# Heart Rate Variability during Hemodialysis and Its Relation to Hypotension

D Hernando[1,2], R Bailón[1,2], P Laguna[1,2], L Sörnmo[3]

[1]Communications Technology Group (GTC), Aragon Institute for Engineering Research (I3A), IIS Aragon, University of Zaragoza, Zaragoza, Spain
[2]CIBER BBN of Bioengineering, Biomaterials and Nanomedicine, Spain
[3]Signal Processing Group, Department of Electrical and Information Technology, Lund University, Lund, Sweden

## Abstract

*Acute hypotensive episodes are common during dialysis sessions, and represent a serious problem. Spectral analysis of heart rate variability (HRV) and barorrefle x sensitivity (BRS) is performed to study the behaviour of the autonomic nervous system (ANS) during the hemodialysis. The ratio between the low frequency (LF) and high frequency (HF) power of HRV, as well as BRS in the HF band, are significantly different in patients being prone and resistant to hypotension (p<0.001 and p<0.05, respectively).*

*Moreover, a very low frequency (VLF) modulation visible in HRV, blood pressure and the series of rotation angles of the heart's electrical axis have been studied. It turns out that the VLF component is more pronounced and with higher coherence in prone patients (p<0.05), suggesting a possible relation with altered or imbalanced ANS regulation.*

## 1. Introduction

Dialysis-induced hypotension is an important problem in hemodialysis treatment and approximately 30% of all sessions are complicated by cardiocirculatory collapse, leading to premature termination. The origin is still not completely known, but it is clearly multifactorial, and may depend on factors like diabetes and overweight. Hypotension not only causes termination of the session, but may also increase mortality in these patients [1, 2]. This type of event leads to higher costs and an increased need for medical service, extra time and the prolongation of patient rehabilitation. In spite of the improvement of technology and research in this field, hypotension is still one of the most common complication, and it is highly desirable to develop methods to prevent these events.

Spectral analysis of heart rate variability (HRV) is a non-invasive tool which assesses changes of the autonomic nervous system (ANS). Three bands are established in the power spectrum of HRV [3]: very low frequency (VLF: $< 0.04$ Hz), low frequency (LF: 0.04 to 0.15 Hz) and high frequency (HF: 0.15 to 0.4 Hz). The HF component is considered to be a marker of the parasympathetic activity, being sensitive to the respiratory frequency. The LF component is a marker of the sympathetic modulation, at least when measured in normalized units. Lastly, the VLF component has been linked with humoral and temperature regulation and with slow vasomotor activity. The ratio between the power of LF and HF components is considered to provide an index of sympatho-vagal balance.

Baroreflex sensitivity (BRS) measures reflex changes in interbeat interval induced by changes in arterial pressure, and may reflect impaired ANS regulation [4].

The hypothesis of this study is that hypotension may be related to impairment in autonomic regulation of the cardiovascular system. We studied HRV and BRS in a database of patients undergoing hemodialysis to determine whether hypotensions and/or patients prone to suffer hypotension can be predicted from HRV and BRS measurements. The following parameters have been studied: HRV through the normalized power in the LF and HF bands and the LF/HF ratio, BRS through spectral coherence between HRV and blood pressure variability (BPV) (only computed when a statistically determined threshold is exceeded), and VLF modulation in HRV, BPV and rotation angles of the hearts electrical axis through spectral coherence.

