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Power spectral analysis of heart rate variability and autonomic nervous system activity measured directly in healthy dogs and dogs with tachycardia-induced heart failure

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Abstract

BACKGROUND—Heart rate variability (HRV), calculated in the frequency or time domain, decreases in congestive heart failure (CHF). In HRV power spectral analysis, the low-frequency (LF) component diminishes in patients with CHF and the decrease is related to an increased risk of sudden death.

OBJECTIVE—Our aim was to clarify the nature of HRV power spectral analysis in normal and CHF dogs.

METHODS—Using an implanted radiotransmitter, we directly studied integrated left stellate ganglion nerve activity (iSGNA), integrated vagal nerve activity (iVNA), and electrocardiographic tracings before and after pacing-induced CHF in 6 ambulatory dogs. In a short-term power spectral analysis of HRV, we measured power spectral density during high, medium, and low sympathetic and vagal nerve activity. We analyzed 38 data segments characterized by the same autonomic nerve activity patterns at baseline and after pacing-induced CHF.

RESULTS—As compared with baseline, the spectral variables during CHF showed decreased total power ($P = .002$), LF power ($P < .0001$), and the LF/high frequency (HF) ratio ($P = .005$) and increased iVNA and iSGNA ($P < .0001$ for both). Only at baseline, iSGNA correlated positively with LF power ($P < .05$, $r = 0.314$). Under the same condition iVNA correlated positively with the HF component expressed as normalized units ($P < .05$, $r = 0.394$) and negatively with the LF component expressed both as absolute power ($P < .05$, $r = -0.464$) and normalized units ($P < .05$, $r = -0.425$).

CONCLUSION—The spectral variables (LF power and the LF/HF ratio) and direct variables measuring sympathetic nerve activity (iSGNA) correlate at baseline but not during CHF. At baseline, the vagal activity (iVNA) is associated with an increase in HFnu and a decrease in LFnu. These data

indicate that the reduction in LF power and LF/HF ratio observed in heart failure dogs are likely to reflect a diminished sinus node responsiveness to autonomic modulation or an abnormal baroreflex function rather than an increased sympathetic activity.

Keywords

Autonomic nervous system; Power spectral analysis; Heart rate variability; Congestive heart failure; Vagal nerve activity; Sympathetic nerve activity; Sudden death

Introduction

Neurohumoral activation in congestive heart failure (CHF) is thought to be important in the mechanisms of sudden cardiac death (SCD) and malignant ventricular arrhythmias. For more than 3 decades, power spectral analysis of heart rate variability (HRV), an indirect technique for assessing autonomic modulation of the cardiovascular signals, has been used as a noninvasive clinical tool for measuring autonomic nervous system (ANS) activity. In recent years, the HRV variables have acquired growing importance in stratifying the risk of SCD^{1–3} and in serving as a clinical marker of CHF severity.^{4,5} Among the HRV variables, in healthy subjects, low-frequency (LF) power (between 0.04 Hz and 0.15 Hz), especially as expressed in the normalized form, and the ratio between LF power and high-frequency (HF) power (LF/HF), increase during sympathetic stress (for example orthostatic testing).⁶ Conversely, during CHF no correlation is found between these spectral variables and increased sympathetic activity.⁵ In patients with CHF, however, decreased (rather than increased) LF power is associated with the risk of SCD^{1–3} or progression of CHF.^{4,5} Despite this behavior, the physiological meaning of LF power remains controversial. Most investigators agree that LF power, especially when expressed in the normalized form, is a marker of sympathetic activity at the sinus node. Others, in earlier and more recent studies, have questioned this interpretation, favoring LF power as a marker of baroreceptor activity.^{7,8} Hence the LF power reduction during CHF is variously interpreted from study to study either as a paradoxical response to spectral sympathetic hyperactivity or as a CHF-induced reduction in baroreceptor activity.

We recently developed methods to record ANS activity in ambulatory dogs before and after the induction of CHF by rapid pacing.⁹ The results showed that during CHF, integrated left stellate ganglion nerve activity (iSGNA) and integrated vagal nerve activity- (iVNA) both increased. The purpose of the present study was to compare short-period power spectra analysis in selected data recording epochs with known direct ANS activity in normal and CHF condition.

