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Parasympathetic Withdrawal Is an Integral Component of Autonomic Imbalance in Congestive Heart Failure: Demonstration In Human Subjects and Verification in a Paced Canine Model Of Ventricular Failure

PHILIP F. BINKLEY, MD, FACC, ENRICO NUNZIATA, MSBME, GARRIE J. HAAS, MD, STEVEN D. NELSON, MD, ROBERT J. CODY, MD, FACC

Columbus, Ohio

Although enhanced sympathetic tone is a well recognized component of the autonomic profile characteristic of congestive heart failure, the contribution of parasympathetic withdrawal to this autonomic imbalance is less well described. The technique of spectral analysis of heart rate variability provides a dynamic map of sympathetic and parasympathetic tone and was thus used to define the nature of sympathetic-parasympathetic interactions in humans with idiopathic dilated cardiomyopathy and in a paced canine model of congestive heart failure. Humans with cardiomyopathy were found to have an augmentation of the sympathetically mediated low frequency area of the power density spectrum.

Parasympathetic withdrawal was demonstrated by significant reductions in the parasympathetically mediated high frequency area ($p < 0.05$) and the ratio of high to low frequency areas ($p < 0.01$). Administration of atropine to normal subjects resulted in a significant reduction in the high frequency area ($p < 0.05$) and the high/low frequency area ratio, both of which decreased within the range noted in patients with congestive heart failure. Administration of isoproterenol in normal subjects led to an augmentation of the low frequency area but to only a small decrease in the high/low frequency area ratio.

Induction of congestive heart failure in a paced canine model resulted in alterations in the autonomic profile that resembled those seen in humans with ventricular failure. The prominent high frequency region of the spectrum at baseline, indicating a predominance of parasympathetic tone, was absent after the evolution of congestive heart failure, and there was a marked augmentation of the low frequency region of the spectrum.

These observations indicate that parasympathetic withdrawal, in addition to the well known augmentation of sympathetic drive, is an integral component of the autonomic imbalance characteristic of chronic congestive heart failure and can be detected noninvasively by spectral analysis of heart rate variability. Furthermore, enhanced sympathetic stimulation alone does not reproduce this characteristic profile, as evidenced by the isoproterenol-induced changes in the power density spectrum in normal subjects.

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Chronic congestive heart failure is characterized by aberrations of the neuroendocrine axis that contribute to hemodynamic decompensation, the perpetuation of symptoms and, apparently, the progression of the disease state (1–10). A major component of this neuroendocrine derangement is the markedly abnormal autonomic profile of the patient with congestive heart failure, which has been described as consisting of an augmentation of sympathetic drive (1–3,7–10). In part because in vivo assessment of parasympathetic tone is technically limited, relatively little information regarding the status of this limb of the autonomic nervous system in congestive heart failure is available (6). Thus, whether the autonomic derangement accompanying ventricular failure consists predominantly of enhanced sympathetic drive or a combination of augmented sympathetic tone and parasympathetic withdrawal remains unresolved.

Analysis of heart rate variability permits assessment of both sympathetic and parasympathetic activity given that frequency-specific variations in heart rate ascribed to each system have been defined (7–26). In general, as demonstrated by Akselrod et al. (13) and others (7–12,14–26), high frequency (>0.1 Hz) variations in heart rate are exclusively under control of the parasympathetic nervous system. Sympathetically mediated variations in heart rate are restricted to the spectrum of frequencies below this range (12,13,16). The technique of spectral analysis of heart rate variability provides a means of quantifying the frequency content of the variation of heart rate over time, thus permitting a measure of both sympathetic and parasympathetic tone (7–26).

We applied the technique of spectral analysis of heart rate

From the Division of Cardiology, Department of Medicine, The Ohio State University, Columbus, Ohio. This study was supported in part by the Seward Schooler Family Foundation, Columbus, Ohio and the American Heart Association Ohio Affiliate, Columbus, Ohio. Dr. Binkley is the recipient of a Clinical Associate Physician Award from the National Institutes of Health, Bethesda, Maryland.

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Address for reprints: Philip F. Binkley, MD, Division of Cardiology, Department of Medicine, Ohio State University Hospital, 607 Means Hall/1654 Upham Drive, Columbus, Ohio 43210.

