estimated using finger photoplethysmography [28], a technology which is easier to use than the ECG. The present results show that just a minor drop in accuracy is observed for an HRV-based classifier, i.e., from 92.1% to 90.2% (Table 4).

An important limitation of the present study is that the dataset is rather small, and that the prone and resistant group are highly imbalanced. In order to reduce the effect of the P group being much larger than the R group, a simple replication technique has been employed [29], with which each R session is used twice. The new database consists of 41 P records and 33 R records. In this way, the classification is repeated using only HRV parameters and taking the diabetes information into account. Using the replication technique, an increase in specificity is observed (72.7 to 83.4) at the expense of a decrease in sensitivity (95 to 87.8); the accuracy increases from 90.2 to 93.2.

Another limitation of the database is that the number of sessions varies from patient to patient. By discarding sessions so that all patients had two sessions, the results were recomputed for the classifier based on HRV indices only (the discarded sessions were chosen randomly). The sensitivity was found to decrease from 95% to 94.3% and the accuracy from 90.2% to 88.7%. Since the removed sessions

are considered to be dependent measurements, the performance is not expected to be very different. Ultimately, the classifiers need to be tested on a much larger database, which includes information on age.

HRV indices can be divided into linear (temporal and spectral, the latter used in this work) and non-linear indices. Temporal HRV indices were first also included in the analysis, but they showed a lower discriminative power between P and R patients, and they were removed from the study. Non-linear indices have previously shown good capability to predict arrhythmic risk [30], but their physiological interpretation is less clear than the one related to spectral indices. Although non-linear indices are related to certain methodological concerns, e.g, data length, such indices provide complementary information which may improve the classification of P and R patients, and therefore should be part of a future study.

Other information could also be used to improve classifier performance. Some authors claim that prone patients suffer from a decrease in peripheral vascular resistance, suggesting a possible cardiac underfilling [31]. It has also been reported that every patient has a relative blood volume which for prone patients is stable with low variability [32]. Other studies suggest that the count of ventricular premature beats and heart rate turbulence are related to IDH [8]. In addition to that, it is important to note that these results are obtained from a database composed of elderly renal failure patients, whose age, pathology and medication also affect ANS regulation over the heart.

6. Conclusions

This study presents a multivariate classifier to discriminate IDH prone and resistant patients. The first 30 min of treatment, when IDH is unlikely to occur, are used to extract ANS related parameters. Heart rate variability (HRV), blood pressure variability and baroreflex sensitivity are analyzed, with the normalized power in the HRV low frequency band as the most discriminative index. Information on diabetes is also included, since diabetic patients are known to have ANS dysfunction. Using only HRV indices, a patient can be classified as IDH prone or resistant with an accuracy of 90.2%.

Conflicts of interest

None declared.

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Ethical approval

The databases have already been published in other contexts, and that they were both ethically approved. Both data collections were approved by the local ethics committee and written informed consent was obtained from each subject before enrollment into the study.

The Park Dialys database was used in: K. Solem, A. Nilsson, L. Sörnmo, “An ECG-based method for early detection of abrupt changes in blood pressure during hemodialysis”, *Journal of American Society for Artificial Internal Organs (ASAIO)*, Vol. 52, pp. 282-290, 2006.

The Copenhagen database was partly used in: F. Sandberg, R. Bailón, D. Hernando, P. Laguna, J.P. Martinez, K. Solem, L. Sörnmo, “Prediction of hypotension in hemodialysis patients”, *Physiological Measurement*, Vol. 35, pp. 1885-898, 2014.

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