Materials and methods

Surgical preparation and electrical recording

The data analyzed came from a previous study conducted in 6 female dogs.⁹ The surgical procedures and the temporal relationship between cardiac arrhythmia and ANS activity have been reported in detail elsewhere.^{9,10} In brief, a pacing lead was implanted in the right ventricular apex and connected to an Irel neurostimulator (Medtronic, Minneapolis, Minnesota) in a subcutaneous pocket. We then implanted a Data Sciences International (DSI, St. Paul, MN) D70-EEE transmitter with 3 bipolar recording channels for simultaneous recording of SGNA, VNA from the left thoracic vagal nerve located above the aortic arch, and subcutaneous electrocardiogram. After implantation, the Irel stimulator was initially turned off for 2 weeks to allow the dogs to recover from surgery and to obtain baseline recordings. The stimulator was then programmed to pace at 150 beats/min for 3 days, at 200 beats/min for 3 days, and then at 250 beats/min for 3 weeks to induce CHF. The pacemaker was then turned off to allow an additional 2 weeks of ambulatory monitoring and recording during CHF. All of the recordings obtained during CHF were obtained within the first week. All dogs underwent

echocardiography and venous blood sampling to determine serum N-terminal brain natriuretic peptide (NT-proBNP) concentrations at baseline and after rapid pacing.

Direct measurement of autonomic nervous activity

Data were recorded real-time at a sampling rate of 1,000 samples per second per channel, then analyzed off-line. The software used has been described elsewhere.^{9,10} In summary, to analyze long-term trends in the large segmented data files effectively, a custom-designed program was developed using Labview software to automatically import, filter, and analyze the DSI transmitter data for ANS activities and heart rates. The software determined the activation cycle lengths (RR intervals) automatically derived from electrocardiogram (ECG), based on a Hilbert transform algorithm.¹¹ The data from stellate ganglion (channel 1) and vagal nerve (channel 2) were high-pass (200 Hz) filtered and rectified over a fixed time segment. The nerve activity was then integrated (Figure 1). The inter-beat intervals (IBIs) were also calculated, resampled at 4 Hz, and after detrending, were used to calculate the HRV variables. Because IBIs shorter than 200 ms were usually caused by either ectopic beats, artifacts, or rhythm disturbances, they were removed and excluded from analysis. ANS activity was integrated and categorized into 3 levels. In brief, nerve activity was first rectified and integrated over 100-ms time segments. We then defined the ANS activation threshold as the 3-fold increase in the integrated nerve activity amplitude over the baseline recording amplitude. The baseline recording was defined as the smallest 100-ms segment of integrated nerve activity recorded within the first hour after midnight. For any segment lasting 300 s, 100-ms time segments of sympathetic and vagal nerve activity that exceeded the ANS activation threshold by >90% were defined as high, by 5% to 90% as medium, and by <5% as low. Four measures were also calculated for integrated nerve activities: iSGNA and iVNA over 24 hours (24-hour iSGNA and 24-hour iVNA); iSGNA and iVNA measured in 300-second segments used to select the ANS pattern (300-second iSGNA and 300-second iVNA).

HRV power spectral analysis

Spectral power for HRV was analyzed on segments comprising of 256 heartbeats, and an autoregressive algorithm was used to analyze digitized signals from the electrocardiographic recordings⁶ (Figures 2A and 2B). We then determined the following power spectral variables: total power (TP); total spectral density; HF component (from 0.15 to 0.40 Hz); LF component (from 0.04 to 0.15 Hz); and a very-low-frequency (VLF) component (below 0.04 Hz).¹² We also reported in Hz the central frequency (CF), and the predominant oscillation in LF and HF powers. The relative value of the LF and HF components was also measured and expressed in normalized units (nu)⁶ calculated as follows: $LFnu = LF \text{ power} / TP - VLF \text{ power} \times 100$; $HFnu = HF \text{ power} / TP - VLF \text{ power} \times 100$. Last, we calculated the ratio between LF and HF powers of RR variability (LF/HF).⁶

