Control of Sympathetic Nerve Activity by Vagal Mechanoreflexes Is Blunted in Heart Failure

Mark E. Dibner-Dunlap, MD, and Marc D. Thames, MD

Background. Previous studies have documented abnormalities of arterial baroreflexes in animals and patients with congestive heart failure. This study determined whether cardiopulmonary reflex control of sympathetic nerve activity was abnormal in a canine model of low-output heart failure induced by rapid ventricular pacing.

Methods and Results. We stimulated mechanoreceptors throughout the cardiopulmonary region by volume expansion and left atrial mechanoreceptors selectively by inflating small balloons at the junctions of the pulmonary veins and left atrium. Responses of renal sympathetic nerve activity and left atrial and systemic arterial pressures were recorded. In the control group, 15% volume expansion raised left atrial pressure 3.5±0.8 mm Hg and resulted in a 70±8% reduction in renal nerve activity. In the heart failure group, 15% volume expansion resulted in a 6.8±3.0 mm Hg rise in left atrial pressure with only a 16±20% reduction in renal nerve activity (p<0.01). When volume expansion was performed after pretreatment with hemorrhage to lower left atrial pressure to the normal range in the heart failure group, the markedly attenuated response in the heart failure group persisted. After vagotomy, volume expansion elicited no change in renal nerve activity. Inflation of the atrial balloons caused a 28±9% reduction in renal sympathetic nerve activity and a 13±4 mm Hg decrease in arterial pressure in the control group. Renal nerve activity (5±3%) and mean arterial pressure (1±1 mm Hg) did not change with balloon inflation in the heart failure group.

Conclusions. We conclude that dogs with low-output heart failure exhibit marked attenuation of cardiopulmonary mechanoreflex control of sympathetic nerve activity. This attenuated response is mediated via cardiac vagal afferent fibers and is due to either abnormalities in cardiopulmonary baroreceptors or abnormalities in the central nervous system. (Circulation 1992;86:1929–1934)

KEY WORDS • baroreceptors • cardiopulmonary receptors • baroreflex • heart failure

N eurohumoral excitation is a hallmark of congestive heart failure.1 Studies in patients with heart failure suggest that patients with the most marked elevation in plasma norepinephrine and renin (markers of neurohumoral excitation) have the worst prognosis.2,3 In normal humans and animals, baroreflexes exert an important tonic restraining influence on sympathetic nerve activity. Previous studies have documented impaired arterial baroreflex control of heart rate in patients with cardiac dysfunction,4 and animal studies have revealed attenuation of arterial baroreceptor sensitivity in animals with low-output heart failure.5,6 A previous study from our laboratory found that despite decreased sensitivity of arterial baroreceptors, the sensitivity of the arterial baroreflex control of sympathetic nerve activity was preserved, suggesting that central components of the baroreflex arc compensated for the reduction in baroreceptor sensitivity.7

Previous studies suggest that cardiopulmonary receptors may behave abnormally in heart failure. By recording from afferent fibers, Greenberg and colleagues7 found reduced pressure-sensitive atrial (type B) receptors in dogs with tricuspid regurgitation and pulmonary stenosis. Zucker et al8 recorded nerve activity from atrial type B mechanoreceptors in dogs with high-output heart failure resulting from a chronic arteriovenous fistula and found that the sensitivity of these receptors was reduced in response to changes in atrial stretch.8 In a subsequent study with a 10–20-ml balloon to distend the left atrium, investigators from the same laboratory found impaired atrial mechanoreceptor modulation of renal nerve activity, although this response was modulated by intact baroreceptors and changes in arterial blood pressure.9 Studies in humans also suggest that cardiopulmonary mechanoreflexes are impaired in patients with heart failure.10,11

The purpose of our study was to determine whether cardiopulmonary baroreceptor control of renal sympathetic nerve activity is abnormal in experimental heart failure. We used a low-output model of heart failure in dogs induced by pacing at a heart rate of 250 beats per minute for 4 weeks. Two techniques were used to stimulate cardiopulmonary baroreceptors. We stimu-
lated a specific group of atrial mechanoreceptors by inflating small balloons at the junctions of the left atrium and pulmonary veins. We also expanded plasma volume by 5%, 10%, and 15% to stimulate low-pressure baroreceptors throughout the cardiopulmonary tree. We measured responses of renal sympathetic nerve activity to each of these stimuli.