## 2. Methods and materials

### 2.1. Study population

The population consists of 16 patients with end-stage renal failure who underwent regular hemodialysis three times a week, and a total of 30 sessions were acquired during the entire clinical treatment at Park Dialys, Lund,

| Characteristic | R | P |
|---|---|---|
| # Patients | 7 | 9 |
| # Measurements | 11 | 19 |
| Male/Female | 6/1 | 6/3 |
| D / ND | 3/4 | 5/4 |
| Age (year) | 58.6 $\pm$ 13.5 | 65.6 $\pm$ 10.6 |
| Weight (kg) | 86.9 $\pm$ 19.5 | 83.1 $\pm$ 19.9 |

Table 1. Study population characteristics

Sweden, and Helsingborg Hospital, Helsingborg, Sweden, lasting from 3 to 5 hours, in order to obtain the electrocardiogram signal (ECG) and the blood pressure (BP) signal. Each patient has been classified as being hypotension-resistant (R) or hypotension-prone (P) based on their previous clinical history. Besides, they have also been classified as being diabetic (D) or non-diabetic patients (ND), making four groups: RD, RND, PD and PND. See Table 1 for study population characteristics.

Symptomatic hypotension occurred in 5 of the 30 sessions (one in the resistant group and the others in the prone group), of which 2 were acute (systolic blood pressure fall larger than 30 mmHg per 10 minutes prior to hypotension).

The ECG signal was recorded using a standard 12-lead configuration, and digitalized at a sampling rate of 1000 Hz and amplitude resolution of 0.06 $\mu$V (Siemens-Elema AB, Sweden); the blood pressure signal was measured in the finger using a Finapres (Ohmeda, Netherlands) and sampled at a rate of 200 Hz with a MP100 data acquisition system (Biopac, USA).

The subsequent analysis was performed in 5-minute segments where stationarity of the cardiovascular signals was assumed.

## 2.2. Heart rate variability

First, QRS detection marks are obtained from the ECG signal by ARISTOTLE [5], using a rule based on the QRS complex center of gravity. The heart rate (HR) signal is derived from the QRS detection marks, following a method based on the integral pulse frequency modulation (IPFM) model, which also accounts for the presence of ectopic beats [6], and sampled at 4 Hz obtaining $d_{\text{HR}}(n)$. The VLF component is obtained by low-pass filtering $d_{\text{HR}}(n)$ using a cut-off frequency of 0.03 Hz and denoted $d_{\text{HRM}}(n)$. Finally, the HRV signal is obtained as $d_{\text{HRV}}(n) = d_{\text{HR}}(n) - d_{\text{HRM}}(n)$.

For each 5-min segment the power spectrum of $d_{\text{HRV}}(n)$ is computed using the Welch periodogram with a rectangular window of 360 s overlapped 120 s. The power in the LF and HF bands is computed integrating the power spectrum in the corresponding bands, and denoted $P_{\text{LF}}^{\text{HR}}$ and $P_{\text{HF}}^{\text{HR}}$, respectively. Then, the following parameters are computed $P_{\text{LFn}}^{\text{HR}} = \frac{P_{\text{LF}}^{\text{HR}}}{P_{\text{LF}}^{\text{HR}}+P_{\text{HF}}^{\text{HR}}}$ and $R_{\text{LF/HF}} = \frac{P_{\text{LF}}^{\text{HR}}}{P_{\text{HF}}^{\text{HR}}}$.

During hemodialysis, some patients present a large amount of ectopic beats. Ectopic beats, false detections and misdetections, hereinafter called incidences, were detected and corrected prior to the estimation of $d_{\text{HR}}(n)$ based on [6]. The number of incidences, $I$, in each segment was also computed and analyzed in relation to hypotension and as a measure of the reliability of HRV-derived parameters.

## 2.3. Baroreflex sensitivity

Systolic blood pressure measures are obtained detecting the maximum value of each pulse wave, using a method based on the derivative of the BP signal and a time-varying threshold. From the value and location of each maximum the systolic blood pressure signal, $d_{\text{BP}}(n)$, is computed using spline interpolation at 4 Hz. Using the same procedure as in the previous section, the following signals and parameters are computed: $d_{\text{BPM}}(n)$, $d_{\text{BPV}}(n)$, $P_{\text{LF}}^{\text{BP}}$ and $P_{\text{HF}}^{\text{BP}}$.