Data and statistical analysis

During CHF, we randomly selected ECG recording segments containing 256 heartbeats (2 to 3 minutes according to the heart rate) without arrhythmias; we then measured iSGNA and iVNA from these short-term ECG recordings; and grouped the data into 9 groups according to previously defined ANS patterns: high sympathetic and low vagal activity (HS-LV); high sympathetic and medium vagal activity (HS-MV); high sympathetic and high vagal activity (HS-HV); medium sympathetic and high vagal activity (MS-HV); medium sympathetic and medium vagal activity (MS-MV); medium sympathetic and low vagal activity (MS-LV); low sympathetic and high vagal activity (LS-HV); low sympathetic and medium vagal activity (LS-MV) and low sympathetic and low vagal activity (LS-LV). Last, we selected baseline ECG recording segments of similar length (256 heartbeats) that contained the same ANS activity pattern. We therefore compared spectral and nonspectral variables referring to the same ANS

recording pattern at baseline and during CHF in the same dog (for example, we compared the spectrum for an HS-LV segment at baseline and during CHF). We also compared the 38 ECG segments in 3 iSGNA groups (HS, MS, and LS) or iVNA groups (HV, MV and LV) in all of the dogs.

All results are expressed as means $\pm$ SD. A paired Student *t* test was used to evaluate differences in data for the same ANS activity (for example HS-MV at baseline versus HS-MV in CHF) for the following variables at baseline and during CHF: mean RR-interval; RR standard deviation; LFnu, HFnu, LF CF, HF CF, 24-hour iSGNA, and 24-hour iVNA. Under the same 2 conditions (for example HS-MV at baseline versus HS-MV during CHF) and before the natural logarithm transformation, a Wilcoxon signed rank test for paired data was used to compare TP, VLF, LF, HF, 300-second iSGNA, and 300-second iVNA.

Kruskal-Wallis and Mann-Whitney *U* tests were used to compare HRV data at baseline and during CHF for each type of ANS activity: HS, MS, LS and HV, MV, and LV. Spearman's correlation was used to assess relations between variables with a nonlinear distribution. A stepwise multiple regression analysis was constructed to study possible associations between variables after transforming the absolute power of power spectral components and ANS activity into the natural logarithm. All data were evaluated with database SPSS-PC+ (SPSS-PC+ Inc, Chicago, Illinois). A *P* value of ≤ 0.05 was considered statistically significant.

Results

After pacing-induced CHF, in all dogs the left ventricular ejection fraction decreased significantly from baseline (from $56\% \pm 4\%$ to $27\% \pm 7\%$, $P < .0001$). NT-proBNP baseline levels increased (from <180 to 273 pmol/l at baseline, to 558 to more than $3,000$ pmol/l on CHF day 1, and 405.7 ± 167 pmol/l (273 to 687 pmol/l) on CHF day 14 ($P < .05$).

Nerve discharge patterns in CHF

During pacing-induced CHF (within 1 week after the pacemaker was turned off), 38 periods of 256 heartbeats without artifacts or arrhythmias were selected and grouped as follows according to invasive measurement of iSGNA and iVNA: 3 HS-LV, 5 HS-MV, 2 HS-HV, 16 MS-MV, 8 MS-LV, and 4 LS-LV. Pacing-induced CHF was not associated with MS-HV, LS-HV, or LS-MV. Recordings obtained before and after pacing-induced CHF contained the same number of data segments and showed the same ANS patterns.

LF and LF/HF before and after induction of CHF

No significant differences were found between the following variables at baseline and during CHF: the mean RR intervals, VLF power, central frequency of LF and HF, and HF expressed as absolute power or normalized units. Conversely, during pacing-induced CHF, standard deviation of RR ($P = .03$), TP ($P = .002$), LF expressed as absolute power ($P < .0001$) or normalized units ($P = .003$) and the LF/HF ($P = .005$) all decreased from baseline (Table 1, PFigure 2). Whereas 24-hour iSGNA and 24-hour iVNA were higher during pacing-induced CHF than at baseline ($< .0001$), 300-second iSGNA and 300-second iVNA remained almost unchanged under both experimental conditions (Table 1).

