THE POWER SPECTRA RESPONSE OF STROKE VOLUME AND ARTERIAL BLOOD PRESSURE VARIABILITY SIGNALS TO AUTONOMIC NERVOUS SYSTEM MODULATION OF THE HEART

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Abstract: This study presents results that describe the short term oscillations in SBPV and SVV signals due to calcium channel blockers poisoning with verapamil treated with continuous infusion of levosimendan. In addition, we used average spectra of these oscillations to observe the activity and sympathovagal balance of the autonomic nervous system. Then, we compared the average spectra obtained from both signals. The frequency contents of the average spectra of SVV and SBPV signals to levosimendan treatment of verapamil-poisoned rats were analyzed and related to the activity of sympathetic and parasympathetic tones. In control group, average spectra of SVV and SBPV exhibited a low-frequency band (LF: $0.03-0.8$ Hz) peaked at ~ 0.4 Hz and a high-frequency (HF: $0.8-3.0$ Hz) peaked at ~ 1 Hz. LF peak was abolished after verapamil infusion. The LF component of both spectra was observed to recover after continuous infusion of levosimendan. Additionally, a new frequency component was observed at 1.5 Hz in the spectrum of SBPV. Significant correlations were found between bands of the average spectra in both signals in all groups of treatment studied in this paper. Our results revealed that, like SBPV, SVV can herald useful information regarding the sympathovagal balance and cardiac output improvements.

1 INTRODUCTION

Power spectra analyses of blood pressure and heart rate variability (HRV) signals have previously been used as a window to monitor the autonomic nervous activity in the cardiovascular system (see e.g. (Julien et al., 2003; Cerutti et al., 1994) and the references therein). Using power spectral techniques, systolic blood pressure variability (SBPV) can be deconstructed into variabilities at different frequencies. These variabilities can be divided into respiratory and vasomotor components in a similar way to that seen with HRV signals. Previously, it has been shown that vasomotor-related SBPV correlates well with vascular sympathetic function of α-adrenoceptors (Brown et al., 1994).

In rats, SBPV exhibits low-frequency (LF), known as Mayer waves (Julien et al., 2003; Brown et al., 1994), and high-frequency (HF) oscillations. The LF oscillations are related to the activity of sympathetic nervous system and the HF one is related to respiratory activity to be mediated by parasympathetic activity (Cerutti et al., 1994; Japundzic et al., 1990). Recently, seeking new methods to provide a clinically useful information about the autonomic nervous system, power spectrum of stroke volume variability (SVV) signal has been employed. Previous studies (Liu et al., 2004; Siebert et al., 2004) have compared the spectra responses of SVV and HRV in healthy subjects.

In the present study, we analyzed the spectral properties of the systolic blood pressure variability

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(SBPV) signal to assess the effects of levosimendan on the autonomic nervous activity in verapamil poisoning in a rodent model and then compare it with the results obtained from applying the same procedure to the estimated stroke volume variability signal. To our knowledge, there are no studies that have compared the spectra of SBPV and SVV estimated from continuous blood pressure recordings.

2 Materials and Methods

The methods used in surgery, instrumentation, treatment and data collection for this research has been described in detail elsewhere (Graudins et al., 2008).

To summarize, experiments were conducted on healthy, anaesthetized, intubated, and ventilated male Wistar rats weighing between 300 and 500 grams. Jugular, femoral venous and carotid catheters were inserted. Continuous recordings of ECG, arterial blood pressure was performed using a PowerLab data acquisition system and Chart Version 5.0 software (ADInstruments, Castle Hill, Australia). After an equilibration period, all rats were then administered verapamil hydrochloride (Abbott Australasia, Botany, Australia) $6\mu g/kg/h$ (Isoptin Injection) until systolic blood pressure (SBP) fell to 50% of baseline values. Then, animals were randomized to one of the following treatment groups:

Group 1. Control: rats received a loading dose of normal saline (1 mL) followed by a continuous infusion (1 mL/h). n = 7 rats.

Group 3. Levosimendan: levosimendan (donated by Abbott Australasia, Sydney, Australia) was administrated to rats by loading dose of $6\mu g/kg$, then levosimendan infusion at $0.4\mu g/kg/min$. n = 6 rats.

