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Supine low-frequency power of heart rate variability reflects baroreflex function, not cardiac sympathetic innervation*

ABSTRACT

Background. Power spectral analysis of heart rate variability (HRV) has been used to indicate cardiac autonomic function. High-frequency power relates to respiratory sinus arrhythmia and therefore to parasympathetic cardiovagal tone; however, the relationship of low-frequency (LF) power to cardiac sympathetic innervation and function has been controversial. Alternatively, LF power might reflect baroreflexive modulation of autonomic outflows. **Objective.** We studied normal volunteers and chronic autonomic failure syndrome patients with and without loss of cardiac noradrenergic nerves to examine the relationships of LF power with cardiac sympathetic innervation and baroreflex function. **Methods.** We compared LF power of HRV in patients with cardiac sympathetic denervation, as indicated by low myocardial concentrations of 6-[^{18}F]fluorodopamine-derived radioactivity or low rates of norepinephrine entry into coronary sinus plasma (cardiac norepinephrine spillover) to values in patients with intact innervation, at baseline, during infusion of yohimbine, which increases exocytotic norepinephrine release from sympathetic nerves, or during infusion of tyramine, which increases non-exocytotic release. Baroreflex-cardiovagal slope (BRS) was calculated from the cardiac interbeat interval and systolic pressure during the Valsalva maneuver. **Results.** LF power was unrelated to myocardial 6-[^{18}F]fluorodopamine-derived radioactivity or cardiac norepinephrine spillover. In contrast, the log of LF power correlated positively with the log of BRS ($r = 0.72$, $P < 0.0001$). Patients with a low BRS ($\leq$ 3 msec/mm Hg) had low LF power, regardless of cardiac innervation. Tyramine and yohimbine increased LF power in subjects with normal BRS but not in those with low BRS. BRS at baseline predicted LF responses to tyramine and yohimbine. **Conclusion.** LF power reflects baroreflex function, not cardiac sympathetic innervation.

Spectral analysis of heart rate variability (HRV) has been used widely as a noninvasive technique for examining sympathetic and parasympathetic nervous outflows to the heart. Low-frequency (LF) and high-frequency (HF) power have been used most commonly. Human and animal experiments have repeatedly confirmed the dependence of HF power on respiration-related alterations in parasympathetic cardiovagal outflow–respiratory sinus arrhythmia; however, whether LF power provides an indirect measure of cardiac sympathetic activity has been contentious. Pagani et al[1] reported that LF power (normalized to total spectral power) increased during states associated with sympathetic noradrenergic activation and that bilateral stellectomy in dogs reduced LF power. Alvarenga et al,[2] however, reported that LF power was unrelated to all measures of norepinephrine kinetics in the heart; and in congestive heart failure, which is associated with a high rate of entry of norepinephrine into coronary sinus plasma (cardiac norepinephrine spillover),[3] LF power is decreased, not increased as might be expected if LF power reflected sympathetic activity.[4–7]

Sleight et al[8] proposed an alternative explanation for the origin of LF power. In a small group of human subjects, power spectral analysis of HRV showed that the amplitude of LF power was related to baroreflex

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TABLE 1
Subject groups

Group	Innerv Nl BRS	Denerv Nl BRS	Innerv low BRS	Denerv low BRS	Sum
PD + NOH	0	1	0	8	9
MSA	3	0	11	0	14
PAF	0	1	3	5	9
PD no NOH	12	2	2	17	33
r/o CAF	2	0	0	0	2
Normal	11	0	1	0	12
COI	12	0	7	0	19
Sum	**40**	**4**	**24**	**30**	**98**
Yohimbine					
PD + NOH	0	0	0	3	3
MSA	0	0	5	0	5
PAF	0	0	3	2	5
PD no NOH	0	0	0	0	0
r/o CAF	2	0	0	0	2
Normal	6	0	1	0	7
COI	0	0	0	0	0
Sum	**8**	**0**	**9**	**5**	**22**
Tyramine					
PD + NOH	0	0	0	7	7
MSA	2	0	12	0	14
PAF	0	0	3	6	9
PD no NOH	5	0	0	1	6
r/o CAF	2	0	0	1	3
Normal	10	0	1	0	11
COI	0	0	0	0	0
Sum	**19**	**0**	**16**	**15**	**50**