Methods

We implanted pacemakers in 14 mongrel dogs weighing 18–22 kg, as described previously. Briefly, a pacemaker lead was placed in the right ventricular apex under fluoroscopic guidance via the left external jugular vein using sterile technique. The lead was tunneled subcutaneously to a pocket in the interscapular area and connected to a modified Medtronic VVI pacemaker. The dogs recovered for 4–7 days after surgery, until all wounds showed good healing. Each animal was connected to an ECG monitor, and rapid ventricular pacing at a heart rate of 250 beats per minute was initiated by appropriate programming of the pacemaker. Weekly ECG strips were taken to confirm continued capture. Pacing was continued for a mean of 32±4 days (range, 15–62 days) until asics and tachypnea were observed. The acute, terminal experiment was performed within 1 week of the appearance of clinical heart failure.

On the day of the experimental protocol, the animals were anesthetized with 1 mg/kg morphine sulfate followed by 60–80 mg/kg α-chloralose i.v. The control animals were pretreated with 8 mg/kg thiamyolol sodium to cause light sedation (normal dogs may have an arousal response to morphine alone); the effects subsided within 30 minutes. All dogs were intubated and placed on mechanical ventilation (Harvard Apparatus). Arterial and venous cannulae were placed in the femoral vessels. A Swan-Ganz catheter was inserted into the pulmonary artery for measurement of pulmonary artery and capillary wedge pressures and for cardiac output determination by thermodilution during normal sinus rhythm. After these measurements, a midline cervical incision was made, and sinoaortic baroreceptor deafferentation was performed. Each aortic nerve was identified within its vagal sheath and placed on bipolar recording electrodes. The signal was amplified (model PS11, Grass Instruments) and fed into a loud speaker for confirmation of its pulse-synchronous activity; then, the nerve was cut. The carotid sinuses were denervated by ligating all tissues between the internal and external carotid arteries. Carotid baroreceptor denervation was considered complete if arterial pressure rose no more than 5 mm Hg with bilateral carotid occlusion, and total denervation was confirmed by the lack of change of heart rate and renal sympathetic nerve activity (see below) in response to nitroglycerin-induced hypotension.

The renal nerves were exposed for recording of postganglionic sympathetic nerve activity via an incision through the left flank. Branches of the renal nerves were separated from the renal artery and surrounding tissues, cut distally, desheathed, and placed on bipolar recording electrodes for recording of action potentials. The nerve and electrode tips were immersed in warm mineral oil. The signal was amplified, bandpass-filtered between 100 and 1,000 Hz, fed into a loud speaker, and fed into a counter that counts spikes at instantaneous frequencies up to 10 KHz (706C Nerve Traffic Analysis System, University of Iowa). Arterial blood gases and pH were checked at intervals throughout the protocol and maintained at pH 7.35–7.45; Pco2, 35–45 mm Hg; and Po2, 70–100 mm Hg. Supplemental chloralose (10 mg/kg) was administered hourly.

Stimulation of Atrial Mechanoreceptors

The technique of Linden et al13 was used to insert small balloons at the junctions of the three left-sided pulmonary veins and left atrium. Briefly, the left fifth rib was removed, and each of the three pulmonary veins was ligated at the hilum of the left lung. To prevent hemodynamic changes due to the mechanical effects of balloon inflation, the base of each lobe (including the pulmonary artery and bronchus) was ligated with umbilical tape. A small incision was made in each of the three pulmonary veins, and a catheter with a 1.5-ml balloon at its tip was inserted into each pulmonary vein so that the balloon (when inflated) exerted pressure at the junction of the pulmonary vein and left atrium. Position was confirmed by inspection and gentle palpation. Each period of atrial receptor stimulation consisted of 1 minute of control measurements, inflation of the three balloons for 2 minutes, and a 1-minute recovery period.

