Baroreflex Control of Renal Sympathetic Nerve Activity Is Preserved in Heart Failure Despite Reduced Arterial Baroreceptor Sensitivity

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The purpose of this study was to determine if arterial baroreflex control of sympathetic nerve traffic is impaired in heart failure. We recorded renal nerve activity during changes in arterial pressure while simultaneously recording from aortic baroreceptor afferent fibers in 10 dogs with heart failure induced by rapid ventricular pacing and in 10 sham animals. Sensitivity of the aortic baroreceptors (percent change in nerve activity per millimeters mercury change in mean arterial pressure) was reduced in the heart failure group (heart failure, 2.3±0.3; sham, 3.6±0.4, p=0.02). Despite the reduced sensitivity of aortic baroreceptors in heart failure, there was no difference in the baroreflex gain of renal nerve activity (heart failure, −5.5±1.4; sham, −5.8±1.3, p=NS). These values tended to decrease in both groups after vagotomy. The relation between baroreceptor input and renal sympathetic output, or central baroreflex gain (percent change in renal nerve activity divided by percent change in aortic nerve activity) was similar in both groups before vagotomy (heart failure, −2.4±0.6; sham, −2.5±0.5, p=NS). Vagotomy reduced central gain in the sham group (−0.9±0.1, p=0.03) but not in the heart failure group (−1.7±0.5, p=NS), suggesting that the contribution of vagal afferents in the baroreflex arc is reduced in heart failure. Baroreflex control of R-R interval was attenuated in heart failure when assessed by blood pressure elevation but not reduction, indicating abnormal parasympathetic but preserved cardiac sympathetic mechanisms in heart failure. Thus, dogs with heart failure exhibit reduced sensitivity of aortic baroreceptors but preserved baroreflex control of renal nerve activity. Reduced baroreceptor sensitivity with preservation of baroreflex control of sympathetic nerve activity may contribute to the sympathoexcitatory state known to exist in heart failure. (Circulation Research 1989;65:1526–1535)

Congestive heart failure is manifested by pronounced neurohumoral abnormalities, which adversely affect patients' symptomatology as well as survival.1–3 These abnormalities include reduced arterial baroreflex control of heart rate,4–7 elevations in plasma levels of vasoconstrictor hormones (especially norepinephrine),2,3,8–9 and blunted reflex vasoconstriction in response to orthostatic maneuvers.10–12

Measurements that are dependent on end-organ responses and are used to demonstrate abnormalities in baroreflex control provide limited insight as to the locus or loci of such abnormalities. For example, blunting of baroreflex-mediated heart-rate changes has been described in heart failure but

Previous studies in a high-output model of heart failure suggested that arterial baroreflex control of renal nerve activity is preserved in heart failure.13 However, baroreflexes in this high-output state may differ from the reflexes in heart failure commonly seen in humans, in which cardiac output is decreased. Furthermore, arterial baroreflex control of heart rate remains blunted after reversal of high-output heart failure in dogs,14 whereas there is normalization of arterial baroreflex control of native sinus node activity after cardiac transplantation in humans.15 These differences may be due to structural alterations in the high-output model that may not be present in low-output heart failure.

Measurements that are dependent on end-organ responses and are used to demonstrate abnormalities in baroreflex control provide limited insight as to the locus or loci of such abnormalities. For example, blunting of baroreflex-mediated heart-rate changes has been described in heart failure but
could be due to abnormal responses in the afferent limb of the baroreflex (either the receptors themselves or the vessel walls in which they are located), abnormalities in the central integration of the signal, or abnormalities in neuroeffector mechanisms, including abnormal nerve signals, release of neurotransmitters, or end-organ responsiveness. Furthermore, altered baroreflex control of heart rate during increases in arterial pressure suggests abnormalities in parasympathetic mechanisms but does not address control of sympathetic nerve activity.

The purpose of our investigations was to test the hypothesis that there are abnormalities in arterial baroreflex control of sympathetic nerve traffic in a low-output model of congestive heart failure produced by rapid ventricular pacing in dogs. Furthermore, the locus or loci of the abnormalities in the baroreflex arc were sought. To determine whether or not nerve traffic (afferent input or efferent output) is altered, we recorded simultaneously from baroreceptor afferent fibers (aortic depressor nerve) and postganglionic sympathetic fibers (renal sympathetic nerve) during blood pressure alterations. This method allowed us to measure changes of sympathetic nerve activity in response to changes in blood pressure and in relation to changes in afferent baroreceptor input.

