Autonomic pathophysiology in heart failure patients. Sympathetic-cholinergic interrelations.

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Research Article

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Autonomic Pathophysiology in Heart Failure Patients

Sympathetic–Cholinergic Interrelations

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Abstract

We conducted this study in an effort to characterize and understand vagal abnormalities in heart failure patients whose sympathetic activity is known. We measured sympathetic (peroneal nerve muscle sympathetic recordings and antecubital vein plasma norepinephrine levels) and vagal (R–R intervals and their standard deviations) activities in eight heart failure patients and eight age-matched healthy volunteers, before and after parasympathomimetic and parasympatholytic intravenous doses of atropine sulfate. At rest, sympathetic and parasympathetic outflows were related reciprocally: heart failure patients had high sympathetic and low parasympathetic outflows, and healthy subjects had low sympathetic and high parasympathetic outflows. Low dose atropine, which is known to increase the activity of central vagal-cardiac motoneurons, significantly increased R–R intervals in healthy subjects, but did not alter R–R intervals in heart failure patients. Thus, our data document reciprocal supranormal sympathetic and subnormal parasympathetic outflows in heart failure patients and suggest that these abnormalities result in part from abnormalities within the central nervous system. (*J. Clin. Invest.* 1990. 85:1362–1371.) microneurography • norepinephrine • sinus arrhythmia • atropine • parasympathetic • sympathetic

Introduction

Although it is accepted widely that heart failure patients have increased levels of sympathetic nervous activity (1–4), mechanisms underlying their hyperadrenergic state are poorly understood, and interrelations between sympathetic and parasympathetic outflows in heart failure patients have not been studied. We characterized sympathetic–parasympathetic interrelations in heart failure patients and age-matched healthy subjects, and attempted to clarify pathophysiologic mechanisms that may be operative. We asked the following questions: Does relative absence of vagally mediated respiratory sinus arrhythmia in heart failure patients (5) mean that respiratory rhythms are not present within their central nervous systems? Do high levels of sympathetic activity in heart failure patients mean that their sympathetic motoneurons receive no inhibitory input from baroreceptors? Do heart failure patients have subnormal levels of vagal activity because their central vagal motoneurons function abnormally?

Methods

Subjects. We studied seven men and one woman with New York Heart Association functional class (6) II–IV congestive heart failure (selected on the basis of clinical criteria [7]), and eight age-matched healthy men after they gave written consent to participate in this approved study. The age of heart failure patients (±SEM) averaged 45±3 (range 35–58) yr, and the age of healthy subjects averaged 37±5 (range 26–64) yr ($P = 0.244$, unpaired t test). No healthy subject was taking medication at the time of study. Clinical characteristics of patients are listed in Table I.

Measurements. Subjects were studied supine in a quiet room. (Three heart failure patients were dyspneic in the recumbent position and were studied at 10–30° head-up elevation.) We recorded the electrocardiogram, R–R intervals, tidal volume (quantitative, but uncalibrated Respitrace Respiration Monitor [Non-Invasive Monitoring Systems, Miami Beach, FL]), arterial pressure (Dinemap, Critikon, Inc., Tampa, FL), and peroneal nerve muscle sympathetic activity.

Plasma norepinephrine. Antecubital vein plasma norepinephrine concentrations were measured with high-performance liquid chromatography with electrochemical detection as described previously (8). Our method detects plasma norepinephrine levels as low as 10 pg/ml, with an intraassay coefficient of variation of 5.6%.

Muscle sympathetic nerve activity. Multiunit postganglionic muscle sympathetic nerve traffic was recorded in the peroneal nerve at the fibular head with tungsten microelectrodes with uninsulated tips of about 1–5 μm, as described previously (9). Nerve activity was amplified 70,000 times, fed through a band-pass filter (700–2,000 Hz) and an amplitude discriminator, and integrated with a resistance-capacitance circuit with a time constant of 0.1. Muscle fascicles were identified by characteristic afferent activity elicited by passive stretch applied to muscle bellies. Muscle sympathetic nerve activity was identified by its cardiac and respiratory periodicities, and by its failure to increase with arousal stimuli.

Echocardiograms. Two-dimensional echocardiograms were obtained in six patients and four healthy subjects with a mechanical sector scanner (MK-300, Advanced Technology Laboratories, Bellevue, WA) to determine the influence of atropine on systolic left ventricular function. Measurements of left ventricular end-diastolic and end-systolic dimensions were made with M-mode echocardiography (10). Five optimal cardiac cycles were evaluated and measurements were averaged. Left ventricular end-diastolic and end-systolic volumes were calculated according to the method of Teichholz et al. (11). Stroke volume was derived by subtraction of end-systolic from end-diastolic volumes.

Atropine. Atropine sulfate was given serially in doses chosen to elicit both central parasympathomimetic and peripheral parasympatholytic effects (12). In preliminary studies in nine healthy subjects, atropine was given intravenously in cumulative doses of 1, 2, 3, 4, 5, 7.5, and 10 μg/kg (Fig. 1). All subjects had R–R interval prolongation with doses of 1, 2, and 3 μg/kg atropine. The greatest R–R interval

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Table I. Clinical Characteristics of Heart Failure Patients