Stimulation of Receptors Throughout the Cardiopulmonary Tree

Five percent dextran in normal saline warmed to 38°C was infused to expand plasma volume by an estimated 5%, 10%, and 15%. Left atrial pressure was measured with a catheter inserted through the left atrial appendage. Arterial pressure and renal sympathetic nerve activity were recorded continuously.

Because left atrial pressure was elevated in the heart failure group, hemorrhage was performed in an additional five dogs to lower left atrial pressure to the normal range before volume expansion. Volume expansion then was performed in these animals to raise left atrial pressure back to baseline plus the additional 5%, 10%, and 15% of estimated plasma volume. After bilateral vagotomy, hemorrhage and volume expansion were repeated in these five animals.

Data Analysis

Analysis of responses of renal sympathetic nerve activity to vein-atrial balloon inflation was performed by the method of Linden et al.13 The second minute of a 2-minute balloon inflation was compared with the mean of a 1-minute preinflation period and a 1-minute recovery period. Nerve activity during this balloon inflation was expressed as percent of control. The inflations were performed three times, and the mean of the three measurements was used for analysis. Student’s t test was used to compare the heart failure and control groups. For volume infusion, the two groups were compared by ANCOVA using change in left atrial pressure as the covariate. A value of p≤0.05 was used to indicate statistical significance. All data are presented as mean±SEM.

Results

The baseline hemodynamic characteristics of the heart failure and control groups are presented in Table 1. Most parameters are similar to those observed by
TABLE 1. Baseline Hemodynamics in the Heart Failure and Control Groups of Dogs

<table>
<thead>
<tr>
<th></th>
<th>Heart failure</th>
<th>Control</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>CO (l/min)</td>
<td>1.5±0.1</td>
<td>2.1±0.2</td>
<td>0.02</td>
</tr>
<tr>
<td>RAP (mm Hg)</td>
<td>9.3±1.1</td>
<td>0.2±0.9</td>
<td>4×10⁻⁶</td>
</tr>
<tr>
<td>MPA (mm Hg)</td>
<td>37.9±2.5</td>
<td>16.6±2.7</td>
<td>6×10⁻⁶</td>
</tr>
<tr>
<td>PCWP (mm Hg)</td>
<td>25.6±2.0</td>
<td>4.0±1.2</td>
<td>3×10⁻⁸</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>107±4.0</td>
<td>120±8.7</td>
<td>0.13</td>
</tr>
<tr>
<td>RR (msec)</td>
<td>428±19</td>
<td>525±89</td>
<td>0.17</td>
</tr>
</tbody>
</table>

CO, cardiac output; RAP, right atrial pressure; MPA, mean pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; MAP, mean arterial pressure; RR, RR interval.

*p values are for individual *t* tests between groups.

other investigators who have used the same heart failure model.\textsuperscript{14,15} Arterial pressure was somewhat higher in the present study than in some other studies, probably due to the use of different anesthetic regimens.

An experimental record from a control animal during inflation of the pulmonary vein–left atrial balloons is shown in Figure 1. At the onset of balloon inflation, there is immediate, complete inhibition of renal sympathetic nerve activity, which recovers to 35% of the control level during the second minute of the 2-minute inflation. Mean results from the heart failure and control groups are illustrated in Figure 2. Renal sympathetic nerve activity was inhibited by 28±9% during the second minute of a 2-minute balloon inflation in the control group. This contrasts with only 5±3% inhibition (*p*=0.03) in the heart failure group. There also was a correspondingly larger decrease in arterial blood pressure in the control group than in the heart failure group (-13±4 versus -1±1 mm Hg). RR interval increased by 9.3±3.5 msec in the control group but did not change (0.4±0.2 msec) in the heart failure group. Left atrial pressure was unchanged in both groups during inflation of the balloons.