**Materials and Methods**

**Induction of Heart Failure**

Custom-modified generators (models 5984, 8420, and 8423, Medtronic, Minneapolis, Minnesota) were implanted under anesthesia (thiamylal sodium, 15 mg/kg i.v.) in 10 mongrel dogs of either sex weighing 17-25 kg. By use of sterile technique, the left external jugular vein was exposed. A catheter was inserted in the pulmonary artery, and baseline cardiac filling pressures and cardiac outputs (thermodilution) were measured. The catheter then was removed, and a pacing electrode was advanced to the right ventricular apex under fluoroscopic guidance. Pacing thresholds and resistances were determined to ensure adequate capture. An incision was made in the interscapular area, and the wire was tunneled subcutaneously from the neck to the incision, where a subcutaneous pocket was made. The generator was placed in the pocket along with 1 million units of penicillin powder. Both incisions were closed, and the dogs were allowed to recover from 1 to 7 days. The pacemaker then was programmed to a rate of 250 beats/min. Weekly electrocardiographic monitoring was performed to ensure continued pacing. Pacing was continued until the animal showed clinical signs of congestive heart failure, including ascites and tachypnea, which occurred in all dogs that were paced rapidly (range 13-48 days). Previous studies have shown that at this stage there are elevations in plasma norepinephrine, renin, angiotensin, vasopressin, aldosterone, and atrial natriuretic factor as well as elevations in cardiac filling pressures with a concomitant reduction in cardiac output and left ventricular ejection fraction. Thus, this model produces biventricular, low-output congestive heart failure with its attendant neurohumoral excitatory state.

An additional 10 dogs were instrumented in a similar fashion to serve as a control group. In these dogs the pacemaker was programmed to the lowest possible rate (30 beats/min), and all dogs remained in normal sinus rhythm. Two of these dogs had electrode wires placed without generators. All dogs received penicillin G (600,000 units i.m.) postoperatively twice daily for 3 days.

**General Methods**

The acute experiments were performed within a few days of the development of overt signs of congestive heart failure, which included a moderate to large amount of ascites, anorexia, and tachypnea. The dogs were anesthetized with morphine (15 mg i.v.) and o-chloralose (30-100 mg/kg). Supplemental chloralose (10-40 mg/kg) was administered hourly. The dogs in heart failure needed less chloralose than the sham-operated dogs for a similar level of anesthesia. After endotracheal intubation, the animals were placed on a respirator (Harvard Apparatus, South Natick, Massachusetts) and were ventilated with a mixture of oxygen and room air. Arterial blood gases were drawn at regular intervals, and either sodium bicarbonate was administered or the ventilator was adjusted to maintain arterial pH between 7.35 and 7.45. Arterial PCO₂ was maintained at 30–45 mm Hg, and P0₂ always exceeded 80 mm Hg. Catheters were placed in a femoral artery and vein, and a catheter was advanced to the pulmonary artery via the right external jugular vein. The surface electrocardiogram, arterial pressure, and pulmonary artery pressure were monitored continuously.

The left vagus nerve was dissected free from the carotid sheath in the midcervical region. With the aid of an operating microscope, the left aortic nerve was located as it emerged from the vagosympathetic trunk just caudal to the superior laryngeal nerve and nodose ganglion. The nerve was placed on bipolar platinum electrodes for recording of action potentials. Aortic baroreceptor traffic was identified by the presence of typical pulse-synchronous discharge. Great care was taken to maintain the integrity of the nerve. A fine silk thread was looped around the aortic nerve for purposes of later identification. A second silk tie was placed around the vagal trunk from which the aortic nerve was excluded. The procedure was repeated on the contralateral side.