No.	Age	Etiology of heart disease	Electrocardiogram abnormalities	NYHA functional class	Pulmonary capillary wedge pressure	Ejection fraction	Cardiac index	Medicines
					mmHg	*%*	*liter/min per M^2*	
1	42	Ischemic	Inferior infarction	III	29	27	2.3	Captopril Digoxin Furosemide Hydrochlorothiazide Nitroglycerin
2	41	Ischemic	First-degree atrioventricular block	II	10	18	2.9	Digoxin Furosemide Nitroglycerin Procainamide
3	57	Ischemic	Anterior infarction	IV	25	10	1.5	Albuterol Captopril Digoxin Diltiazem Furosemide Isosorbide
4	39	Cardiomyopathy	Left ventricular hypertrophy	II	4	23	4.0	Azathioprine Captopril Furosemide Prednisone
5	42	Aortic regurgitation	Left ventricular hypertrophy	III	8	37	2.5	Spironolactone Digoxin Hydrochlorohiazide Quinidine
6	56	Ischemic	Left bundle branch block	III	20	22	2.1	Digoxin Furosemide Metolazone Nitroglycerin Tocainide Verapamil
7	40	Cardiomyopathy		II	6	37	2.4	Digoxin Procainamide Verapamil
8	41	Ischemic		III	16	27	2.6	Diltiazem Isosorbide

prolongation occurred after the 3-μg/kg dose in six subjects, and after 2- and 4-μg/kg doses in two and one subjects. On the basis of these measurements, we chose two cumulative parasympathomimetic (1 and 3 μg/kg) and one parasympatholytic dose (10 μg/kg) for use with study subjects. Dose-ranging studies were not performed with heart failure patients; our results (see below) indicate that low dose atropine does not exert parasympathomimetic effects in heart failure patients.

Protocol. Subjects rested for 20 min after intravenous lines were established and a satisfactory nerve recording site was found. Measurements were obtained during uncontrolled and frequency-controlled (at about 12 breaths/min) breathing. Measurements were made before and 1.0–4.5 min after injections of 5 ml of saline and cumulative atropine doses of 1, 3, and 10 μg/kg. Measurements made after saline injections were used for statistical analysis of baseline characteristics.

Data analysis. Data from experimental animals (13) and humans (14) suggest that if sympathetic motoneurons receive inhibitory input from arterial baroreceptors, their firing rhythm is entrained by the cardiac rhythm. Therefore, we considered that entrainment of sympathetic activity would provide inferential evidence that high levels of sympathetic activity in heart failure patients are not due to absence of inhibitory baroreceptor input. We performed cross-spectral density analyses on baseline electrocardiogram and integrated muscle sympathetic nerve recordings for all subjects, to derive a mathematically rigorous measure of the degree of correlation between the two signals in the frequency domain (15). FM recordings of electrocardiograms and integrated muscle sympathetic nerve signals during controlled breathing and saline infusions were fed through a bandpass filter (0.3–50 Hz) to remove trends and higher frequency oscillations, and digitized at a rate of 100 Hz. Cross spectral analyses were performed by a computer (model 3081, IBM Corp., New York) with PROC SPECTRA, SAS 5.18 software (SAS Institute, Cary, NC). Statistical significance was determined by calculation of 95% confidence intervals above and below the coherence function. If the lower confidence interval lay above 0.50, coherence at that frequency was considered to be significant (16).

Sympathetic traffic was quantified in two ways. First, the number and height of all sympathetic bursts occurring in 210-s blocks of data were measured. Average baseline voltage during sympathetic silence was subtracted from voltage of individual sympathetic bursts to derive burst height. Sympathetic activity was quantified as bursts per minute, bursts/100 heart beats, and bursts per minute times average burst height. For the last measure, the highest control burst for each subject was assigned a value of 1, and all other bursts were normalized against this standard.

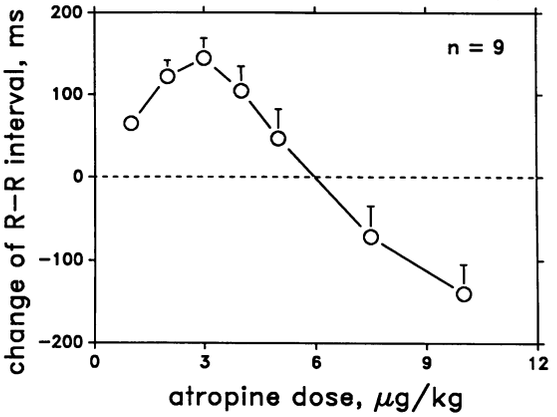

Figure 1. Atropine dose–sinus node response relation. On the basis of this preliminary study conducted in healthy subjects, we chose two parasympathomimetic doses (1 and 3 μg/kg) and one parasympatholytic dose (10 μg/kg) of atropine to study subjects. Brackets encompass 1 SEM.

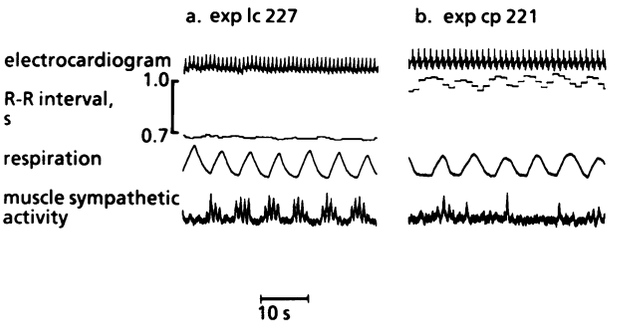

Figure 2. Representative recordings obtained from a patient with heart failure and a healthy subject. Compared with the healthy subject, the patient (*left*) had shorter average R–R intervals, less variability of R–R intervals, and higher levels of baseline sympathetic activity than the healthy subject (*right*).

Secondly, sympathetic bursts were averaged according to their timing in respiratory cycles, as described previously (17). Briefly, an electronic threshold crossing was placed on about the first third of inspiration. If an R wave occurred within 0.5 s after this threshold crossing, a 10.2-s data sweep was collected by a processing digital oscilloscope (model 3001, Norland Instruments, Ft. Atkinson, WI). Each block of data comprised 3.1 s before, and 7.1 s after the occurrence of the early inspiratory R wave. After all bursts had been identified, the highest burst that occurred was assigned a value of 1,000, and all other bursts for that subject were normalized against this standard. Then, neurograms were advanced 1.35 s to compensate for delays in perpheral sympathetic nerve conduction. Finally, after all records had been processed, data from heart failure and healthy groups of subjects were averaged.