The data for volume expansion are illustrated in Figure 3. Before volume expansion, left atrial pressure was 1.4±1.2 mm Hg in the control group and 10.6±3.2 mm Hg in the heart failure group. These pressures were lower than the pulmonary capillary wedge pressures measured immediately after induction of anesthesia (Table 1), possibly because of the effect of thoracotomy (which caused left atrial pressure to drift downward) and/or differences between wedge and left atrial pressures. In the control group, infusion of 15% of estimated plasma volume raised left atrial pressure 3.5±0.8 mm Hg and resulted in a 70±8% reduction in renal nerve activity. This contrasts markedly with the heart failure group, in which left atrial pressure rose to a greater degree (6.8±3.0 mm Hg) but renal nerve activity decreased by only 16±20%. In both groups of animals, decreases in renal nerve activity with volume infusion were linearly related to the increases in filling pressure. However, the slopes of these lines were markedly different (-18.2 versus -2.4%/mm Hg for control and heart failure groups, respectively). The slope in the heart failure group was not significantly different from zero.

In the group of heart failure dogs that underwent pretreatment with hemorrhage, volume expansion raised left atrial pressure from 5.0±1.9 to 22±5.5 mm Hg. With maximal volume expansion, there was a reduction in renal nerve activity of only 30±11%. As is evident from Figure 3, this represented a reflex "sensitivit" (percent change in nerve activity divided by change in left atrial pressure) that was identical to that of the heart failure group that did not undergo pretreatment with hemorrhage and was markedly reduced compared with that of the normal group. Figure 4 shows that the responses of renal nerve activity elicited in the heart failure group were abolished after bilateral vagotomy.

Discussion

Our results show that vagal cardiopulmonary and atrial mechanoreflex control of renal sympathetic nerve activity is markedly abnormal in the rapid ventricular pacing model of heart failure in the dog. We used two techniques to stimulate mechanoreceptors in the cardiopulmonary region in a group of dogs with pacing-induced heart failure and compared these responses with those of a group of control animals. The first

**FIGURE 1.** Experimental recording in a control animal during a 2-minute inflation of three 1.5-ml balloons at the junctions of the left atrium and each of the three left pulmonary veins. Note the inhibition of renal sympathetic nerve activity during the second minute of balloon inflation (35% in this animal).
technique was to apply a constant amount of stretch to the junctions of the pulmonary veins with the left atrium; 1.5-ml balloons distended this region to the same degree in the two groups of dogs, so no assumptions were made regarding myocardial or vascular compliance characteristics. We found that the reflex reduction of sympathetic nerve activity was markedly impaired in the heart failure dogs. Linden et al.\(^\text{13}\) have shown that myelinated receptors mediate the sympathoinhibitory response to inflation of balloons at the pulmonary vein-left atrial junctions. We suggest that the sensitivity of these afferent endings is markedly reduced in the model of heart failure that we studied.

The second technique that we used to stimulate cardiopulmonary receptors was to expand plasma volume progressively by 5%, 10%, and 15% of estimated plasma volume. In normal animals, the sympathoinhibitory response to volume infusion is mediated primarily by unmyelinated vagal C-fiber afferent endings.\(^\text{16}\) Volume expansion raised left atrial pressure of the heart failure group to almost twice that of the control group, suggesting that myocardial or vascular compliance may be altered in heart failure. Despite the much greater elevation of cardiac filling pressure, there was a nonsignificant change in renal nerve activity in heart failure. We suggest that in addition to the defect in myelinated atrial mechanoreceptors, there is marked attenuation of unmyelinated vagal mechanoreceptors.

Previous studies in patients suggest that cardiopulmonary reflexes are abnormal in heart failure. Vasoconstrictor responses to negative pressure applied to the lower body (LBNP)\(^\text{10,11}\) and to orthostatic stress\(^\text{17}\) are diminished in heart failure patients. Mohanty et al.\(^\text{10}\) found that left ventricular end-diastolic volumes decreased in normal subjects during LBNP but did not change with \(\pm 30\) mm Hg LBNP in heart failure patients. This suggested altered left ventricular compliance characteristics in these patients. Because stretch is the primary stimulus for activation of cardiac mechanoreceptors, these findings suggest that for any given stimulus of LBNP there may be different degrees of activation of cardiopulmonary receptors in heart failure patients than in normal patients or animals. Therefore, attenuated responses to LBNP in heart failure patients could be due to either alterations in receptor sensitivity or altered myocardial compliance characteristics.