COI = chronic orthostatic intolerance; Denerv = denervated; Innerv = innervated; MSA = multiple system atrophy; Nl BRS = normal baroreflex-cardiovagal slope; NOH = neurogenic orthostatic hypotension; PAF = pure autonomic failure; PD = Parkinson disease; r/o CAF = rule out chronic autonomic failure

gain and not to the level of sympathetic activity. Carotid sinus stimulation increased LF power only in individuals with normal baroreflex sensitivity and did not do so in those with depressed baroreflex gain. Therefore, results of power spectral analysis of LF power might reflect baroreflex-cardiovagal function.[9]

Studies of patients with dysautonomias provide an unusual opportunity to examine neurocirculatory correlates of LF power. Some chronic autonomic failure syndromes feature cardiac sympathetic denervation, whereas others do not. Parkinson disease with neurogenic orthostatic hypotension and pure autonomic failure feature cardiac sympathetic denervation, whereas multiple system atrophy does not.[10] All 3 diseases involve baroreflex-cardiovagal and baroreflex-sympathoneural failure.[11] Chronic orthostatic intolerance syndromes (postural tachycardia syndrome, neurocardiogenic syncope) do not entail either cardiac sympathetic denervation or baroreflex failure.[12]

For this article, we carried out power spectral analyses of HRV on digitized electrocardiographic recordings from dysautonomia patients and normal volunteers during supine rest, measurement of cardiac norepinephrine spillover, and intravenous infusion of yohimbine and tyramine, 2 drugs that are known to release norepinephrine from cardiac sympathetic nerves.[13,14] Cardiac sympathetic innervation was assessed by 6-[^{18}F]fluorodopamine positron emission tomographic scanning.[15]

We hypothesized that if LF power indicated cardiac sympathetic innervation and function, then patients with neuroimaging or neurochemical evidence of cardiac sympathetic denervation would have low LF power and attenuated increments in LF power in response to yohimbine and tyramine. Alternatively, if LF power was reflective of baroreflex function, alterations of LF power would be independent of cardiac sympathetic innervation status and correlate with changes in baroreflex gain.

METHODS

The study protocols were approved by the Intramural Research Board of the National Institute of Neurological Disorders and Stroke. All subjects were studied at the National Institutes of Health Clinical Center after giving informed, written consent.

Subjects

The study population consisted of a total of 98 subjects who participated in research protocols studying chronic orthostatic intolerance and chronic autonomic failure **(Table 1)**. The subjects underwent autonomic function testing and had reviewable, digitized electrocardiographic data enabling retrospective power spectral analysis of HRV. ECG and blood pressure data were sampled at 1 kHz.

The study subjects were separated into 4 groups, depending on their state of cardiac sympathetic innervation and baroreflex-cardiovagal slope (BRS; see below). There were 40 subjects with intact sympathetic innervation and normal BRS (Innervated-Normal BRS), 24 with intact sympathetic innervation and low BRS (Innervated-Low BRS), 4 with sympathetic denervation and normal BRS (Denervated-Normal BRS), and 30 with sympathetic denervation and low BRS (Denervated-Low BRS).

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Autonomic function testing

Each subject was studied while supine with head on pillow after an overnight fast. Each patient had monitoring of the electrocardiogram and beat-to-beat blood pressure using either noninvasive devices (Finometer, Finapres Medical Systems, Amsterdam, the Netherlands; Portapres, Finapres Medical Systems; or Colin tonometer, Colin Medical Instruments, San Antonio, TX) or a brachial intra-arterial catheter. We previously studied formally and reported excellent agreement between intra-arterial and these noninvasively obtained measures of beat-to-beat blood pressure.[16] Continuous vital signs data were digitized and recorded using a PowerLab (AD Instruments Pty Ltd, Castle Hill, Australia) data acquisition system and stored for later analysis on an Apple PowerBook G4 computer (Apple, Cupertino, CA).

After about a 10-min baseline period, each subject performed a Valsalva maneuver (30 mm Hg for 12 sec) at least 3 times.