The dog then was placed in the right lateral decubitus position, and an incision was made in the left flank. A retroperitoneal dissection was used to expose the renal vessels and nerves. Care was taken to avoid disruption of the peritoneum, especially in dogs with ascites. The renal nerves were
identified as they coursed along the renal vessels and entered the renal pelvis. The distal end of one branch of these nerves was cut, and the nerve was carefully dissected free of the surrounding connective tissue. The nerve was stripped of its sheath, immersed in a warm mineral oil bath, and placed on platinum recording electrodes as described above. Action potentials were recorded from the whole nerve or, in some instances, from fibers that had been separated from the whole nerve to improve the signal-to-noise ratio.

In the heart failure dogs, the pacemaker then was removed, and after an equilibration time of at least 15 minutes, baseline hemodynamic measurements were made. All dogs were in sinus rhythm at the time of study. The aortic nerve and renal sympathetic nerve each were placed on a recording electrode as described previously in detail.18 Briefly, the signal was amplified by a bandpass amplifier (model P511, Grass Instruments, Quincy, Massachusetts) with high-frequency cutoff set at 1,000 or 3,000 Hz and low-frequency cutoff at 30 or 100 Hz. The signal then was fed into a loudspeaker and a display monitor (Gould, Cleveland, Ohio). The amplified signals from these nerves were fed into spike counters (706C Nerve Traffic Analysis System, University of Iowa, Iowa City, Iowa), which counted and integrated all nerve spike activity with amplitudes in excess of that determined by a preselected voltage (just above the noise). The counter was digital in design and could count linearly up to instantaneous frequencies of 10 KHz.

Protocol

Phenylephrine was infused to raise the systolic arterial pressure by 40–60 mm Hg over 2–3 minutes. This required a higher dose of phenylephrine in the heart failure dogs than in the sham dogs. After a recovery period of at least 10 minutes and restitution of baseline blood pressure, nitroglycerin then was infused to lower systolic arterial pressure by 30–40 mm Hg over 2–3 minutes. Again, the heart failure animals required higher doses than the sham dogs.

We also determined if any abnormality in the arterial baroreflex that might be present could be the result of altered input from vagal cardiopulmonary receptors whose activity may be altered in heart failure and may be altered further by phenylephrine or nitroglycerin infusion. To test this possibility, we performed bilateral vagotomy, taking care not to disrupt the aortic nerves. The infusions of phenylephrine and nitroglycerin were repeated, producing pressure changes similar to those induced prior to vagotomy.

After the animals were killed, the hearts were excised and the atria and right and left ventricles were weighed. The thicknesses of the right and left ventricular walls also were measured.

Analytical Methods

Systolic and diastolic blood pressure, R-R interval, and aortic and renal nerve activity were measured at regular intervals during blood pressure changes by use of a digitizer tablet (model 2210, Numonics, Montgomeryville, Pennsylvania) and a custom-designed computer program by the author (M.D.-D.) for an IBM PC XT. During blood pressure changes, measurements were made over one ventilatory cycle (approximately 3.5 seconds), or over 10–15 seconds for the baseline measurements. Between 10 and 30 sets of measurements were taken for each increment or decrement in blood pressure. For analysis of nerve activity, percent change from baseline nerve traffic was used to account for differences in basal traffic due to differences in the sizes of nerves used and the number of active fibers on the recording electrodes. The plots relating percent change in nerve activity to change in mean arterial pressure were visually inspected, and the slope of the linear portion of the plot was used for calculation of gain of nerve activity. For nerve traffic analysis, the phenylephrine and nitroglycerin data were combined to give one slope, which was taken as the gain (aortic baroreceptor or renal nerve).

The relation between changes in baroreceptor input and renal sympathetic output was derived from plots relating percent change in sympathetic nerve activity to percent change in aortic nerve activity. The slope of the linear portion of this relation for each animal was computed (before and after vagotomy) and taken to be overall central baroreflex gain. Analysis of variance (ANOVA) was used to determine if there was a change in the gain of each component of the baroreflex arc (i.e., afferent-aortic nerve, efferent-renal sympathetic nerve, and central). The main effects tested in this two-way ANOVA were 1) group (heart failure versus sham) and 2) vagotomy (prevagotomy versus postvagotomy). Interaction between effects was also evaluated. Student's t test was used for individual comparisons. The heart-rate data showed evidence of significant departures from normal distributions, and Wilcoxon's signed rank test was used to compare those data. Values of p ≤ 0.05 were considered significant. Values are expressed as mean ± SEM.