Statistical analysis. Data are presented as mean values±SEM. Since sample size was small, and since Kolmogorov-Smirnov analysis (18) indicated that several sets of data were not distributed normally, nonparametric statistical tests were used for most analyses (19). Baseline measurements from the two groups were compared with the Mann-Whitney-Wilcoxon test (19). Correlations between normally distributed measurements were evaluated with least squares linear regression (20). When the directions of responses could be predicted on the basis of published data, one-tailed tests were used.

Responses to atropine were compared as follows: First, rank transformations were made after baseline measurements were subtracted. This partly controlled for differences between baseline characteristics of the two groups. Then, repeated measures analysis was used to identify significant overall effects over the four treatment levels (saline and 1-, 3-, and 10-μg/kg atropine doses). Since a significant ($P = 0.0002$) treatment-by-group interaction was found, and overall parallelism could not be established between the two groups, a test for overall significance across treatment levels could not be done. Analysis of variance was used on rank scores to test for treatment effects within each group after baseline differences were controlled. When these were significant, Tukey's multiple comparison test was used at $\alpha = 0.05$ to determine where significant differences lay.

Results

Baseline characteristics. Fig. 2 shows representative baseline recordings from a heart failure patient and a healthy subject. R–R intervals were shorter, and the variability of R–R intervals was less in the patient with heart failure (*left panel*) than in the healthy subject (*right panel*). The patient also had more sympathetic activity than the healthy subject (57.4 vs. 14.7 bursts/min), and his baseline plasma norepinephrine level (not shown) also was greater (2,345 vs. 180 pg/ml).

Table II lists average baseline measurements from all patients and healthy subjects. Systolic and diastolic pressures and respiratory rates were similar in heart failure patients and healthy subjects. Stroke volumes and cardiac outputs (not listed) were significantly less in heart failure than healthy subjects ($P = 0.046$). Parasympathetic activity, as reflected by average R–R intervals and their standard deviations was less in heart failure patients than healthy subjects ($P = 0.041$ and $P = 0.003$). Sympathetic activity, as reflected by sympathetic bursts per minute, bursts/100 heart beats (both $P = 0.001$), and bursts per minute times average burst height ($P = 0.040$), and antecubital vein plasma norepinephrine concentrations ($P = 0.005$) was significantly greater in heart failure patients than healthy subjects.

Correlations among baseline measurements. There were loose but significant linear correlations between baseline R–R intervals and their standard deviations ($r = 0.60$, $P = 0.013$), and between sympathetic bursts per minute and plasma norepinephrine ($r = 0.76$, $P = 0.003$) and epinephrine levels ($r = 0.69$, $P = 0.030$). There was a strong respiratory periodicity in muscle sympathetic nerve recordings in both heart failure patients and healthy subjects (Figs. 2 and 3).

Fig. 4 shows correlations between R waves and sympathetic bursts as a coherence value for a heart failure patient and a healthy subject. In this figure, the cross-hatched area encompasses 95% confidence intervals above and below mean coherence. Significant coherence between sympathetic activity and electrocardiographic R waves was found at a frequency of 79 in the heart failure patient and 71 beats/min in the healthy subject. Results from coherence analyses for all patients and healthy subjects are listed in Table III. In this table, the frequency that yielded the largest coherence value was in most instances virtually identical to each subject's baseline heart rate. 14 of the 16 subjects (7 from each group) had significant correlations between their electrocardiograms and muscle sympathetic nerve activity at their heart rates. These data provide inferential evidence that in almost all patients and healthy subjects studied, muscle sympathetic motoneurons received inhibitory inputs from arterial baroreceptors.

Fig. 5 shows relations between sympathetic outflow and R–R interval standard deviations. Correlations between mus-

Table II. Baseline Characteristics of Heart Failure Patients and Healthy Subjects

No.	Systolic pressure	Diastolic pressure	Respiratory interval	R–R interval	Standard deviation of R–R interval	Plasma norepinephrine	Plasma epinephrine	Muscle sympathetic activity, normalized, arbitrary units: Bursts/min	Bursts/min · height	Bursts/100 heart beats
	mm Hg		*s*	*ms*		*pg/ml*				
Heart failure patients										
1	103	69	2.61	762	12	1,498	—	74	10	95
2	103	60	2.85	1,009	26	—	—	41	5	70
3	105	67	4.98	694	8	2,128	213	53	5	61
4	151	79	3.33	776	27	562	90	68	13	89
5	131	83	4.95	903	16	1,290	115	49	8	74
6	112	64	2.11	802	8	1,406	189	50	6	67
7	105	67	7.33	653	21	—	—	55	8	60
8	97	75	5.83	616	9	2,613	552	95	11	98
Mean	116	70	4.25	778	15	1,438	232	58	8	74
SEM	7	3	1.82	46	3	213	83	1	4	5
Healthy subjects										
9	137	80	4.99	882	77	312	33	28	5	38
10	120	81	4.91	813	45	201	—	25	3	34
11	136	94	3.59	646	34	920	50	42	5	50
12	108	74	—	979	49	285	45	26	4	43
13	132	76	4.93	991	98	352	23	17	9	28
14	102	65	4.60	1,100	76	—	—	23	5	41
15	109	61	5.41	955	27	250	26	18	3	29
16	131	69	3.40	971	50	263	—	27	6	44
Mean	122	75	4.55	918	57	369	35	26	5	38
SEM	5	4	0.76	44	9	94	16	2	1	3
Statistical significance, heart failure vs. healthy subjects (Mann-Whitney-Wilcoxon test):										
P =	0.103	0.290	0.690	0.041	0.003	0.005	0.011	0.001	0.041	0.001

cle sympathetic nerve activity in bursts per minute (*upper panel*), and plasma norepinephrine concentrations (*lower panel*) were fitted best after log transformations of standard deviations ($r = 0.80$, $P = 0.0002$, and $r = 0.89$, $P = 0.0001$). There also were inverse correlations (not shown) between logs of R–R interval standard deviations and sympathetic bursts/100 heart beats ($r = 0.72$, $P = 0.002$), bursts per minute times average burst height ($r = 0.55$, $P = 0.096$), and norepinephrine concentrations ($r = 0.87$, $P = 0.001$). With one exception, significance of correlations was lost when baseline data from heart failure and healthy groups were treated separately. The exception was the significant ($r = 0.88$, $P = 0.021$) inverse relation between plasma norepinephrine concentrations and R–R interval standard deviations in heart failure patients. This relation was not significant in healthy subjects ($r = 0.20$, $P = 0.66$).