Then, BRS parameters are computed in the LF and HF bands as [7]: $\alpha_{\text{LF}}^2 = \frac{P_{\text{LF}}^{\text{HR}}}{P_{\text{LF}}^{\text{BP}}}$ and $\alpha_{\text{HF}}^2 = \frac{P_{\text{HF}}^{\text{HR}}}{P_{\text{HF}}^{\text{BP}}}$, respectively.

BRS parameters are considered only if the spectral coherence between $d_{\text{HRV}}(n)$ and $d_{\text{BPV}}(n)$ is above a statistically determined threshold of 0.7. The threshold is determined as the $97^{th}$ percentile of the statistical distribution of the maximum value of the spectral coherence between two white noises. Spectral coherence is estimated using the minimum variance distorsionless response (MVDR) method [8], which presents higher spectral resolution than Welch periodogram, which is needed especially in the study of VLF modulation (see Section 2.5).

## 2.4. Series of rotation angles

The series of rotation angles of the heart's electrical axis are estimated from the ECG using a least squares minimization of the normalized distance between a reference QRS-vectorcardiographic loop and each observed loop subjected to rotation, amplitude scaling and time synchronization [9]. The envelope of each of the three rotation angles is low-pass filtered using a cut-off frequency of 0.03 Hz, and denoted $\varphi_{\text{XM}}(n)$, $\varphi_{\text{YM}}(n)$ and $\varphi_{\text{ZM}}(n)$.

## 2.5. VLF modulation

The MVDR method is used to estimate the spectral coherence between $d_{\text{HRM}}(n)$, $d_{\text{BPM}}(n)$ and the envelopes of the rotation angle series for each 5-min segment. For segments with a maximum coherence value exceeding the threshold (0.7), the value and the location of the maximum are calculated and denoted $\Gamma_{\text{VLF}}^{\text{X}_1\text{X}_2}$ and $f_{\text{VLF}}^{\text{X}_1\text{X}_2}$, respectively, where $\text{X}_1$ and $\text{X}_2$ represent $d_{\text{HRM}}(n)$, $d_{\text{BPM}}(n)$, or $\varphi_{\text{M}}(n)$, $\varphi_{\text{M}}(n)$ being the envelope showing the highest coherence among $\varphi_{\text{XM}}(n)$, $\varphi_{\text{YM}}(n)$ and $\varphi_{\text{ZM}}(n)$.

| Parameter | P | R | $p$-value |
|---|---|---|---|
| $P^{\text{HR}}_{\text{LFn}}$ | 0.43 $\pm$ 0.03 | 0.79 $\pm$ 0.01 | <0.0005 |
| $R_{\text{LF/HF}}$ | 0.77 $\pm$ 0.05 | 3.99 $\pm$ 0.71 | <0.0005 |
| $I$ | 2 $\pm$ 1 | 5.5 $\pm$ 3 | NS |
| $\alpha^2_{\text{LF}}$ | 0.26 $\pm$ 1.0e-04 | 1.83 $\pm$ 1.8e-04 | NS |
| $\alpha^2_{\text{HF}}$ | 0.24 $\pm$ 1.2e-05 | 4.64 $\pm$ 9.2e-05 | <0.05 |

Table 2. Median$\pm$MAD of HRV and BRS parameters in prone (P) and resistant (R) groups. NS: non-significant, $p > 0.05$.

## 2.6. Statistical analysis

Each subject is characterized by the median value of parameters $P^{\text{HR}}_{\text{LFn}}$, $R_{\text{LF/HF}}$, $I$, $\alpha^2_{\text{LF}}$, $\alpha^2_{\text{HF}}$, $\Gamma^{\text{x}_1\text{x}_2}_{\text{VLF}}$ and $f^{\text{x}_1\text{x}_2}_{\text{VLF}}$. The percentage of the segments where the maximum coherence is above the threshold is also computed and denoted $T^{\text{x}_1\text{x}_2}_{\text{VLF}}$.