3 SIGNAL PROCESSING AND SPECTRUM ANALYSIS

The blood pressure signal was processed by an algorithm that extracts the cyclical features of the signal such as SBP (P_s), diastolic pressure (P_d), pulse pressure (P_p), integrated mean blood pressure (MAP), stroke volume (SV), cardiac output (CO), heart rate (HR), systolic time (T_s), and diastolic time (T_d). To summarize, ABP signal, sampled at 400 Hz, has to pass through four stages of processing which are: 1) low-pass filtering to remove the high frequency noise, 2) a windowed and weighted slope sum function to support and enhance the up slope of the arterial blood pressure signal and remove the remainder of the signal, 3) a logic circuit that detects the edges of the processed slope sum function, and 4) threshold and decision rule that is used to suppress the edges resulting from the dicrotic notch and noise. To obtain SBPV signal, SBP was detected from the continuous recording of ABP signal as follows: after low-pass filtering of ABP signal, the signal is processed using the slope sum function (Moody et al., 2003) defined as follows:

$$s_k = \sum_{j=k-w}^{k} \Delta y_j, \tag{1}$$

where

$$\Delta y_j = \begin{cases} \Delta x_j & \text{if} \quad \Delta x_j > 0, \\ 0 & \text{if} \quad \Delta x_j \leq 0. \end{cases} \tag{2}$$

Here w is the number of samples representing the analyzing window of the first derivative of the BP signal $\Delta x_j = x_j - x_{j-1}$, and x_j is the ABP signal. w is chosen to be 32 samples which is equal to the upslope of the ABP peaks. Pulse contour method (Kouchoukos et al., 1970) was used to estimate beat-by-beat values of SV.

The time series of $SBPV$ and SVV signals were extracted from the raw beat-by-beat ABP and divided into epochs after down and equidistant sampling were applied to the signals. For each block of discrete data, power spectral density was calculated directly from the signal itself using the FFT algorithm. Average spectral densities of $SBPV$ and SVV obtained from all rats within each group was then calculated and compared. For each data block, the spectral density estimates were smoothed. In this study, the spectral estimate was performed on 312 data blocks of 512 samples overlapping by a half to reduce the loss of stability.For each data set, the linear trends were removed to reduce their contributions to the LF component. Average spectra were evaluated approximately every 5 minutes for each block of data. Spectral estimates were found in each group before and after drugs infusion has started.

4 Results

The extracted physiological parameters observed from control group (baseline), after verapamil poisoning, and after continuous infusion of levosimendan are summarized in Table 1.

Figure 1 shows the average spectra of SBPV and SVV signals obtained from control group before administration of any of the study drugs. Spectra of SBPV and SVV exhibited LF band ($0.03 - 0.8$ Hz), which corresponds to the activity of the sympathetic

Table 1: Cardiovascular parameters extracted form continuous recording of ABP signals. Values included are the average values obtained within each group. ABP: arterial blood pressure.

Variable	Control	Verapamil	Levosimendan
$P_s(mmHg)$	124.138±8.218	56.149±4.086*	57.108±5.087†
$MAP\ (mmHg)$	92.731±7.258	63.709±12.537§	66.643±2.953†
$SV\ (\mu L/beat)$	271.178±5.43	141.773±2.583§	182.178±0.827§
$CO\ (mL/min)$	76.089±1.89	24.278±1.670§	56.598±6.975§
$HR\ (beats/min)$	328.393±6.12	262.503±4.366*	301.737±10.293*

Values shown as Mean±SD. Paired t-test § $p < 0.05$, * $p < 0.01$, and †: not significant.

part of the autonomic nervous system, and a HF one $(0.8-3)$ Hz. Two clear peaks were detected in each frequency band; the HF peak at ~ 1 Hz which synchronized by respiration and related to the parasympathetic tone, and the LF peak at ~ 0.4 Hz which is related to sympathetic nervous activity. Note the dominance of the vagal tone in the non-stressed state prior to the induction of verapamil toxicity. This is evidenced by the HF component being larger than the LF one. Significant positive correlation between spectra of $SBPV$ and SVV are seen in both LF and HF bands (figure 2).

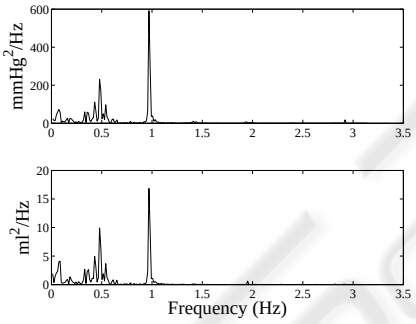

Figure 1: Average spectra for both signals SBPV (top panel), and SVV (bottom panel) estimated from control group prior administration of any drugs.