Responses to atropine. Figs. 6 and 7 show responses of heart failure patients and healthy subjects to 3- and 10-μg/kg doses of atropine. In heart failure patients, low dose atropine (3 μg/kg) did not prolong average R–R intervals (average values were 778±46 ms after saline and 794±48 ms after 3 μg/kg atropine, $P > 0.99$), and high-dose atropine (10 μg/kg) shortened average R–R intervals significantly (to 673±34 ms, $P = 0.001$). In healthy subjects, low-dose atropine lengthened average R–R intervals significantly, from 918±44 to 1012±36 ms ($P \leq 0.050$), and high-dose atropine shortened average R–R intervals significantly, to 649±50 ms ($P = 0.001$). Average R–R interval lengthening after the cumulative 1- and 3-μg/kg (parasympathomimetic) doses of atropine, and shortening after the 10-μg/kg (parasympatholytic) dose of atropine were significantly ($P = 0.014$, $P = 0.0003$, and $P = 0.010$) less in patients than healthy subjects (Fig. 7).

Fig. 8 illustrates a third way to characterize interrelations between sympathetic and parasympathetic outflows. In this figure, baseline muscle sympathetic nerve activity (in bursts per minute) is plotted as a function of the average R–R interval after the parasympathomimetic dose of atropine (3 μg/kg) less the average R–R interval after the parasympatholytic dose of atropine (10 μg/kg). The relation for all subjects combined was described well by a quadratic equation ($r = -0.73$, $P = 0.007$). There was almost complete separation of measurements between the two groups: all R–R interval changes measured in healthy subjects were larger than the largest change measured in heart failure patients, and with one exception, baseline sym-

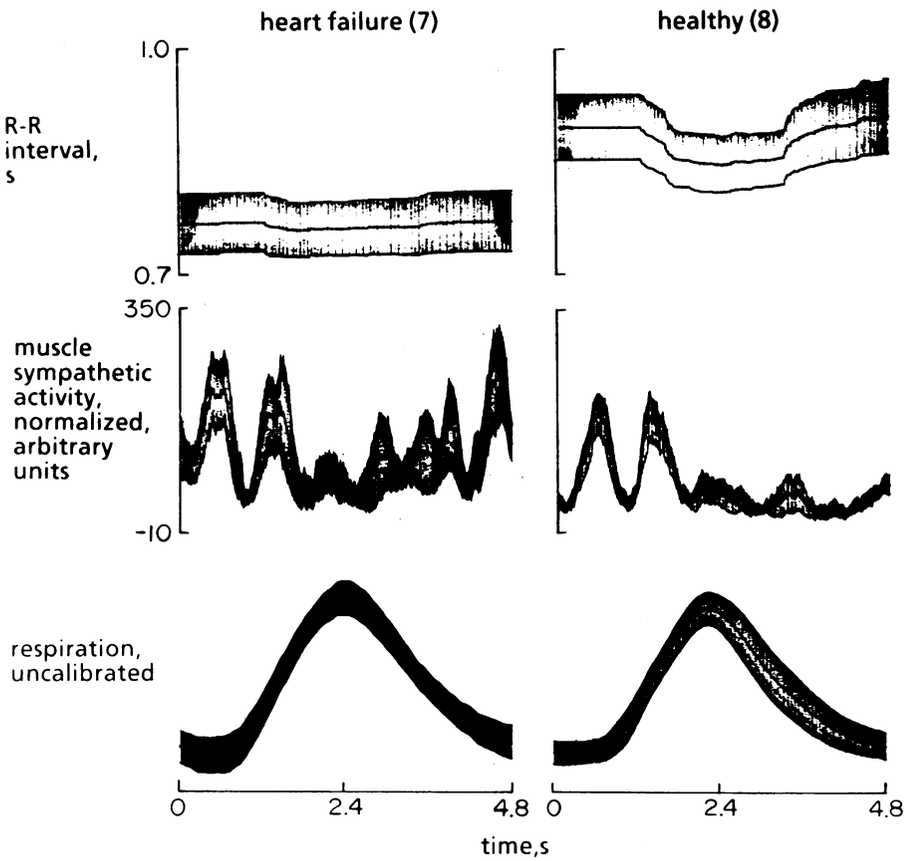

Figure 3. Respiratory modulation of autonomic outflow. Mean (±SEM) R–R intervals and muscle sympathetic nerve activity averaged over a single breath (control observations, after saline injection). The timing and magnitude of changes of sympathetic activity were comparable in heart failure patients and healthy subjects; the magnitude of R–R interval changes was significantly ($P = 0.007$) less in heart failure than healthy subjects.