Results

The hemodynamic data, cardiac weights, and ventricular wall thicknesses for the two groups of dogs are summarized in Table 1. Before pacemaker implantation there were no observed differences in hemodynamics between the two groups of animals. The mean pulmonary capillary wedge pressures, mean pulmonary artery pressures, and right atrial pressures were significantly elevated in the heart failure group, and the mean arterial pressure was reduced in this group compared with the sham.
TABLE 1. Baseline Characteristics of Heart Failure and Sham Groups

<table>
<thead>
<tr>
<th></th>
<th>Heart failure</th>
<th>Sham</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CO (l/min)</td>
<td>1.6±0.2</td>
<td>2.0±0.2</td>
<td>0.13</td>
</tr>
<tr>
<td>PCWP (mm Hg)</td>
<td>13±3</td>
<td>4±1</td>
<td>0.01</td>
</tr>
<tr>
<td>MPA (mm Hg)</td>
<td>25±3</td>
<td>14±1</td>
<td>0.008</td>
</tr>
<tr>
<td>RA (mm Hg)</td>
<td>5±1.5</td>
<td>1±0.5</td>
<td>0.03</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>88±6</td>
<td>146±11</td>
<td>0.0004</td>
</tr>
<tr>
<td>Atria (g)</td>
<td>33±1</td>
<td>23±2</td>
<td>0.0009</td>
</tr>
<tr>
<td>RV free wall (g)</td>
<td>35±2</td>
<td>38±2</td>
<td>NS</td>
</tr>
<tr>
<td>LV (g)</td>
<td>95±5</td>
<td>99±5</td>
<td>NS</td>
</tr>
<tr>
<td>LV wall (mm)</td>
<td>12.1±0.9</td>
<td>11.3±0.4</td>
<td>NS</td>
</tr>
<tr>
<td>RV free wall (mm)</td>
<td>5.5±0.5</td>
<td>5.5±0.3</td>
<td>NS</td>
</tr>
</tbody>
</table>

*p, probability; CO, cardiac output; PCWP, pulmonary capillary wedge pressure; MPA, mean pulmonary artery pressure; RA, right atrial pressure; MAP, mean arterial pressure; RV, right ventricle; LV, left ventricle; NS, not significant.

There was a tendency for a reduction in cardiac output that did not reach statistical significance (p=0.13) in these anesthetized animals, indicating that they were able to maintain output only at the expense of elevated cardiac filling pressures. The mean weight of the atria in the heart failure group was higher than in the sham group, but there were no significant differences in weights or wall thicknesses of the right or left ventricles between the two groups.

Figure 1 illustrates a typical phenylephrine infusion with the resultant increase in aortic nerve and decrease in sympathetic nerve activity. Figure 2 illustrates graphically the responses in one animal, along with the regression lines for each nerve.

Aortic Nerve Data

The data were acceptable for analysis in 39 of 40 drug infusions and are summarized in Figure 3. The mean gain of the aortic receptors (percent change in nerve activity per millimeters mercury) for the heart failure group was reduced significantly compared with the sham group (ANOVA p=0.002). Differences were noted both before and after vagotomy. Before vagotomy the gain in the sham dogs was 3.6±0.4 compared with 2.3±0.3 in the heart failure group. After vagotomy the gain in the sham group was 5.4±1.0, while that of the heart failure group was 2.6±0.5. There was no interaction between the effects of group and vagotomy.

We were able to define "threshold" and "saturation" for the aortic nerve in seven dogs in the sham group and four dogs in the heart failure group. For these experiments, we fitted a four-parameter logistic regression of the form

\[ Y = A_4 + A_1 / (1 + \exp[A_2(X-A_3)]) \]