Patterns of ANS activity and LF power

At baseline, LFnu was significantly higher during HS than in LS data segments (Figures 3 and 4), conversely no significant differences were found during CHF. The reduction in LF power, LFnu, and the LF/HF between baseline and CHF was confirmed also by considering data segments as a function of sympathetic activity alone: HS ($n = 10$ segments; LF: $P = .009$; LFnu: $P = .028$; LF/HF: $P = .013$) (Figure 5); MS ($n = 24$; LF: $P = .003$; LFnu: $P = .034$; LF/HF: P

= .034) (Figure 5). The comparison between LS at baseline and during CHF failed to yield significant results either for LF power or for LF/HF, probably because of the small number of data segments studied (baseline and CHF only 4 segments).

LF power, LFnu, and the LF/HF were nearly always significantly higher at baseline when data segments were analyzed as a function of vagal activity alone: LV ($n = 15$ segments: LF power: $P = .015$; LFnu: $P = \text{NS}$; LF/HF: $P = \text{NS}$); MV ($n = 21$: LF: $P = .001$; LFnu: $P = .009$; LF/HF: $P = .009$). Because of the small number of dogs (only 2 dogs at baseline and during CHF), we were unable to compare LF power, LFnu, and the LF/HF in HV. At baseline, the Spearman correlation disclosed a positive relationship between 300-second iSGNA and LF power expressed as absolute power and a negative relation between 300-second iVNA and LF power expressed as absolute power or normalized units (Table 2). At baseline, iVNA always correlated with HFnu. Stepwise multiple regression analysis disclosed an inverse relation between 300-second iVNA and $\ln \text{LF/HF}$ ($\ln \text{LF/HF}$: $B = -3.1$, $SE = 1.2$, $\text{Beta} = -0.4$, $t = -2.4$, $P = .024$).

Discussion

Our main finding in this study conducted on an experimental canine model of CHF is that the data on ANS activity we recorded noninvasively by power spectral analysis of HRV appeared unrelated to the information acquired invasively by assessing iSGNA and iVNA after pacing-induced CHF. None of the spectral changes, the diminished HRV, expressed as the standard deviation of the RR-interval and as TP, the decrease in LF power of HRV, expressed as absolute power and as normalized units, or the reduction in LF/HF, were directly associated with a change in ANS activity but they were related to the presence or absence of underlying CHF.

Poor sinus node response to ANS activation

Hence, our new data obtained in a canine model of CHF argue strongly against the suggestions that diminished LF power could be a marker of sympathetic activity.^{4,5,12,13} Our study now provides evidence to the contrary, showing that during CHF, LF power diminishes not because the LF signal originating from sympathetic activity oversaturates, but because CHF renders the sinus node itself less efficient in responding to sympathetic nerve impulses. This phenomenon could have 2 explanations, both depending on how LF power is interpreted. If LF power is considered as a marker of sympathetic activation, then our findings could suggest that during CHF, the sinus node is unable to respond properly to the tonic sympathetic activation (sinus dysfunction) and is therefore unable to elicit the characteristic RR interval oscillations seen in HRV spectra from a healthy person.^{14,15} This mechanism is confirmed by the observation that sympathetic effects on the sinus node seem to be differentially processed under CHF and healthy conditions.^{4,5,12,13} Conversely, if we interpret LF power as a marker of baroreceptor function,^{6,7} then the reduced LF power during CHF must be considered as a CHF-induced reduction in baroreceptor sensitivity. Given that the data from our study are unable to prove either the hypothesis of sinus dysfunction or that of diminished baroreceptor sensitivity, both hypotheses currently remain open.

An important technical point in interpreting our heart rate data is that heart rate remained unchanged at baseline and during CHF because we compared ECG segments containing equal ANS activity. The higher heart rate usually found during CHF depends on the fact that the recording epochs compared take no account of ANS control. Another important point is that LF power decreased more than the other spectral components of HRV during CHF, suggesting that the heart is not completely denervated in this condition. If it were denervated, after an experimentally induced simultaneous sympathovagal block with atropine and pro-pranolol, then both spectral components would decrease.¹⁶