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variability to more completely characterize the autonomic profile that evolves in the setting of ventricular dysfunction and to test the hypothesis that attenuation of parasympathetic tone is a necessary component of the autonomic response to ventricular failure. Specifically, the power density spectrum of heart rate variability obtained in patients with congestive heart failure who were not receiving vasodilator medications was compared with the spectrum obtained in normal subjects at baseline and in response to pharmacologic interventions designed to mimic augmented sympathetic drive and withdrawal of parasympathetic tone. To further investigate the evolution of autonomic dysfunction in a prospective fashion, heart rate variability was analyzed in a paced canine model of congestive heart failure and compared with the spectrum observed in humans with congestive heart failure (27–29).

Methods

Studies in Normal Human Subjects and Patients With Congestive Heart Failure

Study patients. Informed consent was obtained from all subjects before entry into the protocol in accordance with the Human Subjects Review Committee of The Ohio State University, which reviewed and approved the protocol. Fifteen men ranging in age from 21 to 41 years (mean 28.9 ± 7.1) with normal results on physical examination and without a history of significant medical illness formed the normal group. Ten patients (six men and four women) ranging in age from 32 to 65 years (mean 49.2 ± 10.6) with congestive cardiomyopathy and an ejection fraction of 12% to 40% (mean 23.5 ± 9.9) constituted the heart failure study group. The etiology of congestive heart failure was idiopathic dilated cardiomyopathy in all patients. All vasodilators were withheld for ≥5 half-lives before study. Seven patients were receiving stable maintenance doses of digoxin during the study period and seven were receiving stable maintenance doses of furosemide and one of these was receiving a triamterene/hydrochlorthiazide preparation as well. These diuretic drugs were administered on the evening before the evaluation of autonomic tone. No patient had been prescribed any other medications, such as a beta-adrenergic blocking agent, which may directly influence sympathetic or parasympathetic tone. All subjects had sinus rhythm without frequent ectopic ventricular or supraventricular beats during the evaluation.

Measurement of autonomic tone at rest. Normal subjects and patients with congestive heart failure were studied in the supine posture. All examinations were performed between 9 and 11 AM. Electrocardiographic (ECG) electrodes for recording standard limb leads were attached and a lead demonstrating predominant positive or negative QRS deflection (facilitating QRS recognition by a signal-processing algorithm) was selected for recording and analysis. Subjects rested in the supine posture for a 20-min equilibration period before signal acquisition and were instructed to relax as much as possible throughout the recording period. After the equilibration period, the selected ECG lead was recorded for a minimum of 4 min with use of a RACAL V STORE FM tape recorder at a speed of 3.75 in. (9.53 cm)/s. If somatic artifact or ectopic beats were noted at any time, the recording was halted and reinitiated after such interference had resolved. The ECG signal was subsequently analyzed for generation of the power density spectrum.

Pharmacologic manipulation of autonomic tone in normal subjects. Given that beta-adrenergic activity modulates low frequency heart rate variability (12,13,16,25,30), verification that the spectral analysis technique accurately reflects augmented beta-adrenergic stimulation, such as that encountered in chronic congestive heart failure, was performed in seven normal subjects. Each subject received isoproterenol, with recording of the ECG signal for spectral analysis of heart rate variability. After acquisition of the baseline ECG recording, isoproterenol was infused at a rate of 2 μg/min until the heart rate was increased by 25 beats/min (31). The ECG signal was recorded continuously throughout the infusion period.

To further assess the sensitivity of the spectral analysis technique to alterations in parasympathetic tone and to compare the autonomic profile in normal subjects during parasympathetic blockade with that in patients with congestive heart failure, atropine (1 mg) was administered to an additional seven normal subjects after acquisition of baseline rest heart rate data. The ECG was recorded for ≥4 min after a stable increase in heart rate was noted (within 15 min of atropine administration in all subjects).

Spectral analysis of heart rate variability. The tape-recorded ECG signal was preprocessed with use of an antialiasing filter and digitized by means of a 12-bit analog/digital converter board (Metrobyte Co.) installed in an IBM/AT computer at a sampling rate of 512 Hz. Once digitized, the ECG signal was passed through a digital band pass filter having a central frequency of 85 Hz. A dynamic user-interactive threshold technique was applied to the filtered signal to detect the R waves and compute the RR interval sequence. Subsequently, the RR interval sequences were passed through a statistical filter to eliminate rapid transitions due to signal detection faults. Data points outside the 95% confidence interval of the previous 10 points were eliminated and a point derived by linear interpolation of the preceding and following points was substituted. A plot of the instantaneous heart rate versus time (heart rate variability signal) was generated from the RR interval sequence (32). The heart rate versus time series was then passed through a Parzen window and the power spectrum density of heart rate variability was generated with use of the modified periodogram method of Welch (33). This method is based on the multiple computation and average of the fast Fourier transform of overlapped data segments (33). With this method, the variance of the estimated power spectral density is reduced by a factor proportional to the number of data