where Y is the percent change from baseline of aortic nerve traffic. X is the change in mean arterial pressure, and A1 through A4 are the parameters of this nonlinear equation from which threshold, saturation, and range of both nerve activity and blood pressure can be calculated. The curves for both groups are depicted in Figure 4. Figure 4A illustrates the relation between aortic baroreceptor stimulus (change in arterial pressure) and response (percent change in aortic nerve activity). Figure 4B illustrates the instantaneous gain (i.e., sensitivity), which is the first derivative of the curves in Figure 4A, for the receptors. There were no significant differences in blood pressure at threshold (heart failure, -12.2±6.4; sham, -15.4±3.0 mm Hg with respect to baseline, p=0.62) or saturation (heart failure, 16.4±11.9; sham, 30.9±6.9 mm Hg with respect to baseline, p=0.28) between the two groups. For aortic nerve activity, the range over which nerve activity changed (percent change from baseline) was reduced significantly in the heart failure group (heart failure, 94.9±20.7%; sham, 252.6±41.5%, p=0.02). As illustrated in Figure 4A, this difference in range was primarily due to reductions in nerve activity at saturation (heart failure, 39.3±20.4%; sham, 172.2±41.2%, p=0.05), not at threshold (heart failure, -55.6±13.6%; sham, -80.4±7.2%, p=0.11).

**FIGURE 1.** Recording during phenylephrine infusion. Top two tracings are integrated signals from renal sympathetic and aortic nerves, respectively. Renal nerve activity is ablated, and aortic nerve traffic becomes saturated at high pressures.
Central

The operational point is a measure of the relative position on the blood pressure-nerve activity response curve that occurs under basal conditions and from which baroreceptors are able to either increase or decrease their firing. This can be expressed as a ratio between the location of the set point (where blood pressure change=0 mm Hg) on the curve and the range over which blood pressure is changed (set point minus threshold, divided by range). Although there was no significant difference in operational point between the two groups (heart failure, 0.74±0.26; sham, 0.38±0.09, p=0.14), there was a tendency for the operational point of the heart failure group to be closer to saturation. We would like to emphasize that this tendency was evident from data obtained from only four heart failure and seven sham dogs, from which full sigmoidal curves were generated.

Renal Nerve Data

All 40 series of blood pressure changes were acceptable for analysis of renal nerve activity. When percent changes in renal nerve activity were plotted as a function of change in mean arterial pressure (percent change in nerve activity per millimeters mercury), there were no differences between the two groups (ANOVA p=0.9). Before vagotomy, renal nerve gain was -5.5±1.4 in the heart failure group and -5.8±1.3 in the sham group. Vagotomy tended to reduce the gain for responses of sympathetic nerve traffic (ANOVA p=0.06) to -3.9±0.6 in heart failure and -3.4±0.5 in the sham group. There was no interaction between group and vagotomy.

Baroreflex Input/Output Relation (Central Gain)

There was no overall difference between the two groups in net baroreflex gain (ANOVA p=0.31). Before vagotomy, the gain (percent change renal nerve activity divided by percent change aortic nerve activity) was -2.3±0.5 in the sham group and -2.4±0.6 in the heart failure group. Vagotomy reduced these values (ANOVA p=0.04) to -0.9±0.1 (sham) and -1.7±0.5 (heart failure). Individual t tests revealed that this reduction after vagotomy was significant in the sham group (p=0.03) but not in the heart failure group (p=0.43). There was no interaction between the effects of group and vagotomy.

Heart Rate Data

These data are illustrated in Figure 5. The slopes of the lines relating R-R interval changes to changes in mean arterial pressure for phenylephrine were 4.5±1.1 msec/mm Hg for the sham group and 2.3±0.7 msec/mm Hg (p=0.04) in the heart failure group. There were no differences between the two groups.
groups for the nitroglycerin infusions (heart failure, 2.0±0.5; sham, 2.7±1.1 msec/mm Hg).

Discussion

The major findings of this study are that 1) aortic baroreceptors exhibit reduced sensitivity (gain) in heart failure; 2) baroreflex control of efferent sympathetic traffic is preserved in heart failure in spite of the abnormality in the afferent limb; 3) the relation between efferent sympathetic discharge to baroreceptor afferent input is preserved in heart failure; 4) cardiopulmonary vagal afferents contribute to net baroreflex gain in normal but not in heart failure dogs; and 5) baroreflex control of heart rate is reduced in heart failure. In the following paragraphs we will discuss these findings as well as their physiological significance.