Baroreflex function

As an index of baroreflex function, we used the slope of the relationship between cardiac interbeat interval and systolic blood pressure during phase II of the Valsalva maneuver.[17] BRS, in units of msec/mm Hg, was calculated from the linear regression equation for the relationship between interbeat interval (with 1-beat delay) and systolic pressure. A BRS value of ≤ 3 msec/mm Hg was considered low.[11]

Pharmacologic testing

Pharmacologic testing was performed on completion of the autonomic evaluation, using either tyramine or yohimbine. If a subject received both drugs, each drug administration was on a separate day. The durations of drug infusion were sufficient for heart rate and blood pressure to reach plateau values.

In a total of 22 subjects **(Table 1)**, yohimbine was infused intravenously at 62.5 μg/kg over 3 min and then at 0.5 μg/kg/min for 12 min. In a total of 50 subjects, tyramine was infused at a rate of 1 mg/min for 10 min. In patients with severe supine hypertension (systolic pressure more than 200 mm Hg) and orthostatic hypotension, the test drugs were infused during head-up tilting (15° to 30°), to decrease baseline pressure, or else the drugs were not given.

HRV analysis

LF power (0.04 to 0.15 Hz), HF power (0.16 to 0.4 Hz), and total power (TP, 0.0 to 0.4 Hz) were calculated using Chart 5.4.2 and the HRV module version 1.03 (PowerLab, AD Instruments Pty Ltd, Castle Hill, Australia). Stable heart rate epochs 3 to 5 min in duration were chosen for analysis. One epoch was sampled immediately before initiation of drug testing; the second followed attainment of steady-state hemodynamic effects. Interbeat interval data were reviewed carefully to eliminate artifacts from noise and T waves, using segments with little to no premature beats. LF power and HF power were calculated as absolute power ($msec^2$), with or without normalization for total power (0.04 to 0.4 Hz). Reported LF or HF power was integrated within their defined frequency bands.

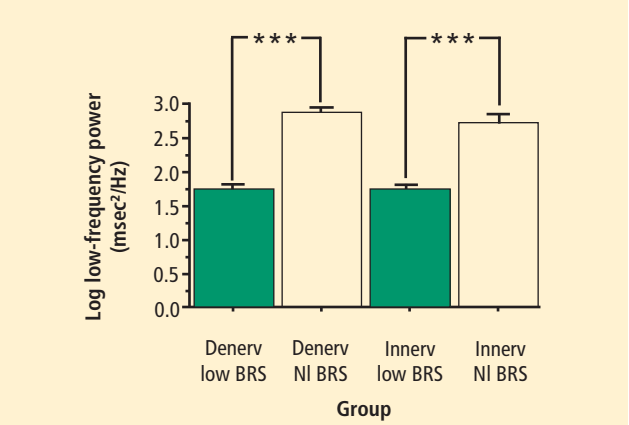

FIGURE 1. Mean (± SEM) values for the log of low-frequency power of heart rate variability in subject groups with innervated (Innerv) or denervated (Denerv) hearts, as indicated by low 6-[^{18}F] fluorodopamine-derived radioactivity, and normal (Nl) or low baroreflex-cardiovagal slope (BRS), as indicated by slope ≤ 3 msec/mm Hg during the Valsalva maneuver. ***Significant difference, $P < 0.001$.

Cardiac sympathetic neuroimaging

For cardiac sympathetic neuroimaging the subject was positioned supine, feet-first in a GE Advance scanner (General Electric, Milwaukee, WI), with the thorax in the gantry. After positioning the patient with the thorax in the scanner and transmission scanning for attenuation correction, 6-[^{18}F]fluorodopamine (usual dose 1 mCi, specific activity 1.0 to 4.0 Ci/mmole, in about 10 mL normal saline) was infused intravenously at a constant rate for 3 min, and dynamic scanning data were obtained for thoracic radioactivity, with the midpoint of the scanning interval at 7.5 min after injection of the tracer (data collection interval between 5 and 10 min). Cardiac sympathetic denervation was defined by low concentrations of 6-[^{18}F] fluorodopamine-derived radioactivity in the interventricular septum (< 5,000 nCi-kg/cc-mCi) or left ventricular free wall (< 4,000 nCi-kg/cc-mCi) corresponding to about 2 SD below the normal means.