segments used. The power spectral density was then normalized so that the total power was equal to the signal mean square. A plot of the values of the power spectrum density against frequency was then generated. An area under the curve method was used to quantify the power within specified frequencies. Specifically, the total area, the area under the low frequency (0.02 to 0.1 Hz) region of the curve, which reflects sympathetic nerve activity, and the high frequency (>0.1 Hz) region, which reflects parasympathetic tone, were calculated (12,13,16,23). In addition, to compare relative contributions of high and low frequency variability, the ratios of high frequency to total area, low frequency to total area and high frequency to low frequency area were computed. Thus, the relative balance of parasympathetic and sympathetic tone under varying conditions may be quantified by this system of analysis.

Prospective Evaluation of Autonomic Dysfunction in a Paced Canine Model of Congestive Heart Failure

Experimental preparation. To prospectively examine the evolution of autonomic dysfunction characteristic of congestive heart failure, analysis of heart rate variability was performed in a paced canine model of ventricular failure (27–29). The protocol was reviewed and approved by the Animal Use Committee of The Ohio State University. In four conditioned beagles, general anesthesia was maintained with vaporized halothane and nitrous oxide, and a screw-in unipolar pacemaker lead (Medtronic, model 5300) was passed through a jugular venous cutdown into the right ventricle. Under fluoroscopic guidance, the tip was positioned in the right ventricular apex and consistent capture of the ventricle was verified. A subcutaneous pocket for implantation of a pulse generator (Medtronic, model 5985) was made in the right scapular region, a subcutaneous tunnel for passage of the pacer lead to the pulse generator connection block was created and the implant pocket was closed.

Cardiac pacing protocol. After a 3-day recovery period, the dogs were lightly anesthetized with acepromazine (0.55 mg/kg body weight) and placed in the left lateral recumbent posture. A two-dimensionally directed M-mode echocardiogram was performed from the right parasternal window with a Hewlett-Packard 77020A ultrasound system. A scalar ECG lead was then recorded for 4 min using electrodes attached to the fore and hind limbs of the animal. The pacemaker was then programmed for a rate of 250 beats/min. After verification of consistent capture of the right ventricle, the dogs were returned to the animal care facility, where they were closely observed for physical signs of congestive heart failure.

At weekly intervals, the dogs were lightly anesthetized with acepromazine and placed in the left lateral recumbent posture. Pacing was interrupted for 30 to 40 min, during which time echocardiographic evaluation was performed and ECG signals for spectral analysis of heart rate variability were recorded. After ECG signals were obtained, pacing was resumed at 250 beats/min. This protocol was continued until the dogs exhibited symptoms of severe congestive heart failure, at which time they were killed by administration of sodium pentobarbital. The ECG signals were subsequently analyzed for heart rate variability and generation of power spectrum density as described for the studies in humans. Echocardiographic recordings were used to derive the percent fractional shortening of the left ventricle, defined as [(End-diastolic dimension − End-systolic dimension)/End-diastolic dimension] × 100% (34).

Statistical analysis. All data are presented as mean values ± 1 SD. Student's *t* test for unpaired data was used to compare the variables of heart rate variability between normal human subjects and patients with heart failure. The paired *t* test was used for comparison of changes in heart rate variability accompanying atropine and isoproterenol administration in humans and changes in variables of heart rate variability and in echocardiographic variables of ventricular performance during evolution of congestive heart failure in the canine model. Statistical significance was defined at the $p < 0.05$ level.

Results

Heart Rate Spectrum in Patients With Congestive Heart Failure and Normal Subjects

Normal versus congestive heart failure power density spectrum. A representative plot of instantaneous heart rate versus time in a normal subject is shown in Figure 1A. It is readily noted that higher frequency oscillations in heart rate are superimposed on slower cyclic variations. These features of the pattern of heart rate variability are represented in the power density spectrum and are displayed for this normal subject in Figure 2A. The spectrum is characterized by a significant degree of variability in both the high and the low frequency bands as quantified by the area under the curve determined for these regions (Fig. 3). In contrast to the normal subjects, in the patients with congestive heart failure the plot of heart rate versus time is characterized by a predominance of low frequency oscillations in heart rate and a paucity of high frequency variability (Fig. 1B). Accordingly, the power density spectrum in patients with congestive heart failure demonstrated a virtual absence of high frequency (>0.1 Hz) variability and an augmentation of the low frequency components of the spectrum (Fig. 2C). These differences in the normal and heart failure power density spectrum are quantified by a marked and statistically significant ($p < 0.05$) decrease in the parasympathetically mediated high frequency area under the curve in the patients with heart failure as compared with normal subjects (Fig. 3).