Sympathetic tone and vagal tone

Our new findings in a canine model call for a reappraisal of 2 statements commonly used in the semantics of CHF. First, they imply that the concept of sympathetic hypertone may be inappropriate in the setting of CHF. Our experiments suggest that the cardiovascular circumstances during CHF are unexpectedly dynamic because we found at least 6 different patterns of neuroautonomic activity. We therefore consider that the term hypertone could be more appropriately replaced with sympathetic predominance. The second term we would like to reappraise is sympathovagal imbalance, namely increased sympathetic and reduced vagal activity during CHF. Our results showed that during CHF iSGNA and iVNA both increased (Table 2). In almost 60% of the recoding epochs (22 of 38), the iSGNA and iVNA showed similar activation patterns (2 HS-HV, 16 MS-M, and 4 LS-LV), whereas in the remaining 40% of the recordings, sympathetic activity predominated (3 HS-LV, 5 HS-MV, and 8 MS-LV). These ANS patterns raise the interesting possibility that vagal activity increases during CHF to neutralize sympathetic predominance. Hence, during CHF, sympathovagal imbalance may not always be present, whereas sympathetic and vagal tone invariably reach a dynamic balance.

Pacing-induced CHF as a model for HRV studies

The experimental model of tachycardia-induced CHF combined with power spectral analysis of HRV has often provided controversial results that are hard to compare because of the different study protocols used and the various ways of reporting and analyzing the results.^{17–19} Although we confirmed reduced LF power during pacing-induced CHF, we failed to confirm a reduction in HF power in the same model. This discrepancy could also arise from the different duration of pacing-induced tachycardia, and from our decision to select the arrhythmia-free data segments obtained immediately after the pacemaker was turned off for analysis only. This selection criterion might have allowed partial recovery of the sinus node and HF power.¹⁹

Study limitations

We first wish to underline a limitation inherent in our study design, namely that despite being an interesting experimental model, tachycardia-induced CHF only partly overlaps the real CHF syndrome. Another limitation of the study is that we recorded ANS activity from the left side although the sinus node is located in the right atrium. Although previous studies have documented wide interindividual variability in the distribution of efferent fibers, our previous study using bilateral stellate ganglia recordings showed that left and right SGNA usually occur together. Unilateral SGNA is rare (<10% of cases).²⁰ From this viewpoint, another limitation might be interindividual variability in sympathetic innervation.^{21,22}

Nevertheless, a direct recording of the ANS innervating sinus node would be necessary to define accurately the relationship between ANS activity and sinus node responses in healthy and failing hearts. A point we consider useful to clarify is that recordings of left SGNA simultaneously record neural firing from efferent as well as afferent sympathetic fibers, the fiber group chiefly involved in cardiac nociception and cardiopulmonary reflexes. Because none of our dogs had myocardial ischemia induced and none of them underwent maneuvers designed to stimulate cardio-pulmonary reflexes, we conjecture that the electric signals we recorded came predominantly from efferent fibers.

Last, although the data segments we analyzed during CHF and at baseline came from recordings with the same heart rate and similar ANS control, these cardiovascular conditions do not guarantee similar cardiac output. Unfortunately, we have no hemodynamic data such as cardiac output or stroke volume, nor do we know each dog's workload at the time of the recording. These deficiencies notwithstanding, we can reasonably presume that a given heart rate corresponds to a lower cardiac output and hence a lower stroke volume.

Conclusions

In conclusion, our findings in a canine model of pacing-induced CHF suggest that power spectral analysis of HRV, especially the LF component, is an excellent noninvasive marker of ANS activity under normal cardiovascular conditions. Conversely, under conditions leading to sinus node dysfunction, such as CHF, power spectral analysis of HRV may not accurately predict the underlying sympathetic or vagal control. These findings seem of basic importance in planning and interpreting future studies.

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Figure 1. Simultaneous stellate ganglion nerve activity (SGNA) and vagal nerve activity (VNA) during severe congestive heart failure (CHF). Upper panel: SGNA, middle panel VNA, lower panel electrocardiographic (ECG) trace. On the left, raw recording (**A**), and on the right filtered recording to eliminate ECG contamination (**B**).

Figure 2.