A Kolmogorov-Smirnov test is applied to the data to find out whether the data follows a normal distribution or not. The result of this test is negative, so the Kruskal–Wallis analysis is used to test equality of population medians among groups. Whenever the $p$-value is below 0.05, the two groups are considered significantly distinct.

## 3. Results

The median and median absolute deviation (MAD) of HRV and BRS parameters is computed among all subjects in the prone and resistant groups, and displayed in Table 2 with the associated $p$-value.

Prone and resistant patients present major differences both in $P^{\text{HR}}_{\text{LFn}}$ and $R_{\text{LF/HF}}$. The temporal evolution of $R_{\text{LF/HF}}$ can be seen in Fig. 1, where the median of $R_{\text{LF/HF}}$ among subjects is displayed for each 5-min segment in P and R groups. Only BRS in the HF band is significantly different in the P and R groups.

In order to study the parameters of prone and resistant subjects independently from diabetes, which is known to alter ANS regulation, new groups are suggested to study: prone-diabetic (PD) vs. resistant-diabetic (RD), and prone-non diabetic (PND) vs. resistant-non diabetic (RND). Tables 3 and 4 show the results. Despite the small number of subjects in each group, it can be observed that $P^{\text{HR}}_{\text{LFn}}$ and $R_{\text{LF/HF}}$ are significantly different in prone and resistant both in diabetic and non-diabetic subgroups, while $\alpha_{\text{HF}}$ is only different in the diabetic subgroup.

Figure 2 displays a segment of $d_{\text{HRM}}(n)$, $d_{\text{BPM}}(n)$ and

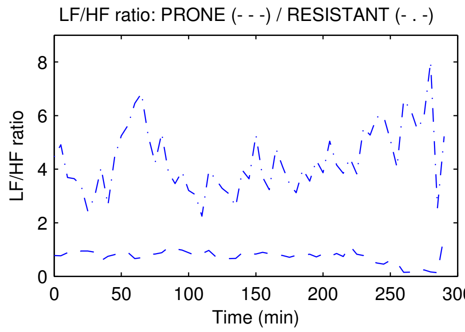


Figure 1. Evolution of the median value of $R_{\text{LF/HF}}$ during the dialytic session for P and R groups.

| Parameter | PD | RD | $p$-value |
|---|---|---|---|
| $P^{\text{HR}}_{\text{LFn}}$ | 0.28 $\pm$ 0.02 | 0.60 $\pm$ 0.01 | <0.05 |
| $R_{\text{LF/HF}}$ | 0.38 $\pm$ 0.06 | 1.53 $\pm$ 0.12 | <0.05 |
| $\alpha^2_{\text{HF}}$ | 0.23 $\pm$ 1.2e-05 | 30.69 $\pm$ 9.2e-05 | <0.05 |

Table 3. Median$\pm$MAD of HRV and BRS parameters PD and RD groups. NS: non-significant, $p > 0.05$.

$\varphi_{\text{XM}}(n)$, where the VLF modulation is visible. Table 5 shows the $p$-value corresponding to the parameters which characterize VLF modulation in P and R groups, as well as in D and ND groups. While there are not significant differences in VLF parameters in D and ND groups, P and R groups show significantly different maximum coherence values and different periods of time where the coherence is above the threshold.

## 4. Discussion and conclusion

Despite the fact that different approaches to reducing the incidence of intradialytic hypotension have been proposed and extensively evaluated in recent years, the problem has not yet found a satisfactory solution. Many patients suffer from a large number of ectopic beats, sometimes implying

| Parameter | PND | RND | $p$-value |
|---|---|---|---|
| $P^{\text{HR}}_{\text{LFn}}$ | 0.49 $\pm$ 3.1e-03 | 0.86 $\pm$ 0.01 | <0.005 |
| $R_{\text{LF/HF}}$ | 0.97 $\pm$ 0.02 | 6.35 $\pm$ 0.96 | <0.005 |
| $\alpha^2_{\text{HF}}$ | 11.33 $\pm$ 1.2e-05 | 4.64 $\pm$ 9.2e-05 | NS |

Table 4. Median$\pm$MAD of HRV and BRS parameters PND and RND groups. NS: non-significant, $p > 0.05$.