Further definition of the differing autonomic profile of the heart failure and normal groups is provided in the ratio between the areas bounded by the high and low frequency regions (Fig. 3). This ratio was 7 ± 6% in the congestive

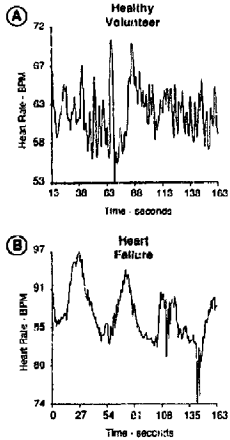

Figure 1. Representative plots of instantaneous heart rate in beats/min (BPM) **(vertical axis)** versus time in seconds **(horizontal axis)** for a normal subject **(A)** and a patient with congestive heart failure **(B)**. The normal subject displays both low and high frequency heart rate variability. In contrast, the patient with congestive heart failure has markedly diminished high frequency variations in instantaneous heart rate, with a predominance of low frequency variability.

heart failure group, which was significantly ($p < 0.01$) less than the ratio of 31 ± 25% noted in the normal group.

Finally, the low frequency region of the curve comprised a significantly ($p < 0.05$) greater proportion of the total area in the patients with heart failure than in the normal subjects (87 ± 14% vs. 77 ± 13%, respectively).

Influence of parasympathetic blockade and adrenergic stimulation on the heart rate power density spectrum. *Effect of atropine.* High frequency heart rate variability was greatly diminished after administration of atropine in normal subjects. The plot of instantaneous heart rate versus time demonstrated a marked decrease in the high frequency variations in heart rate (Fig. 4). This was further manifested in the power density spectrum of heart rate variation as a significant decrease in the region of the curve > 0.1 Hz (Fig. 2B). The high frequency area bounded by the power density spectrum decreased significantly ($p < 0.05$) in normal subjects after the administration of atropine and, in fact, fell into the range of the high frequency area noted in the congestive heart failure group (Fig. 2B and 3). Similarly, the high frequency/low frequency ratio significantly ($p < 0.005$) decreased with atropine administration and again was within the range observed in the patients with congestive heart failure (Fig. 3).

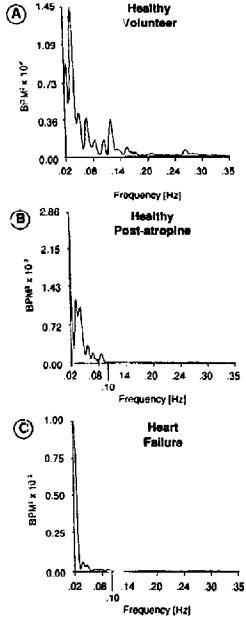

Figure 2. Power spectral density of heart rate variation in a normal subject (A), in the same subject after the administration of atropine (B) and in a patient with congestive heart failure (C). The normal subject has both high frequency (>0.1 Hz) and low frequency variability in heart rate. After atropine, there is a virtual absence of variability in the parasympathetically mediated frequencies >0.1 Hz. The spectrum in the patient with congestive heart failure resembles that seen in the normal subject after atropine in that there is an absence of variability at frequencies >0.1 Hz. In addition, in congestive heart failure, there is an augmentation of low frequency variability compared with the normal baseline value (note that the magnitude of the scale in C [10^{-3}] is 10 times that in A [10^{-4}]). BPM^2 = beats/min^2.

Effect of isoproterenol. Administration of isoproterenol was associated with the expected significant ($p < 0.05$) increase in the low frequency region of the curve (Fig. 5 and 6). Despite this increase, there was no significant change in the high frequency/low frequency area ratio (Fig. 6), and the ratio did not approach that noted in patients with congestive heart failure or in normal subjects after atropine administration (Fig. 4).