RR power spectral analysis at baseline and after the induction of congestive heart failure (CHF). (A) The baseline tachogram, (B) its corresponding power spectrum. (C) The tachogram for CHF, (D) its corresponding power spectrum. Note that because short-term power spectral analysis recordings are too short to obtain the ultra-low frequency (ULF) and very-low frequency (VLF) components, total power (TP) consists mainly of low-frequency (LF) and high-frequency (HF) components. Note also that when CHF is induced, total power (TP), low-frequency (LF) power, measured as absolute power and in normalized power (nu), central frequency (CF), and the LF/HF all diminish from baseline.

Figure 3.

At baseline, LF power measured in normalized units was significantly lower in the low sympathetic nerve activity than in the high sympathetic nerve activity groups. In the box plots, the central line represents the median distribution; each box spans from 25 to 75 percentile points, and error bars extend from 10 to 90 percentile points.

Figure 4.

RR power spectral analysis at baseline (normal heart) in 2 different conditions of sympathetic nerve activity in the same dog. The left panel shows medium sympathetic (MS) and vagal (MV) nerve activity. The right panel shows high sympathetic (HS) and vagal (MV) activity obtained from an iSGNA recording in the same dog. Note that during HS activity, low-frequency (LF) power, measured as absolute power and in normalized units (nu), and the LF/HF both increased.

Figure 5. Reduction of LF power after the onset of CHF during both high sympathetic and medium sympathetic nerve activity. In the box plots, the central line represents the median distribution. Each box spans from 25 to 75 percentile points, and error bars extend from 10 to 90 percentile points.

Table 1

RR power spectral and direct autonomic nervous activity data in the 38 ambulatory dogs with pacing-induced congestive heart failure

Variables	Baseline N = 38 segments	CHF N = 38 segments	P values
RR mean, ms	678 ± 148	719 ± 151	NS
RR standard deviation	241 ± 96	199 ± 81	.030
ln TP (ms ²)	10.7 ± 1.1	10.3 ± 0.9	.002
ln VLF (ms ²)	7.6 ± 1.1	7.9 ± 1.1	NS
ln LF (ms ²)	9.3 ± 1.5	8.4 ± 0.9	<.0001
LF central frequency (Hz)	0.10 ± 0.02	0.11 ± 0.02	NS
ln HF (ms ²)	9.7 ± 1.5	9.5 ± 1.3	NS
HF central frequency (Hz)	0.23 ± 0.05	0.26 ± 0.07	NS
LFnu	38 ± 29	19 ± 11	.003
HFnu	47 ± 27	54.9 ± 17	NS
LF/HF	1.8 ± 2	0.5 ± 0.5	.005
300 s iSGNA (mV)	97.1 ± 63.8	96.0 ± 58.0	NS
300 s iVNA (mV)	39.8 ± 13.9	41.7 ± 15.9	NS
24 h iGSNA (mV)	142.7 ± 28.0	186.5 ± 95.0	<.0001
24 h iVNA (mV)	2.8 ± 1.1	7.8 ± 4.9	<.0001

Data are expressed as mean ± SD.

ln TP = natural logarithm total power; ln VLF = natural logarithm very-low frequency; ln LF = natural logarithm low frequency; ln HF = high frequency; iSGNA = integrated left stellate ganglion nerve activity; iVNA = integrated vagal nerve activity.

Table 2

Spearman correlation between RR power spectral and direct autonomic nervous activity data

Variables	Baseline		CHF	
	300 s iSGNA	300 s iVNA	300 s iSGNA	300 s iVNA
RR standard deviation	0.109 NS	−0.025 NS	0.239 NS	0.201 NS
TP	0.110 NS	−0.024 NS	0.320 NS	0.109 NS
VLF	−0.142 NS	0.378 <i>P</i> = .011	−0.033 NS	−0.173 NS
LF	0.314 <i>P</i> = .029	−0.464 <i>P</i> = .002	0.210 NS	−0.043 NS
HF	0.077 NS	0.172 NS	0.232 NS	−0.070 NS
LFnu	0.141 NS	−0.425 <i>P</i> = .004	0.237 NS	−0.124 NS
HFnu	−0.209 NS	0.394 <i>P</i> = .008	0.212 NS	0.074 NS
LF/HF	0.156 NS	−0.407 <i>P</i> = .013	−0.279 NS	−0.129 NS

Abbreviations as in Table 1.