FIGURE 4. Responses of aortic nerve (percent change from baseline) to changes in blood pressure in heart failure and sham groups. A four-parameter logistic regression was fitted for each experiment in which threshold and saturation responses were obtained. Panel A shows curves generated by means of parameters for sham group (n=7) vs. heart failure group (n=4). Panel B depicts instantaneous gain of aortic nerve (percent change from baseline). HF, heart failure; MAP, mean arterial pressure.

FIGURE 5. Gain of R-R interval, calculated from slope of lines relating changes in R-R interval to changes in arterial pressure. Gain in heart failure group was significantly reduced for phentolamine (p=0.04) but not for nitroglycerin (p=0.7). CHF, congestive heart failure.
Aortic Baroreceptors

Our results show that the sensitivity of afferent baroreceptors is reduced in heart failure. Previous work by Niebauer and Zucker\(^{20}\) using a high-output model of heart failure showed that when static pressures were applied to the isolated carotid sinus, the gain of carotid sinus nerve activity was reduced in heart failure. In that study reductions in gain were not apparent when dynamic pressure changes were used. Our study (with baroreceptors intact) used the animals’ own pulsatile blood pressure changes to alter baroreceptor traffic, thereby presenting dynamic stimuli to the receptors. It is likely that differences in the models can explain differences observed in receptor characteristics. In the high-output model of heart failure, sodium and water content, as well as wall strain of the carotid sinus, are normal.\(^{20}\) Zelis et al\(^{21}\) have demonstrated that in the rapid ventricular pacing model of heart failure, increases in vessel wall sodium content may alter either vessel wall or receptor characteristics. Patients with low-output heart failure have impaired vasodilation that improves after treatment with diuretics,\(^{22}\) thus supporting a role for abnormal vascular sodium content leading to abnormal vascular responses in humans with heart failure. Our study does not determine whether reduced baroreceptor sensitivity is due to alterations in the vessel wall or in the receptors.

Reflex Control of Efferent Sympathetic Nerve Activity

Another possible locus of abnormal baroreflex responsiveness in heart failure is in components of the baroreflex that control efferent sympathetic nerve activity. We calculated baroreflex slopes from the relation between percent change in renal sympathetic nerve activity and change in mean arterial pressure. We found no evidence for decreased responsiveness of renal sympathetic nerve traffic in heart failure animals compared with normal animals. Previous work by Zucker et al\(^{13}\) showed that with arterial and cardiopulmonary baroreflexes intact, sympatheoinhibition in response to phenylephrine and sympatoexcitation in response to nitroprusside remained preserved in dogs with high-output heart failure, though there was a tendency for slightly reduced responses. What is surprising, however, is that control of renal sympathetic nerve activity was preserved in our study, even though we found a reduction in baroreceptor sensitivity to dynamic pressure changes. This suggests that there is compensation in central components of the baroreflex that serves to normalize reflex control of nerve activity. The specifics of this control will be discussed in the following section dealing with central gain.

Our findings are consistent with those of Lanoce et al,\(^{22}\) who recently found that baroreflex-mediated changes in hind-limb vascular resistance (which are mediated predominantly by changes of sympathetic nerve traffic) are normal despite abnormal heart-rate control in this same low-output model of heart failure. Our findings also extend these observations on reflex control of sympathetic outflow in heart failure to a second vascular bed.

Central Baroreflex Gain

To determine if central mechanisms of baroreflex control are altered in heart failure, we measured baroreceptor afferent input and sympathetic nerve outflow simultaneously. This is particularly important because the response of sympathetic traffic then can be expressed in terms of activity of the afferent signal (which is responsible for the reflex change) and indicates if there is impairment in central nervous components of the baroreflex. It is a measure of central gain due solely to neurogenic mechanisms and requires no assumptions regarding vessel or receptor characteristics or altered end-organ responsiveness. We found no evidence for a central abnormality in the heart failure group. In fact, there was a tendency for central gain to be higher in heart failure as compared with sham in the postvagotomy state (\(p=0.13\)). Such an augmentation centrally might compensate for the abnormalities we detected in the afferent limb.