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TABLE 2
Power spectral heart rate variability parameters as a function of cardiac sympathetic innervation and baroreflex slope (BRS)

Innervation	BRS	HF power
Denervated	Low	129 ± 57
Denervated	Normal	329 ± 69
Innervated	Low	59 ± 15*
Innervated	Normal	489 ± 106
Innervation	**BRS**	**LF Nu**
Denervated	Low	53 ± 5
Denervated	Normal	65 ± 7
Innervated	Low	56 ± 5
Innervated	Normal	64 ± 3
Innervation	**BRS**	**HF Nu**
Denervated	Low	35 ± 3
Denervated	Normal	30 ± 6
Innervated	Low	33 ± 4
Innervated	Normal	32 ± 3
Innervation	**BRS**	**LF/HF**
Denervated	Low	2.3 ± 0.4
Denervated	Normal	2.7 ± 0.9
Innervated	Low	3.1 ± 0.6
Innervated	Normal	3.0 ± 0.4

HF Nu = high-frequency power divided by summed power; HF power = high-frequency power; LF Nu = low-frequency power divided by summed power; LF/HF = low-frequency power divided by high-frequency power

*Significant difference from Innervated-Normal BRS, $P = 0.0006$

Cardiac norepinephrine spillover

Subgroups of subjects (3 PD + NOH, 3 MSA, 3 PAF, 5 normal volunteers) underwent right heart catheterization for measurement of cardiac norepinephrine spillover. ^{3}H-Norepinephrine was infused intravenously, and arterial and coronary sinus blood was sampled and coronary sinus blood flow was measured by thermodilution for measurements of cardiac norepinephrine spillover as described previously.[18] In some subjects, yohimbine was infused during cardiac catheterization. Patients with chronic autonomic failure received the doses described above; normal volunteers and patients with chronic orthostatic intolerance received twice the doses described above.

Data analysis

Statistical analyses were performed using StatView version 5.0.1. (SAS Institute, Cary, NC). Mean values in the baseline condition for the several subject groups were compared using single-factor ANOVA. Responses to drugs were analyzed by dependent-means *t* tests. Differences in response to pharmacologic tests among subject groups were compared using repeated measures analyses of variance. Relationships between individual hemodynamic values were assessed by linear regression and calculation of Pearson correlation coefficients. Post-hoc testing consisted of the Fisher PLSD test. Multiple regression analysis was done on the individual data, with the log of LF power as the dependent measure and the log of baroreflex slope and septal 6-[^{18}F] fluorodopamine-derived radioactivity as independent measures. Mean values were expressed ± SEM.

RESULTS

Baseline

Across the 7 subject groups (N = 98), LF power was unrelated to subject group (F = 1.2). When individual subjects were stratified in terms of cardiac sympathetic denervation or innervation, based on concentrations of 6-[^{18}F]fluorodopamine-derived radioactivity more than 2 SD below the normal mean, then LF power was lower in the Denervated group (mean 221 ± 55 msec^2/Hz, N = 34) than in the Innervated group (516 ± 93 msec^2/Hz, N = 64, F = 4.8, $P = 0.03$). LF power normalized for total power, HF normalized for total power, and the ratio of LF:HF were not related to 6-[^{18}F]fluorodopamine-derived radioactivity.

When subjects were stratified in terms of BRS, then LF power was lower in the Low BRS group (223 ± 105 msec^2/Hz, N = 46) than in the Normal BRS group (617 ± 97 msec^2/Hz, N = 25, F = 6.1, $P = 0.02$). The Low BRS group did not differ from the Normal BRS group in normalized LF power (F = 0.8).

When individual subjects were stratified into 4 groups, based on both cardiac 6-[^{18}F]fluorodopamine-derived radioactivity (Innervated or Denervated) and on baroreflex-cardiovagal slope (Normal BRS or Low BRS), then both LF power and the log of LF power varied highly significantly as a function of subject group (F = 9.5, $P < 0.0001$; F = 4.6, $P = 0.0004$). The Denervated-Low BRS group had lower LF power than did the Denervated-Normal BRS group ($P = 0.05$), and the Innervated-Low BRS group had lower LF power than did the Innervated-Normal BRS group ($P < 0.0001$). When level of baroreflex function was taken into account, the Innervated and Denervated groups did not differ in LF power **(Figure 1)**.