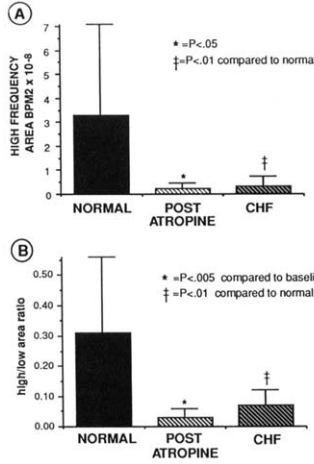

Figure 3. Mean ± SD of the parasympathetically mediated (>0.1 Hz) region of the power density spectrum of heart rate variability in normal subjects, normal subjects after the administration of atropine and patients with congestive heart failure (CHF). **A**, The high frequency area in patients with congestive heart failure is significantly less than that observed in normal subject at baseline. After administration of atropine in normal subjects, the high frequency area decreases significantly to within the range noted in the patients. **B**, Mean ± SD of the ratio of high to low frequency area in normal subjects, normal subjects after the administration of atropine and patients with congestive heart failure. The ratio is significantly lower in the patients than in the normal subjects. A significant decrease in the ratio is seen in normal subjects after atropine when the ratio decreases to the range noted in the patients. BPM2 = beats/min^2. ★ = p values in comparison with baseline values; ‡ = p values in comparison with values in normal subjects.

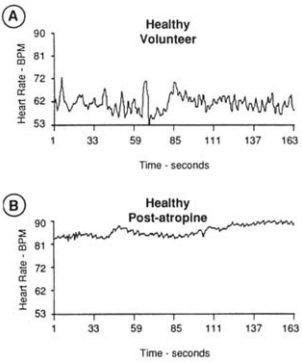

Figure 4. Instantaneous heart rate (**vertical axis**) versus time (**horizontal axis**) in a normal subject at baseline (**A**) and after the administration of atropine (**B**). Both are plotted on the same scale. A marked reduction in high frequency variability in instantaneous heart rate is noted after atropine. BPM = beats/min.

Autonomic Changes in the Paced Canine Model of Congestive Heart Failure

All four dogs developed progressive ventricular dysfunction as well as symptoms of congestive heart failure. Profound ventricular failure necessitating induced death occurred at periods ranging from 1 to 4 weeks of pacing (at 1 week in one dog, 3 weeks in two dogs and 4 weeks in the remaining dog). Rapid ventricular pacing was associated with a significant reduction in the percent fractional shortening of the ventricle, which was measured during interruption of pacing and which decreased from a baseline value of 28.3 ± 4.6% to 16.3 ± 4.1% ($p < 0.01$).

Effect on power density spectrum. The baseline power density spectrum was characterized by a predominance of the high frequency parasympathetically mediated region (Fig. 7). With evolution of congestive heart failure, there was a marked decrease in the parasympathetic region and an increase in the low frequency sympathetically mediated region of the spectrum (Fig. 7). This was quantified by a marked decrease in the area under the high frequency region from $8.4 \times 10^{-7} \pm 6.8 \times 10^{-7}$ to $0.16 \times 10^{-6} \pm 0.11 \times 10^{-6}$ (beats/min)^2, which showed a trend toward statistical significance ($p = 0.09$) and a significant ($p < 0.05$) decrease in the high frequency area/total area ratio from 70 ± 36% to 15 ± 9% (Fig. 8). The low frequency area/total area ratio increased significantly from 30 ± 36% to 84 ± 9% ($p < 0.05$). The high frequency/low frequency area ratio markedly decreased from 628 ± 503% to 19 ± 12% ($p = 0.09$) (Fig. 8).

Discussion

Autonomic dysfunction in heart failure. Although it has been recognized that chronic congestive heart failure is characterized by a marked augmentation of sympathetic drive, the contribution of the parasympathetic nervous system to the autonomic abnormalities that accompany ventricular failure have been less well described (1,6,18,23). In part because of methodologic limitations, it has been difficult to distinguish enhanced sympathetic drive from diminished parasympathetic tone as contributing factors to this autonomic imbalance. The current investigation builds on prior observations regarding autonomic balance in congestive heart failure and is unique in its contribution to the further understanding of autonomic dysfunction in the following: 1) Patients with congestive heart failure having nonischemic

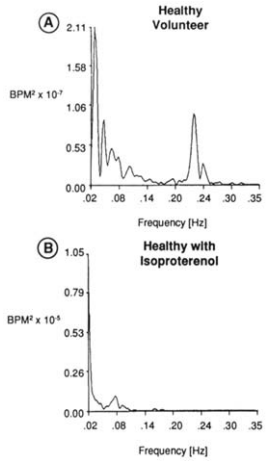

Figure 5. Power density spectrum in a normal subject at baseline (A) and during isoproterenol infusion (B). A marked increase in the low frequency region of the curve is noted with isoproterenol infusion, consistent with beta-adrenergic stimulation (note that the bottom scale is 100 times the baseline scale). BPM^2 = beats/min^2.