Role of Cardiopulmonary Vagal Afferents

We used phenylephrine and nitroglycerin to alter arterial pressure. We have shown in previous work that phenylephrine elevates not only arterial pressure but cardiac filling pressures as well, thereby contributing to sympatheoinhibition by the stimulation of mechanosensitive vagal afferents.\(^{24}\) Therefore, we measured changes in nerve activity before and after selective vagotomy to assess both the independent influence of the arterial baroreceptors and the contribution of cardiopulmonary baroreceptor afferents in heart failure.

Vagotomy decreased central gain (ANOVA \(p=0.04\)). This effect was significant in the sham group (\(p=0.03\)) but not in the heart failure group (\(p=0.43\)). This result occurred despite greater changes in cardiac filling pressures in the heart failure group than in the sham group with both phenylephrine and nitroglycerin infusions. We interpret these findings to suggest that cardiopulmonary receptors contribute significantly to baroreflex control of sympathetic nerve traffic in normal animals but not in heart failure, indicating impaired input from cardiopulmonary mechanosensitive fibers. Since net baroreflex (central) gain is preserved in heart failure despite the reduced contribution of vagal afferents, our findings also can be interpreted to suggest that central components of the arterial baroreflex compensate not only for reduced arterial baroreceptor signals but for abnormalities in vagal cardiopulmonary baroreflexes as well.

Our findings of abnormalities in cardiac vagal afferent control in heart failure agree well with
several other studies. Humans with congestive heart failure have abnormal reflex responses to changes in central filling pressures. Moreover, the discharge of left atrial stretch receptors per millimeter mercury change in left atrial pressure is reduced in dogs with heart failure. Thus, there are abnormalities of both arterial and cardiopulmonary baroreceptors in heart failure.

Heart-Rate Changes

Prolongation of R-R interval during phenylephrine-induced hypertension is mediated predominantly by parasympathetic mechanisms. Conversely, R-R interval shortening during nitroglycerin-induced hypotension relies more on sympathetic mechanisms. We found that the baroreflex gain of R-R interval was reduced in heart failure when assessed by phenylephrine-induced pressure increases, implying that there are abnormal parasympathetic mechanisms in heart failure. This is consistent with findings from several previous studies. Our finding of preserved baroreflex gain of R-R interval in response to nitroglycerin-induced hypotension was different from that of another study in conscious animals with high-output heart failure that showed a reduction in baroreflex gain as a result of bolus nitroprusside injections. However, this finding agrees well with our renal sympathetic nerve data, which point to preserved sympathetic baroreflex control in heart failure.

Physiological Significance

Previous studies have noted that after treatment of heart failure with angiotensin-converting enzyme inhibitors, calcium channel blockers, or cardiac transplantation, there is either improvement or normalization of heart-rate responses to changes in arterial pressure. The significance of our experiments is that improvement in arterial baroreflex responses after treatment of heart failure is probably not related to effects on reflex control of sympathetic nerve traffic, since this control is preserved even in heart failure. It is possible that one mechanism responsible for normalization of baroreflex control of heart rate is at the baroreceptor level, since the baroreceptor level is one site of baroreflex abnormalities in heart failure.

Both arterial and cardiopulmonary baroreceptors normally serve to restrain sympathetic outflow. When normal animals undergo acute sinoaortic denervation, there are pronounced increases in renin, vasopressin, and sympathetic nerve activity. The similarity between sympathoexcitation after acute combined sinoaortic and cardiac denervation and that seen in heart failure has led some authors to propose that blunted arterial and cardiopulmonary baroreceptors may contribute to sympathoexcitation in heart failure. Our study supports this hypothesis. Our findings of reduced gain of the arterial baroreceptors and reduced contribution of cardiopulmonary receptors in the baroreflex arc, in concert with our findings of preserved (and possibly augmented) reflex control of sympathetic traffic, suggest that sympathetic activity is less well restrained in heart failure. Furthermore, we found evidence for reduced baroreceptor afferent nerve activity at saturation in heart failure, indicating less capacity to buffer increases in blood pressure by sympathoinhibition. This lack of sympathetic restraint may contribute to the sympathoexcitation known to be present in heart failure.