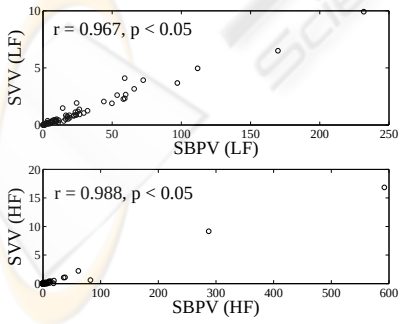

Figure 2: Correlation analysis between LF bands in SBPV and SVV (top panel), and between HF band (bottom panel) in control group.

Shock state was introduced by an overdose infusion of verapamil. As shown in figure 3, this completely abolished the LF component and shift the HF component to ~ 0.9 Hz of both SBPV and SVV spectral traces. The HF peaks in both spectra were enhanced suggesting that sympathovagal balance was shifted to the parasympathetic predominance. A highly significant correlation ($R^2 = 0.977$, $p < 0.05$) between the two frequency bands LF and HF in both spectra was obtained.

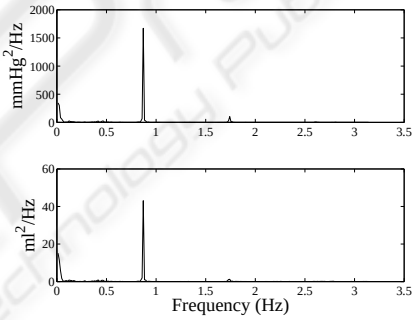

Figure 3: Average spectra for both signals SBPV (top panel), and SVV (lower panel) estimated after verapamil infusion.

The shape of power spectra of SBPV and SVV observed after the continuous infusion of levosimendan were markedly altered (figure4). Clearly, compared with spectra obtained immediately after the induction of verapamil, the LF component of both spectra was observed to recover with concomitant reduction in the HF band peak. These results suggest that there is a recovery of sympathetic tone after the continuous infusion of levosimendan. This may be due to the improvements of the contractility profile of the heart. Additionally, a new frequency component was observed at ~ 1.5 Hz in the spectrum of the SBPV which does not appear in SVV spectrum. Significant correlation were noted between LF ($R^2 = 0.943$, $p < 0.05$) and MF ($R^2 = 0.978$, $p < 0.05$) bands from both spectra, while a poor correlation was noticed between HF ($R^2 = 0.295$, $p = 0281$) bands.

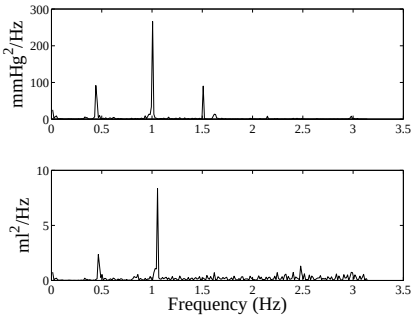

Figure 4: Average spectra for both signals SBPV (top panel), and SVV (lower panel) estimated after a continuous infusion of levosimendan.

5 DISCUSSION

Spectral analysis of HRV has been used to study the sympathovagal balance of the autonomic nervous system due to therapeutic verapamil infusion in humans after acute myocardial infarction (Pinar et al., 1998), in hypertensive patients (Sahin et al., 2004), and normal humans (Fauchier et al., 1997).

In the present study, verapamil overdose resulted in a sharp drop in systolic, diastolic, mean blood pressure, SV, HR, and CO. Additionally, it completely abolished the LF component and enhanced the HF one in both spectra suggesting that verapamil has an anti sympatholytic properties contributing to its negative inotropic effects and its vasodilatory properties. Hemodynamically, compared with period maximal verapamil toxicity seen prior to the administration of levosimendan, it significantly improved CO with no improvements in blood pressure while significant improvements were noticed in SV and HR. In this study, levosimendan produced improvements in cardiac function in heart failure induced by verapamil poisoning. The results of our study correlate well with the hemodynamic parameters reported by Graudins et al. (2008) in verapamil poisoned rats. Levosimendan helped restore the LF component and reduced the HF component suggesting that both drugs restored sympathovagal balance seen prior to the administration of verapamil. This dominance of sympathetic tone may be the reason for the improvements of the myocardial muscle contractility which cause the improvements in cardiac output heralded by a new frequency component at ~ 1.5 Hz in both spectra of SBPV and in SVV.

6 CONCLUSIONS

Spectral analysis of SVV signal may provide, along with SBPV, useful information to clinicians regarding the activity of the autonomic nervous system, cardiac output, and responses to therapies aimed at improving hemodynamic stability in hypotension patients.

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