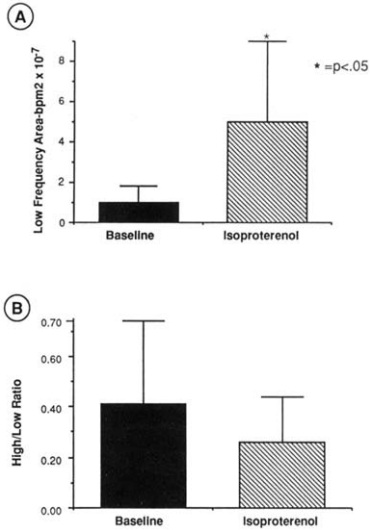

Figure 6. A. Mean ± SD of the area bounded by the low frequency (<0.1 Hz) region of the power density spectrum of heart rate variability in normal subjects at baseline and during isoproterenol infusion. A significant increase in the low frequency area is noted with isoproterenol infusion. **B.** Mean ± SD of the ratio of high to low frequency areas of the power density spectrum in normal subjects at baseline and during isoproterenol infusion. A small decrease in the ratio that does not attain statistical significance is noted. bpm2 = beats/min^2.

cardiomyopathy who were not receiving vasodilator medications were studied at supine rest. Therefore, the confounding influence of variables such as myocardial ischemia, vasodilator therapy and upright posture on the power density spectrum of heart rate variability were eliminated. 2) We demonstrated that normal subjects and patients with congestive heart failure can be differentiated on the basis of the ratios between the parasympathetically mediated high frequency and sympathetically influenced low frequency bands. Furthermore, the power density spectrum in normal subjects can be made to resemble that seen in patients with congestive heart failure through parasympathetic blockade but not beta-adrenergic stimulation alone. 3) The prospective confirmation of the evolution of these changes in the autonomic profile can be accomplished using an animal model of ventricular failure. 4) Significant autonomic changes associated with disease states and pharmacologic intervention may be noninvasively detected without the need for provocative techniques such as the analysis of heart rate response to alterations in blood pressure.

Analysis of heart rate variability as a measure of autonomic tone. The variability of physiologic signals such as heart rate has been found to be influenced by the autonomic nervous system (7–26). Furthermore, frequency-specific variations in heart rate variability that may be ascribed to the sympathetic and parasympathetic nervous systems have been defined (11,13,16). High frequency variations >0.1 Hz are governed exclusively by the parasympathetic nervous system (11,13,16). Conversely, the variability ascribed to sympathetic influence and mediated by beta-adrenergic activity are contained exclusively in the frequency band <0.1 Hz (11,13,16). Spectral analysis of heart rate variability allows quantification of the contribution of these specific frequency bands to the overall variability of heart rate (11,13,16, 17,19,23,33). As illustrated in Figure 2, the resultant power spectrum density may be simplistically interpreted as displaying on the vertical axis the magnitude of contribution of a specific frequency, represented on the horizontal axis, to overall heart rate variability (33). Thus, the power density spectrum in essence provides a dynamic map of the component limbs of the autonomic nervous system. Recent investigations (24) have demonstrated that analysis of the proportional frequency content of heart rate variability can be

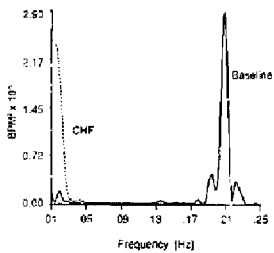

Figure 7. Power density spectrum of heart rate variation in a dog at baseline and after the induction of congestive heart failure (CHF) by rapid ventricular pacing. The baseline spectrum (solid line) demonstrates a prominent peak in the region >0.1 Hz consistent with a predominance of parasympathetic tone. With congestive heart failure (dotted line) there is a marked absence of variability >0.1 Hz and an augmentation of the low frequency region of the curve. BPM^2 = (beats/min)^2.

reflective of changes in sympathetic tone as measured by muscle sympathetic nerve activity.