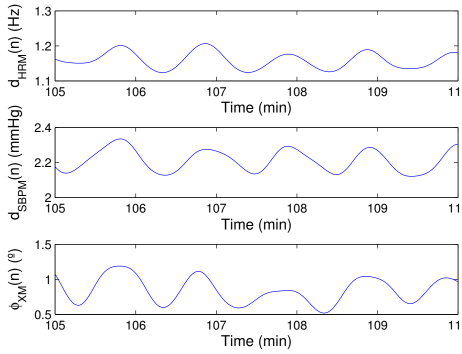


Figure 2. VLF modulation in $d_{\text{HRM}}(n)$, $d_{\text{BPM}}(n)$ and $\varphi_{\text{XM}}(n)$ signals.

| $d_{\text{HRM}}(n)$-$\varphi_{\text{M}}(n)$ | $f_{\text{VLF}}^{\text{X}_1\text{X}_2}$ | $\Gamma_{\text{VLF}}^{\text{X}_1\text{X}_2}$ | $T_{\text{VLF}}^{\text{X}_1\text{X}_2}$ |
|---|---|---|---|
| P/R | NS | 0.01 | 0.0001 |
| D/ND | 0.01 | NS | NS |
| $d_{\text{HRM}}(n)$-$d_{\text{BPM}}(n)$ | $f_{\text{VLF}}^{\text{X}_1\text{X}_2}$ | $\Gamma_{\text{VLF}}^{\text{X}_1\text{X}_2}$ | $T_{\%}$ |
| P/R | NS | NS | <0.05 |
| D/ND | NS | NS | NS |
| $d_{\text{BPM}}(n)$-$\varphi_{\text{M}}(n)$ | $f_{\text{VLF}}^{\text{X}_1\text{X}_2}$ | $\Gamma_{\text{VLF}}^{\text{X}_1\text{X}_2}$ | $T_{\%}$ |
| P/R | NS | 0.01 | NS |
| D/ND | NS | NS | NS |

Table 5. Statistical analysis for the VLF modulation

that the HRV analysis may not be reliable, so that alternate measurements of ANS activity can be helpful [10]. Still, knowledge on ANS by HRV analysis is desirable, and it has been shown that such analysis can be used to classify a patient into prone or resistant. The $R_{\text{LF/HF}}$ ratio was shown to be a good marker of the autonomic response to circulatory perturbations [11], which is in concordance with our results, since $R_{\text{LF/HF}}$, as well as $P_{\text{LFn}}^{\text{HR}}$, is able to distinguish prone and resistant subjects, regardless of their diabetic condition, which is known to affect ANS response.

The BRS parameter $\alpha_{\text{HF}}^2$ can discriminate between prone and resistant patients when considering either our whole database or the diabetic subgroup, but not in the non diabetic subgroup. In [12] BRS is stated to be unaltered in intradialytic hypotension.

The temporal evolution of the proposed parameters has been studied in relation to the occurrence of a hypotensive episode, but no significant differences were found prior to these events. However, the reduced number of acute hypotensive events in our database (2) is a limitation which should be overcome in a future study.

The VLF modulation visible in HRV, BPV and the series of rotation angles or the heart electrical axis has been characterized using spectral coherence and parameters extracted from it have been able to distinguish prone and resistant patients. However, these results are only based on the segments where the coherence was high enough, which is less than 15% of the time for the majority of the patients. The origin of this VLF modulation is still uncertain and it may be related to other fields, where it has also been observed [13, 14].

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