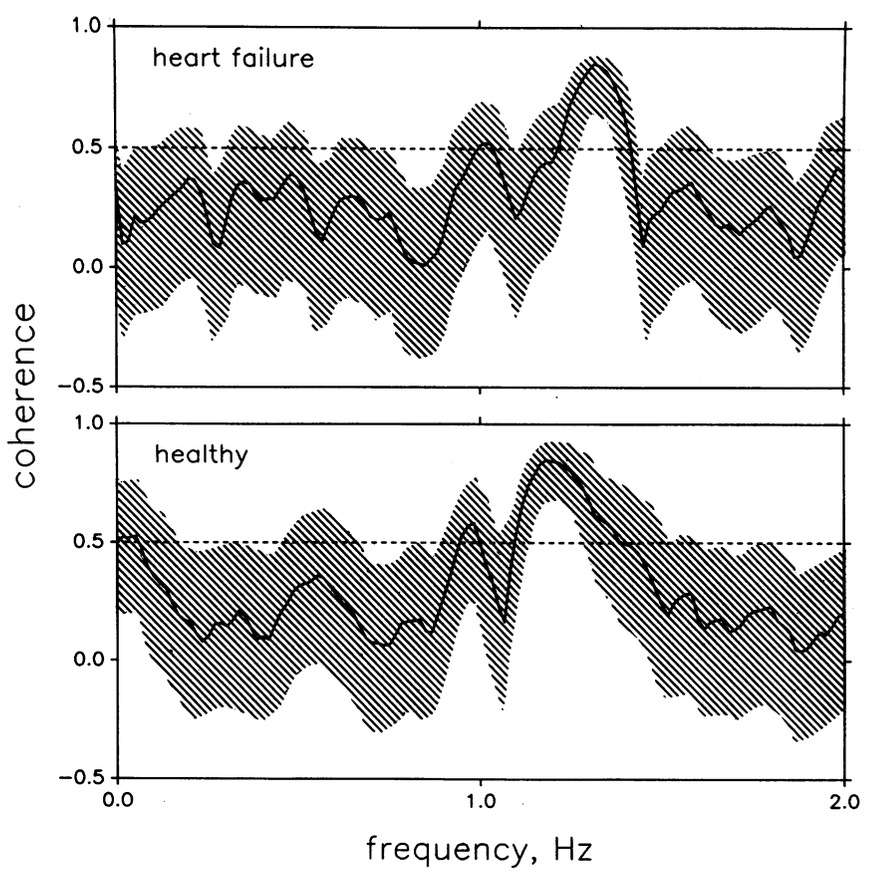

Figure 4. Electrocardiogram-muscle sympathetic correlograms. Correlation between electrocardiographic R waves and muscle sympathetic bursts shown as a coherence function for one heart failure patient (No. 4, *upper panel*) and one healthy subject (No. 14, *lower panel*). The cross-hatched area encompasses 95% confidence intervals above and below the coherence function. Correlations between cardiac and sympathetic periodicities were considered to be significant when lower confidence limits lay above 0.50 (see Methods).

Table III. Coherence Analysis for All Subjects

Subject	Frequency	Coherence	Confidence interval	
			Lower	Upper
Heart failure				
1	0.85	0.92	0.83	0.96
2	1.55	0.94	0.87	0.97
3	1.15	0.77	0.55	0.88
4	1.32	0.85	0.69	0.92
5	1.00	0.93	0.85	0.96
6	1.25	0.97	0.94	0.99
7	1.33	0.99	0.94	0.99
8	0.93	0.73	0.29	0.78
Healthy				
9	1.18	0.88	0.75	0.94
10	0.93	0.81	0.62	0.90
11	0.93	0.84	0.67	0.91
12	1.52	0.81	0.63	0.90
13	1.05	0.84	0.67	0.91
14	1.18	0.85	0.69	0.92
15	1.02	0.92	0.83	0.96
16	1.00	0.64	0.34	0.80

pathetic activity was higher in heart failure patients than the highest sympathetic activity measured in healthy subjects.

The exception was a healthy subject (No. 11, Table II), who differed from other healthy subjects and patients in other ways: although he is not hypertensive, he had the highest diastolic pressure (94 mm Hg) of any subject studied; the smallest baseline R–R interval (646 ms) of all but one subject (a heart failure patient); the highest plasma norepinephrine concentration (920 pg/ml) of any healthy subject, which was 2.6 times the level of the next highest healthy subject; and the greatest R–R interval shortening after the parasympatholytic atropine dose (476 ms, or, from a heart rate of 73–174 beats/min) of any subject. Exclusion of this subject as an outlier (which he is [21]) further increased the significance of differences between muscle sympathetic nerve activity and plasma norepinephrine in heart failure and healthy subjects.

Average standard deviations of R–R intervals did not in-

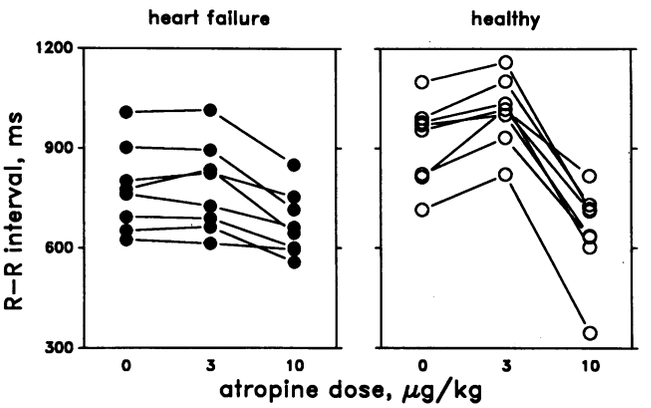

Figure 6. Individual responses to atropine. Individual responses of heart failure patients and healthy subjects to parasympathomimetic (3 μg/kg) and parasympatholytic (10 μg/kg) doses of atropine.