Evidence for autonomic imbalance in congestive heart failure. Prior work by Eckberg et al. (6), utilizing pharmacologic manipulation of blood pressure and analysis of resultant heart rate responses, suggested that withdrawal of parasympathetic tone is a component of the autonomic dysfunction observed in congestive heart failure. However, the refinement of techniques for the assessment of heart rate variability has permitted an analysis of autonomic tone at rest without the need for provocative maneuvers (11–26). The current investigation utilized the technique of spectral analysis of heart rate variability as a probe of the sympathetic and parasympathetic limbs of the autonomic nervous system. The power spectral density of heart rate variability noted in the patients with heart failure in this investigation is consistent with a profound reduction in parasympathetic drive. This was demonstrated by the marked decrease in the high frequency region of the spectrum, which showed a 10-fold decrease in area compared with that in the normal subjects (Fig. 2 and 3). The unique capability of the spectral analysis technique to simultaneously display sympathetic and parasympathetic tone provides further evidence regarding the imbalance between these two limbs of the autonomic system as demonstrated by the high frequency/low frequency area ratio (Fig. 3). The greatly diminished value of this ratio in congestive heart failure combined with the significant reduction in absolute high frequency area demonstrates that the autonomic profile in congestive heart failure consists of an imbalance of autonomic tone comprising both an attenuation of parasympathetic activity and a predominance of sympathetic drive.

The use of sympathetic stimulation and parasympathetic blockade to selectively simulate the autonomic environment of congestive heart failure further confirms the integral contribution of attenuated parasympathetic tone to autonomic imbalance in ventricular failure. Atropine administered to normal

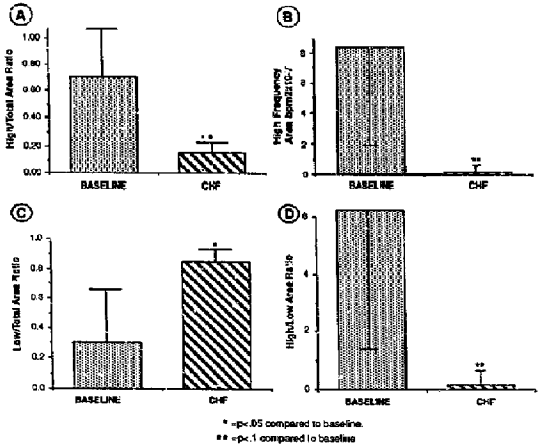

Figure 8. Mean ± SD of areas bounded by the heart rate power density spectrum and ratio of areas at baseline and after pacing-induced congestive heart failure (CHF) in dogs. **A**, A significant decrease in the ratio of the high frequency (>0.1 Hz) area to total area under the curve is noted with congestive heart failure, consistent with a withdrawal of parasympathetic tone. **B**, A decrease in absolute high frequency area is noted with congestive heart failure. **C**, The ratio of low frequency area to total area under the curve is significantly increased with congestive heart failure, indicating an augmentation of sympathetic drive. **D**, The ratio of high frequency area to low frequency area decreases with congestive heart failure, consistent with an imbalance of parasympathetic and sympathetic tone as compared with baseline. *p = <0.05 compared with baseline value; **p <0.1 compared with baseline value.

subjects resulted in a significant decrease in the high frequency area, which in fact did not differ significantly from the high frequency area noted in the patients with congestive heart failure (Fig. 3 and 4). Similarly, the high frequency/low frequency area ratio after atropine administration decreased to the range noted in congestive heart failure (Fig. 3). In contrast, the power density spectrum resulting from sympathetic stimulation alone did not completely mimic that noted in the patients with congestive heart failure (Fig. 5 and 6). Although the low frequency portion of the spectrum was increased, as is expected with beta-adrenergic stimulation (12,13,16,25,30), there was relatively little change in the high frequency area. The relative proportion of high frequency variability as reflected by the high frequency/low frequency area ratio decreased insignificantly and did not approach the range observed in the patients with heart failure. These findings demonstrate that augmented sympathetic drive itself does not mimic the heart rate variability spectrum of congestive heart failure and emphasizes that parasympathetic withdrawal is a necessary component of the autonomic profile characteristic of chronic ventricular failure. Accordingly, the high to low frequency area ratio in this group of patients appears to be a variable that effectively discriminates between normal subjects and patients with ventricular dysfunction.