Limitations of the Study

The changes in blood pressure induced in our study did not reach threshold and saturation for the aortic nerve in every experiment in every dog. However, the responses covered most of the range of the linear portion of the baroreflex curve. In addition, both elevations and depressions of blood pressure were used to stimulate or reduce nerve traffic, so it is likely that the observed responses occurred within the true linear portion of the response curves.

There was a wide range (13–48 days) in the period of pacing until the animals developed heart failure. The study was timed in each animal to occur within a few days of the development of a moderately large amount of ascites. This condition correlated well with elevated filling pressures, as indicated in Table 1. We estimate that the animals in this study were in a moderate degree of heart failure, though we recognize that there may have been some variability in the severity of heart failure from dog to dog. The fact that we found a reduction in sensitivity of the aortic baroreceptors indicates that at this stage of heart failure central components of the baroreflex were able to compensate for impairment of the afferent limb. We cannot exclude the possibility that at a later stage of heart failure there may be abnormalities in sympathetic control that were not present at this stage of heart failure.

All nerve recordings were performed when the dogs were in sinus rhythm, between 1 and 5 hours after termination of rapid ventricular pacing. Though there was a tendency for filling pressures to fall during this time, Moe et al. showed that pulmonary capillary wedge pressure and mean pulmonary artery pressure are significantly elevated up to 24 hours after termination of rapid ventricular pacing in dogs with heart failure. In addition, our measurements of heart-rate responses were made at the same time that pressure changes were induced to alter nerve traffic, and we found that reflex control of heart rate was abnormal at the same time that reflex control of renal sympathetic nerve traffic was preserved. Furthermore, the differences in both central gain and aortic baroreceptor sensitivity between the two groups were greater after vagotomy, which occurred later in the protocol. Thus, our failure to observe abnormalities of renal sympathetic nerve traffic cannot be attributed to rapid normalization of the neurohumoral excitatory state.
Whole nerve recordings of aortic and sympathetic nerves were used in these experiments. Therefore, baseline differences in sympathetic activity cannot be measured with this technique. However, other investigators have shown that baseline nor-epinephrine levels are increased in this model of heart failure and baseline levels of norepinephrine and muscle sympathetic nerve traffic are elevated in patients with heart failure.

Our study could be criticized for its exclusive reliance on multifiber baroreceptor recordings, which were used to determine if there were abnormalities in the afferent limb of the baroreflex in heart failure. There are several reasons to support our use of multifiber preparations: 1) In dogs with renal hypertension, similar abnormalities in carotid baroreceptor behavior were noted in single-unit and multiunit recordings. Thus, multiunit recordings can be used to detect abnormal baroreceptor input. 2) We recognize that activity changes in multiunit preparations are a function of changes in the activity of individual fibers as well as recruitment (or dropout) of previously inactive (active) fibers. Although multiunit recordings do not differentiate between these mechanisms for changes in baroreceptor activity, they provide a better overall estimate of the relation of baroreceptor input over the full operating range of arterial pressures studied. 3) We were able to detect the presence of abnormal baroreceptor behavior. Had we failed to detect this abnormality, then it could have been argued that single-unit recordings might have been necessary to detect more subtle abnormalities in baroreceptor behavior. 4) Finally, the abnormalities described in this study are qualitatively similar to those described in a previous study that used single-fiber recordings of carotid baroreceptor activity in dogs with high-output heart failure.

In summary, the sensitivity of aortic baroreceptors is reduced, but baroreflex-mediated changes in sympathetic nerve traffic are preserved in experimental heart failure. This preservation in gain of the baroreflex occurred despite blunted responses of baroreceptor afferents in heart failure. Additionally, cardiac vagal afferents facilitate central gain of the arterial baroreflex in normal animals but not of those in heart failure, thus indicating that not only is there blunting of the influence of mechanosensitive vagal afferents in heart failure but also that there is central compensation in the arterial baroreflex arc for abnormalities of vagal input in heart failure. In addition to altered baroreceptor characteristics, abnormalities in baroreflex mechanisms in heart failure must therefore occur either through abnormalities at neuroeffector sites or via other neural pathways (e.g., parasympathetic mechanisms).

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References

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Baroreflex control of renal sympathetic nerve activity is preserved in heart failure despite reduced arterial baroreceptor sensitivity.

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