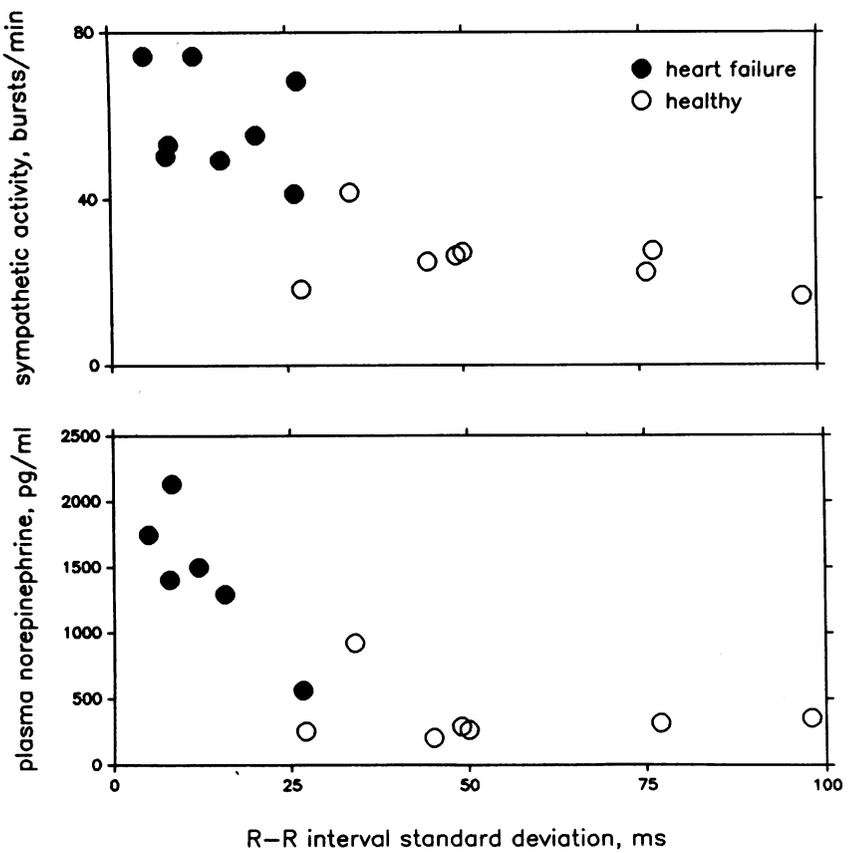

Figure 5. Sympathetic–parasympathetic interrelation. Baseline sympathetic activity (measured directly, above, or indirectly as plasma norepinephrine concentrations, below), plotted as a function of R–R interval standard deviation. For the entire material, significant inverse relations were found between sympathetic activity measured directly (*upper panel*) or indirectly (*lower panel*) and log transformations of standard deviations ($r = 0.80$, $P = 0.0002$ and $r = 0.89$, $P = 0.0001$). For data from healthy subjects (○) alone, there was no significant relation between resting sympathetic and parasympathetic outflows.

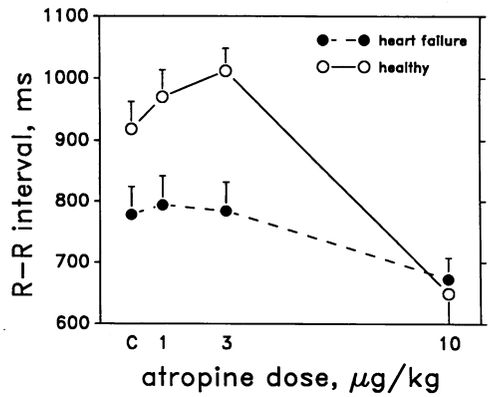

Figure 7. Group responses to atropine. Average R–R intervals for heart failure patients and healthy subjects after saline injections (*C*) and after cumulative atropine doses of 1, 3, and 10 μg/kg. The first three average R–R intervals were significantly shorter in heart failure patients than healthy subjects (P = 0.040, 0.030, and 0.002).

crease significantly after the two low doses of atropine in either group; however, in healthy subjects (but not heart failure patients), standard deviations fell significantly (P = 0.007) after the 10-μg/kg dose of atropine. Systolic and diastolic pressures were not altered significantly by atropine in either group. Muscle sympathetic nerve activity in bursts/min and plasma norepinephrine levels were not affected significantly by atropine in either group; however, sympathetic activity expressed as bursts/100 heart beats declined significantly in both groups after the cumulative parasympatholytic dose (10 μg/kg) of atropine. In patients, the reduction was from 74±4 to 57±7, and in healthy subjects, the reduction was from 38±3 to 19±4 bursts/100 heart beats (P = 0.008 for both groups). In six heart failure patients and four healthy subjects, echocardiographic measurements suggested that atropine does not reduce left ventricular stroke volume.

Discussion

Our data provide new insights into autonomic pathophysiology in heart failure. First, heart failure patients have significant, reciprocally related elevations of sympathetic and depressions of parasympathetic activity at rest. Secondly, heart failure patients have strong central respiratory modulation of sympathetic outflow, but lack important respiratory modulation of vagal outflow. Thirdly, patients do not respond to parasympathomimetic doses of atropine, which are known to exert their effects within the central nervous system. Fourthly, neither small nor large intravenous doses of atropine alter muscle sympathetic outflow, expressed as sympathetic bursts per minute. Fifthly, responses of heart failure patients to parasympatholytic doses of atropine are subnormal, and are inversely, not directly related to their resting levels of sympathetic activity.

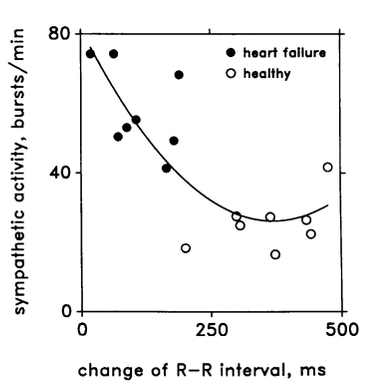

Figure 8. Baseline sympathetic activity related to atropine responses. Relation between the shortening of R–R interval that occurred between the cumulative atropine doses of 3 and 10 μg/kg and baseline sympathetic activity for all subjects. These data were modeled well by a quadratic function (r = −0.73, P = 0.007).