Values for HF power also varied with subject group when individual subjects were stratified in terms of both cardiac sympathetic innervation and BRS (F = 4.9, $P = 0.004$; **Table 2**). The Innervated-Low BRS group had

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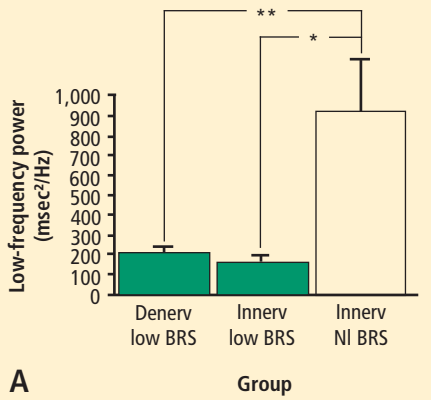


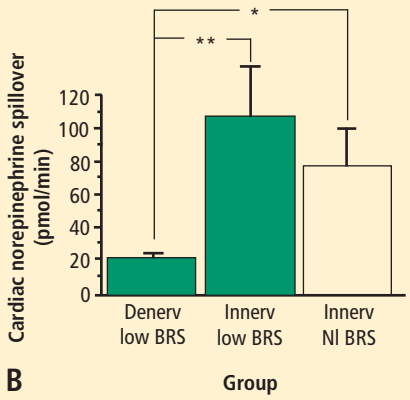
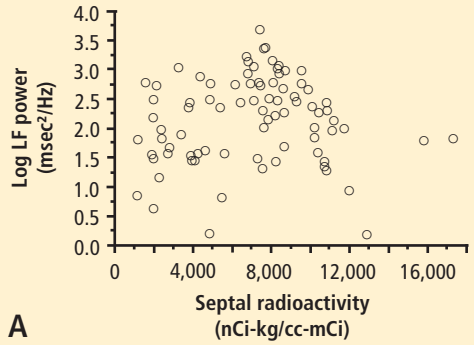


FIGURE 2. Mean (± SEM) values for **(A)** low-frequency power of heart rate variability and **(B)** cardiac norepinephrine spillover during right heart catheterization in subject groups with innervated (Innerv) or denervated (Denerv) hearts, as indicated by low 6-[^{18}F]fluorodopamine-derived radioactivity, and normal (Nl) or low baroreflex-cardiovagal slope (BRS), as indicated by slope ⩽ 3 msec/mm Hg during the Valsalva maneuver. *Significant difference, $P < 0.05$. **Significant difference, $P < 0.01$.



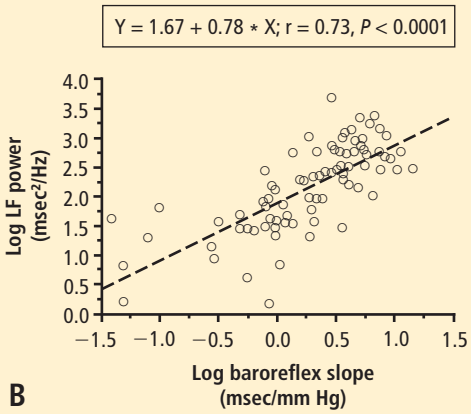


FIGURE 3. Individual values for the log of low-frequency (LF) power as a function of **(A)** septal 6-[^{18}F]fluorodopamine-derived radioactivity and **(B)** the log of baroreflex-cardiovagal slope.

lower HF power than did the Innervated-Normal BRS group ($P = 0.003$); however, the Denervated-Low BRS group did not differ from the Denervated-Normal BRS group in HF power. Normalization of LF and HF power for total power, and the ratio of low-to-high frequency did not reveal additional group differences **(Table 2)**. In particular, the LF:HF ratio did not vary with the subject group ($F = 0.6$).

Analysis of data from subjects during cardiac catheterization showed that LF power varied as a function of subject group ($F = 5.3$, $P = 0.03$, **Figure 2**). The Innervated-Low BRS group had lower LF power than did the Innervated-Normal BRS group ($P = 0.04$), whereas the Denervated-Low BRS and Innervated-Low BRS groups did not differ in LF power. As expected, the Denervated-Low BRS group had lower cardiac norepinephrine spillover than the Innervated-Low BRS group.

Individual values for LF power were positively correlated with BRS. When values for both variables were log-transformed, the log of LF power correlated positively with the log of BRS slope ($r = 0.72$, $P < 0.0001$, **Figure 3**). Individual values for the log of LF power were also correlated with the magnitude of decrease in systolic pressure during performance of the Valsalva maneuver ($r = -0.60$, $P < 0.0001$) and with the orthostatic change in systolic pressure ($r = 0.58$, $P < 0.0001$). In contrast, the log of LF power was unrelated to the septal myocardial concentration of 6-[^{18}F]fluorodopamine-derived radioactivity, the plasma norepinephrine concentration, or cardiac norepinephrine spillover.