Evolution of autonomic dysfunction in the canine model of congestive heart failure. The changes in the heart rate power density spectrum that are observed in the canine model of congestive heart failure closely parallel those noted in the patients with congestive heart failure (Fig. 7 and 8). Although prior investigations (21,23,27,28) utilizing this model demonstrated the evolution of humoral changes characteristic of human congestive heart failure, there have been no reports describing the autonomic imbalance that accompanies ventricular failure in this model.

The baseline power spectral density in this model reflects the well recognized predominance of parasympathetic tone characteristic of dogs (Fig. 7) (13,16). This baseline profile is in marked contrast to that noted during the evolution of ventricular failure. With clinical and echocardiographic evidence of ventricular dysfunction, the heart rate power spectral density displays a virtual absence of high frequency variability and a pronounced augmentation of the low frequency region of the curve. Like the spectrum observed in humans with congestive heart failure, there is an impressive decrease in the ratio of the high to the low frequency area as heart failure develops, indicative of an autonomic imbalance comprising parasympathetic withdrawal and augmented sympathetic drive. That an exact parallel in the changes in the power spectral density is observed under the controlled conditions of the canine model substantiates the concept that the autonomic imbalance observed in the patients with heart failure is an integral response to ventricular failure.

Relation of previous studies and limitations of the current study. The current observations provide direct evidence regarding the balance between sympathetic and parasympathetic tone at rest in normal subjects and patients with congestive heart failure. A few previous investigations (23) have utilized the heart rate power spectrum density to assess autonomic tone in congestive heart failure. However, unlike prior reports (6,35) in which ambulatory heart rate recordings were obtained in patients treated with vasodilator medications, this investigation was undertaken in the absence of vasodilator therapy and under controlled conditions of supine rest, thus eliminating the confounding variables of drug therapy and the autonomic changes induced by upright posture.

Other factors that may influence the power density spectrum independent of the process of congestive heart failure include the influence of pharmacologic agents, particularly digoxin, age and the modulation of heart rate variability by respiratory rate. Although a subgroup of the patients with congestive heart failure were maintained on stable doses of digoxin, the anticipated autonomic effects of this agent would tend to normalize the pattern of heart rate variability and thus minimize rather than artificially accentuate differences between normal subjects and patients with congestive heart failure (36–39). Although the mean age of the patients with congestive heart failure and the normal subjects was different, recent evidence (25) suggests that parasympathetically mediated high frequency variation in the heart rate decreases until 30 years of age (the approximate mean age of the normal control group in this report). Thus, although not chronologically equal, the two groups would appear to be biologically equivalent in terms of age-dependent high frequency heart rate variability (29).

Although respiratory rate was not strictly controlled in this investigation, the respiratory rate of patients with congestive heart failure typically exceeds that of normal subjects. As a result, parasympathetically mediated high frequency heart rate variability would be augmented, thus minimizing differences between the two groups. That parallel autonomic changes evolve in the canine model of congestive heart failure, in which such intergroup differences in these variables do not play a role, further substantiates the conclusion that the different patterns in heart rate variability in normal subjects and patients with congestive heart failure may be ascribed to autonomic changes occurring with the development of ventricular failure.

Clinical implications. The contribution of attenuated parasympathetic tone to the abnormal circulatory function typical of congestive heart failure must be further defined on the basis of the current observations. The parasympathetic limb of the autonomic nervous system is the high frequency response component of the system (11,13,16). It would thus appear to be necessary for rapid autonomic mediation of vascular control and homeostasis. The inability to rapidly modulate vascular dynamics in response to a given perturbation may contribute to further inefficiencies in circulatory function and potentially contribute to progressive ventricular failure. Attenuation of parasympathetic tone may contribute to the high incidence of lethal ventricular arrhythmias seen in congestive heart failure. Kleiger et al. (40) reported a higher incidence of sudden death in patients recovering from

myocardial infarction, having a shift in the balance of the heart rate power density spectrum toward the lower frequency bands and away from the parasympathetically mediated high frequency regions.

Conclusions. Spectral analysis of heart rate variability provides a window on the autonomic nervous system that can be applied to further elucidate the mechanisms of vascular control in congestive heart failure. Application of this noninvasive technique for the analysis of autonomic tone in patients with congestive heart failure and in an animal model of ventricular failure demonstrates an autonomic imbalance consisting of both an attenuation of parasympathetic tone and an augmentation of sympathetic drive. The manner in which the autonomic changes that accompany progressive ventricular failure mediate changes in cardiovascular homeostasis may be further examined in future studies employing this technique.

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