Reciprocal abnormalities of baseline sympathetic and parasympathetic activity. We found reciprocal abnormalities of resting sympathetic and parasympathetic cardiovascular outflows in heart failure patients. Ours is the third article which documents increased levels of directly measured sympathetic traffic in heart failure patients (4, 48). Several of our findings are in agreement with those of Leimbach and co-workers (4). We assume that the high levels of sympathetic traffic we recorded in muscle sympathetic neurograms reflect high levels of sympathetic traffic to the heart. Hasking and co-workers (3) reported that increased antecubital vein plasma norepinephrine levels in heart failure patients (which correlate strongly with muscle sympathetic nerve activity [4]; this study) are associated with increased norepinephrine spillover from the myocardium.

Our study also points toward decreased levels of vagal-cardiac nerve activity in heart failure patients, as reflected by baseline R–R intervals and their standard deviations. Although it long has been recognized that heart failure patients have rapid heart rates, we are aware of only two other studies (from one group [5, 22]) which document in heart failure patients reduced heart rate variability. In some of the patients we studied, standard deviations were almost as low as those found in heart transplant patients (5, 23, 24), whose donor sinus nodes are denervated. Two patients had baseline R–R interval standard deviations of 8 and 5 ms. Subnormal R–R interval shortening after parasympatholytic doses of atropine in heart failure patients (Figs. 5 and 6) provides additional indirect evidence for decreased levels of vagal-cardiac activity in heart failure patients. This finding confirms observations made earlier in patients with heart diseases by Müller in 1891 (25), Crawford in 1923 (26), and Eckberg et al. in 1971 (27).

Our findings of reciprocal elevation of sympathetic, and depression of parasympathetic, outflows may be related to those of earlier studies. Jose and Taylor (28) measured heart rate changes after large doses of atropine and propranolol, and found that although all healthy subjects experienced tachycardia after combined β-adrenergic and parasympathetic blockade, several patients with functionally severe heart disease experienced bradycardia. This suggests that in heart failure patients, levels of sympathetic activity are high, levels of parasympathetic activity are low, and there is little resting vagal-cardiac nervous outflow to oppose. Also, Goldstein (29) showed in 54 hypertensive and normotensive subjects that plasma norepinephrine concentrations are related inversely to the slopes of vagally mediated baroreflex responses to bolus phenylephrine injections. The shape of the relation he defined is similar to that which we observed in heart failure patients (Fig. 5).

Although our entire material (including heart failure and healthy subjects) points toward a reciprocal relation between resting levels of muscle sympathetic and cardiac-vagal efferent activities, measurements obtained from healthy subjects alone did not delineate any such reciprocity (Fig. 5). This finding,

which is contrary to that of Goldstein (29), was strengthened by subsequent laboratory experience with a total of 18 heart failure patients and 46 healthy subjects. These cumulative results are depicted in the Appendix (see Fig. 9).

Central abnormalities of autonomic control. We attempted to discover central nervous system abnormalities in heart failure patients in several ways. First, we asked, is relative absence of respiratory sinus arrhythmia in heart failure patients (5) due to absence of respiratory rhythms within the central nervous system? Since our analysis documented strong respiratory modulation of sympathetic outflow (Figs. 2 and 3), near-absence of vagally mediated respiratory sinus arrhythmia in heart failure patients cannot be explained simply on the basis of absence of central respiratory rhythms.

Secondly, we asked, do high levels of sympathetic activity in heart failure patients mean that their sympathetic motoneurons receive no inhibitory input from baroreceptors? We employed power spectral coherence analysis to document cardiac rhythms in muscle sympathetic outflow (Fig. 4 and Table III). We used this approach because two studies suggest that the fixed-phase relation that exists between cardiac and sympathetic activities results from baroreceptor entrainment of sympathetic motoneurons. Taylor and Gebber (13) showed that the phase relation between cardiac and sympathetic activities in anesthetized cats is abolished by baroreceptor and vagal denervation or hemorrhage. Fagius et al. (14) showed in two healthy human subjects that correlations between muscle sympathetic and cardiac activities are lost when afferent baroreceptor input (and efferent vagal output) is abolished by bilateral injections of local anesthetic at the base of the skull.

Since we found that there was significant coherence between cardiac and sympathetic activities in all but one heart failure patient, we concluded that in these patients, baroreceptors entrain (and therefore inhibit) sympathetic motoneurons. However, this does not necessarily mean that baroreceptor inhibition of sympathetic firing is quantitatively normal; there is abundant evidence that baroreceptor firing is subnormal in heart failure (30–32).

Thirdly, we asked, do heart failure patients have subnormal levels of vagal activity because of abnormal central vagal motoneuron function? We measured R–R interval responses to low doses of atropine, which are known to stimulate central vagal-cardiac motoneurons in experimental animals (12) and humans (33). We believe ours to be the first documentation of reduced responses to low dose atropine in heart failure patients. However, Alicandri et al. (34) found that another group of patients, those with primary hypertension, have less R–R interval lengthening after low dose atropine than normotensive subjects. Our study does not indicate whether presumed subnormal vagal-cardiac motoneuron activity in heart failure patients is due to intrinsic abnormalities of vagal motoneurons, or to relative lack of stimulation of these neurons by sensory inputs. Another study from our laboratory (35) indicates that in some heart failure patients, carotid baroreceptor-cardiac reflex responses are subnormal.

Absence of accentuated antagonism in heart failure. In open chest anesthetized dogs, electric sympathetic nerve stimulation augments sinus node inhibition provoked by vagal stimulation (36), a property styled as "accentuated antagonism" (37). This phenomenon is attributed to both pre- and postganglionic sympathetic–cholinergic interactions (38). Preganglionic interactions are of particular interest: acetylcholine inhibits release of norepinephrine from sympathetic nerve terminals, an effect which is muscarinic because it can be prevented by pretreatment with atropine (39, 40). On the basis of this interaction, it might have been expected that in the presence of inordinately large sympathetic stimulation in heart failure patients, blockade of muscarinic receptors would lead to exaggerated release of norepinephrine, and substantial cardioacceleration (39).