From multiple regression analysis for the log of LF power as the dependent measure and the log of baroreflex slope and septal 6-[^{18}F]fluorodopamine-derived radioactivity as independent measures, the regression coefficient for the log of baroreflex slope was 0.92 ($P < 0.0001$), whereas the regression coefficient for 6-[^{18}F]fluorodopamine-derived radioactivity was 3×10^{-6}.

At baseline, the log of HF power correlated positively with the log of LF power ($r = 0.77$, $P < 0.0001$). HF power varied with the subject group ($F = 4.9$, $P = 0.004$). As with LF power, HF power was greater in

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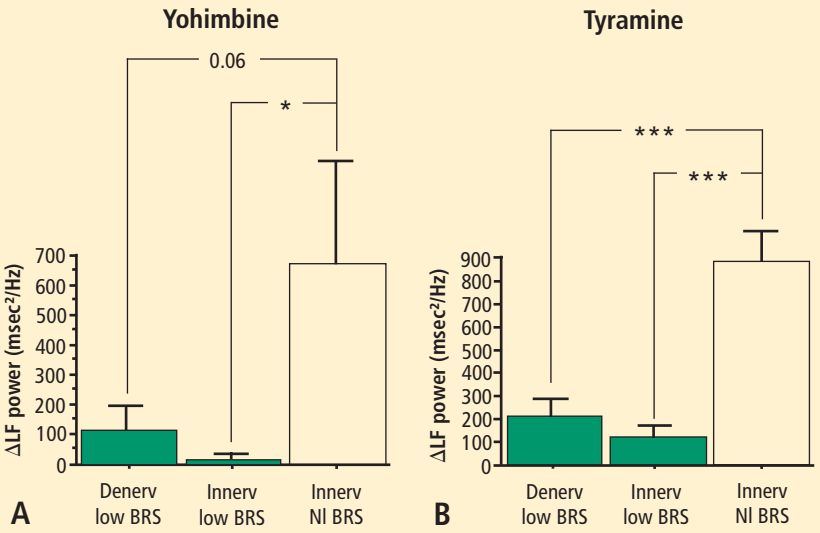

FIGURE 4. Mean (± SEM) values for the change in low-frequency power (ΔLF power) of heart rate variability during **(A)** intravenous infusion of yohimbine or **(B)** tyramine in groups with innervated (Innerv) or denervated (Denerv) hearts, as indicated by low 6-[^{18}F]fluorodopamine-derived radioactivity, and normal (Nl) or low baroreflex-cardiovagal slope (BRS), as indicated by slope ⩽ 3 msec/mm Hg during the Valsalva maneuver. *Significant difference, $P < 0.05$. ***Significant difference, $P < 0.001$.

the Innervated-Normal BRS than in the Innervated-Low BRS ($P = 0.001$, **Table 2**). As expected, the log of HF power correlated positively with the log of BRS (r = 0.60, $P < 0.0001$). The log of HF power also correlated negatively with the magnitude of decrease in systolic pressure during the Valsalva maneuver (r = −0.24, $P = 0.02$) and positively with the orthostatic change in systolic pressure (r = 0.40, $P = 0.004$).

Yohimbine

Yohimbine infusion increased LF power (t = 2.9, $P = 0.007$). The group with cardiac sympathetic denervation did not differ from the group with intact cardiac innervation in terms of the change in LF power during yohimbine infusion (F = 0.7). Yohimbine infusion increased LF power in the Innervated-Normal BRS group (t = 2.8, $P = 0.01$), but not in the innervated or denervated groups with low BRS **(Figure 4)**. The Innervated-Normal BRS group had a larger increase in LF power during yohimbine infusion than did the Innervated-Low BRS group ($P = 0.02$). Too few patients with cardiac denervation and normal BRS were studied to include in the ANOVA. The log of the change in LF power during yohimbine administration was positively correlated with the log of BRS at baseline **(Figure 5)**.

Yohimbine increased HF power in the Innervated-Normal BRS group (t = 2.1, $P = 0.05$) but not in the innervated or denervated groups with low BRS.

The change in LF power in response to yohimbine during cardiac catheterization was unrelated to the change in cardiac norepinephrine spillover (r = −0.09, N = 12).

Tyramine

Overall, tyramine infusion increased LF power (t = 2.9, $P = 0.008$). The group with cardiac sympathetic denervation did not differ from the group with intact cardiac innervation in terms of the change in LF power during tyramine infusion (F = 1.7). Tyramine increased LF power in the Innervated-Normal BRS group but not in the Innervated-Low BRS or Denervated-Low BRS groups (**Figure 4**; data for 2 outliers excluded). The log of the change in LF power during tyramine administration was positively correlated with the log of BRS at baseline (**Figure 5**; data for 2 outliers excluded).

DISCUSSION

In this study, patients with neuroimaging evidence of cardiac sympathetic denervation had low LF power of heart rate variability. At first glance, this finding would seem to support the view that LF power can provide an index of cardiac sympathetic outflow. As explained below, several lines of evidence from the present study led us to infer that the association between low LF power and cardiac sympathetic innervation is determined mainly by concurrent baroreflex function.

Patients with low BRS had low LF power, and patients with normal BRS had normal LF power, regardless of the status of cardiac sympathetic innervation as assessed by 6-[^{18}F]fluorodopamine scanning. Neither normalization of LF and HF power for total power nor use of the LF:HF ratio improved the association with indices of cardiac sympathetic innervation.

Neurochemical findings during cardiac catheterization supported the above results based on cardiac

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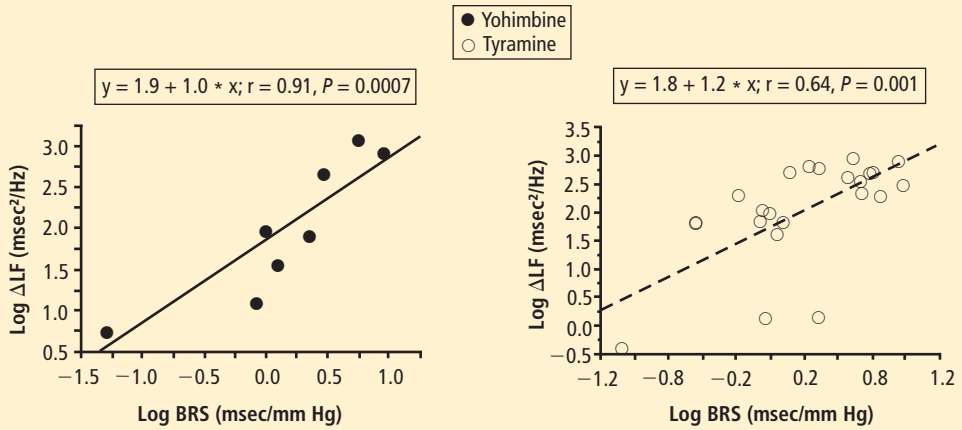

FIGURE 5. Individual values for the log of change in low-frequency power (log ΔLF power) as a function of baroreflex-cardiovagal slope at baseline. Left: yohimbine infusion. Right: tyramine infusion.

sympathetic neuroimaging. Among patients with innervated hearts who had normal cardiac norepinephrine spillover, LF power was decreased only in the group with low BRS and was normal in the group with normal BRS. As expected, cardiac norepinephrine spillover was decreased in patients with neuroimaging evidence of cardiac sympathetic denervation.

Effects of pharmacological manipulations that increase norepinephrine release from sympathetic nerves provided further support for an association between baroreflex failure and low LF power, independent of cardiac sympathetic function. Both tyramine and yohimbine increased LF power only in the subjects with normal BRS. In subjects with low BRS, neither drug increased LF power, even in the group with intact cardiac sympathetic innervation. Moreover, individual values for responses of the log of LF power to both drugs were correlated positively with the log of BRS at baseline.