The large dose of atropine we used did not increase plasma norepinephrine levels or trigger large cardioacceleration in the heart failure patients we studied, who had extremely high levels of plasma norepinephrine. On the basis of literature on sympathetic–cholinergic interactions (41), we would have expected that large dose atropine would augment plasma norepinephrine levels and shorten R–R intervals to a greater, not lesser extent in heart failure patients than healthy subjects. (However, one healthy subject, No. 11 Table II, who had very high levels of plasma norepinephrine had such a pattern.) In addition, accentuated antagonism should result in enhanced, not depressed vagally mediated baroreflex responses to bolus phenylephrine injections or neck suction in heart failure patients. The opposite has been found (27, 35). These results should provoke discussion of the implications of accentuated antagonism under circumstances in which sympathetic activity is increased pathologically.

Absence of accentuated antagonism in heart failure patients may be due to several factors. First, it may result from reduced myocardial beta-adrenergic receptor populations and responsiveness to sympathetic stimulation (42). Secondly, it may result from the unusually high levels of neuropeptide-Y found in heart failure patients (43). Neuropeptide-Y is related significantly to plasma norepinephrine levels during drug-induced arterial pressure reductions (44), and is known to oppose vagally mediated R–R interval lengthening (45). Thirdly, it may reflect extremely low resting levels of vagal-cardiac nerve activity believed to be present in heart failure patients ([5, 22]; this study). Large dose atropine may have led to minimal R–R interval shortening because in these patients, there is very little acetylcholine released at the sinoatrial node to block.

Limitations. Two possible limitations of our study are that some of the patients we evaluated did not have severe heart failure, and that the medications heart failure patients were taking may have contributed to the sympathetic and parasympathetic abnormalities we found. As mentioned, heart failure patients were chosen on the basis of clinical symptoms, rather than on the basis of hemodynamic or biochemical measurements. Although some patients had normal pulmonary capillary wedge pressures on treatment (Table I), all had subnormal left ventricular ejection fractions. Importantly, all had supranormal plasma norepinephrine levels, which correlate with the severity of heart failure (1). Also, we did not select healthy subjects on the basis of their plasma norepinephrine levels; we have no explanation for the elevated norepinephrine concentration found in one healthy subject (No. 11, Table II).

We did not discontinue medical therapy in the heart failure patients we studied because several were judged to be too ill to have their therapy withdrawn. We doubt that medical therapy contributed to the abnormalities we documented, because, at least some of the agents our patients were receiving would be expected to improve, rather than impair autonomic cardiovascular control. Thus, digoxin may increase vagal outflow (46, 47) and reduce muscle sympathetic nerve activity (48), and captopril may improve reflex control of vagal and sympathetic outflows (49–51).

Clinical implications. There is substantial evidence that parasympathetic and sympathetic inputs modulate electric stability of the left ventricle, and that imbalances between these inputs promote or oppose the occurrence of ventricular dysrhythmias. Sudden cardiac death is a major cause of mortality in congestive heart failure patients (52), and one powerful predictor of sudden death in these patients is the magnitude of plasma norepinephrine elevations (2). Conversely, cholinergic stimulation secondary to phenylephrine-induced pressure elevations (53) or electric vagus nerve stimulation (54) raises ventricular fibrillation thresholds in normal and ischemic hearts. Our study suggests that the balance between baseline sympathetic and parasympathetic activities in heart failure patients is such as to promote ventricular dysrhythmias; ventricular fibrillation thresholds may be low in part because they have high resting levels of sympathetic stimulation, which are not counterbalanced by opposing levels of vagal inhibition.

In summary, we studied the relation between sympathetic and parasympathetic outflows in heart failure patients and healthy subjects, and changes of these outflows after parasympathomimetic and parasympatholytic doses of atropine. We found baseline elevations of sympathetic activity and reductions of parasympathetic activity in heart failure patients. Since there was strong coherence between cardiac and sympathetic activities, it is unlikely that high levels of sympathetic outflow in heart failure patients are due simply to absence of an influence of baroreceptors on sympathetic motoneurons. Since patients had strong respiratory modulation of muscle sympathetic nerve activity, it is unlikely that near absence of respiratory sinus arrhythmia is due to absence of respiratory rhythms within the central nervous system. In addition, we found that heart failure patients fail to respond to centrally acting, parasympathomimetic doses of atropine, and that their R–R interval responses to large dose atropine are inversely, not directly related to baseline levels of sympathetic activity.

Appendix

After measurements were obtained from the 16 subjects described in this report, we measured R–R interval standard deviations (with controlled respiration at 12 breaths/min) and antecubital vein plasma norepinephrine in an additional ten heart failure patients and 38 healthy subjects. The total experience is depicted in Fig. 9. This much larger material strengthens our conclusion that sympathetic and parasympathetic activities are related reciprocally in heart failure patients, but that there is no such relation in healthy subjects.

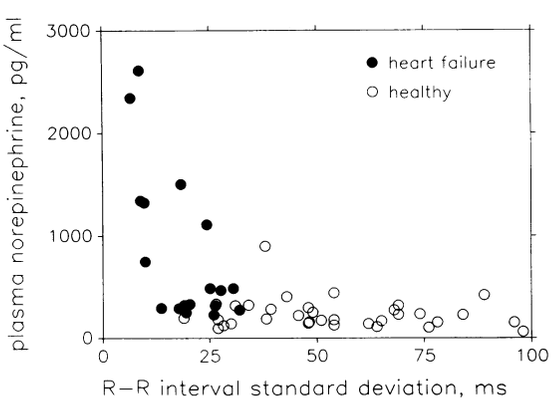

Figure 9. Baseline sympathetic–parasympathetic relation. These data were obtained subsequent to the completion of the present study, and include an additional ten heart failure patients (total $n = 18$) and 38 healthy subjects (total $n = 46$). There was no significant relation between plasma norepinephrine and R–R interval standard deviation in healthy subjects ($r = 0.129$, $P > 0.05$).

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