The fact that HF power was positively correlated with LF power could also fit with the notion of baroreflex function acting as a common determinant of values of both variables. We cannot exclude concurrent parasympathetic cardiovagal and sympathetic denervation as an explanation for the association between HF and LF power. Inhibition of the effects of parasympathetic activity after atropine administration results in the almost complete absence of both LF and HF HRV, further suggesting a common determinant.[19]

Several previous investigations have cast doubt on the validity of LF power as a measure of sympathetic activity because of dissociations between LF power and cardiac norepinephrine spillover, directly recorded sympathetic nerve traffic, and plasma norepinephrine levels.[4,6,20] Such dissociations are especially glaring in patients with congestive heart failure, which is characterized by decreased LF power[9] despite marked cardiac sympathetic activation.[3]

Other pathophysiologic states do result in both decreased sympathetic nervous system activity and decreased LF power. In these pathophysiologic states, the possibility remains that low LF power might reflect failure of baroreflexive modulation of sympathetic neuronal outflows, rather than sympathoinhibition itself. For instance, Wiklund et al[21] noted low LF power in patients with palmar hyperhidrosis undergoing bilateral transthoracic sympathectomy; however, baroreflex-cardiovagal sensitivity also declines after thoracic sympathectomy.[22]

Sleight et al[8] suggested dependence of LF power on baroreflex function, based on effects of carotid baroreceptor stimulation in 3 patients: 1 with normal BRS; 1 with ischemic heart disease, congestive heart failure, and normal BRS; and 1 with ischemic heart disease, congestive heart failure, and initially low BRS who subsequently had an improved clinical state and BRS. In the baseline state, both congestive heart failure patients had low LF power, despite a presumably hypernoradrenergic state. Direct baroreceptor stimulation at 0.1 Hz increased LF power in the normal subject and in the patient with congestive heart failure and normal BRS. The congestive heart failure patient with low BRS did not have an increase in LF power until BRS normalized. These data revealed an initial dissociation between cardiac noradrenergic state in the patients with congestive heart failure and LF power. During carotid sinus stimulation, LF power increased only when BRS was normal. Low BRS obviated this effect.

Because congestive heart failure is well known to be associated with baroreflex-cardiovagal inhibition,[23–25] the finding of low LF power in heart failure also supports an association between LF power and BRS, inde-

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pendently of increased tonic release of norepinephrine from sympathetic nerves in the heart. Cevese et al[26] inhibited noradrenergic vasomotor tone using an alpha-adrenoceptor blocker in human subjects while maintaining mean blood pressure at control levels using angiotensin II. This drug combination, which would be expected to attenuate sympathetically mediated vasomotor tone and thereby decrease arterial baroreceptor input, markedly decreased or abolished LF power of HRV, suggesting that, at least under resting supine conditions, a baroreflex mechanism accounts almost entirely for LF power of HRV.

deBoer et al[27] developed a beat-to-beat model of the human circulation using a set of differential equations and the following principles of operation: (1) the baroreflex regulates heart rate and peripheral vascular resistance; (2) Windkessel properties characterize the systemic arterial tree; (3) contractile properties of the ventricular myocardium follow the Starling law; and (4) respiration exerts mechanical effects on blood pressure. The model attributes LF power to a resonance in the circulatory control system, produced by a slow time constant for reflexive sympathetically mediated responses to beat-to-beat blood pressure changes. The resonance can be upregulated or downregulated by the state of baroreflex activity. The model of deBoer et al predicts that changes in blood pressure would lead heart rate changes at 0.1 Hz through a delayed sympathetic response. Changes in HR would depend on summed effects of sympathetic and vagal effects, with the sympathetic response delaying the overall response. At the respiratory frequency (0.2 to 0.3 Hz), blood pressure and HR changes would occur with little delay because of fast parasympathetic control. In essence, the response of the sympathetic nervous system behaves as a low band pass filter, with a peak response at 0.1 Hz and little response at frequencies above 0.2 Hz. Systolic blood pressure would lead to changes in heart rate via the baroreflex. In general the results of this study fit with the deBoer model.

In conclusion, LF power derived from the interbeat interval spectrogram predominantly reflects baroreflex-mediated, phasic changes in cardiovagal and sympathetic noradrenergic outflows. In the setting of baroreflex failure, baseline LF power is reduced, regardless of the status of cardiac sympathetic innervation.

LIMITATIONS

The combination of cardiac sympathetic denervation and normal baroreflex function seems quite rare. One must exercise caution in drawing inferences from the findings in the Denervated-Normal BRS group, which contained only 4 subjects, even though the difference in mean log-transformed LF power from the Denervated-Low BRS group was highly statistically significant.

All of the testing in our study was done with the subjects supine. LF power measured in other positions might have different sources and meaning.

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