Zucker and colleagues\(^\text{8}\) suggested that left atrial receptors in dogs with high-output heart failure have reduced sensitivity and that inhibition of renal nerve activity during activation of cardiopulmonary receptors was reduced in heart failure.\(^\text{9}\) However, their dogs were studied first with arterial baroreceptors intact and then after carotid sinus denervation but with aortic baroreceptors intact. It is likely that arterial baroreflexes modulated the observed responses. In addition, distension of 10–20-ml left atrial balloons may have resulted in unloading left ventricular receptors due to reduced filling, thereby offsetting the responses to atrial/caridiopulmonary receptor stimulation. We studied dogs with total sinoaortic denervation, resulting in responses mediated exclusively by cardiac mechanoreceptors—not by arterial baroreflexes. Furthermore, our technique for atrial receptor stimulation had no effect on left ventricular filling pressures. Finally, we used a model of low-rather than high-output heart failure, which is more like heart failure usually seen in patients.

Inflation of the vein-atrial balloons resulted in immediate cessation of renal sympathetic nerve activity in the
normal animals and was followed quickly by partial recovery of nerve activity (Figure 1). This immediate sympatho-inhibitory response also was present in most of the heart failure dogs but was followed quickly by near-complete recovery of nerve activity. This suggests that aortic mechanoreceptors were able to increase their firing transiently and inhibit sympathetic outflow but were unable to sustain this decrease in nerve activity.

Each of the two techniques that we used to stimulate cardiopulmonary receptors has limitations. The balloons were used to provide a stimulus of known volume to distend the vein-atrial junctions to the same degree. It is likely that there was some degree of distention present already in the heart failure group. However, the fact that we saw an initial sympathoinhibitory response even in the heart failure group suggests that the stimulus was of sufficient magnitude to stimulate these receptors. The volume expansion that we used to stimulate mechanosensitive afferents throughout the cardiopulmonary tree may have resulted in a different stimulus intensity in the heart failure group due to altered myocardial compliance characteristics. However, the fact that we found a nonsignificant change in renal nerve activity when left atrial pressure was changed in the heart failure group by more than twice that of the control group provides compelling evidence for grossly abnormal cardiopulmonary control of sympathetic nerve activity in heart failure. Similar responses in a group of heart failure dogs that were hemorrhaged before volume expansion strengthens this view.

We used morphine and chloralose anesthesia to maintain hemodynamic profiles and cardiovascular reflexes as close as possible to the conscious state. However, we cannot exclude that there may have been some effects of anesthesia. Any intergroup differences were minimized by frequent assessment of the depth of anesthesia in all animals, ensuring a constant, stable plane of anesthesia.

Visceral afferent fibers that course to the spinal cord along with sympathetic fibers ("cardiac sympathetic afferents") are sensitive to both chemical and pressure stimuli, activation of which results in increases in efferent sympathetic nerve activity. The method that we used to stimulate vagal mechanoreceptors also may have activated sympathetic mechanoreceptors. We performed vagotomy to exclude the possibility that attenuated sympato-inhibitory responses to volume expansion in the heart failure group might be due to excessive activity of cardiac sympathetic afferents in heart failure that may have masked any inhibition of sympathetic efferent activity mediated by vagal afferents. We found that volume expansion resulted in no change in efferent sympathetic nerve activity after bilateral vagotomy. Therefore, if there was any activation of cardiac sympathetic afferents, it was insufficient to cause significant reflex response.

Both arterial and cardiopulmonary receptors normally serve to restrain sympathetic outflow. Some have speculated that reduced baroreceptor sensitivity in heart failure may lead to excessive sympathetic excitation. The present study demonstrates that cardiopulmonary baroreflex control of sympathetic nerve activity is attenuated in heart failure. This may result in decreased inhibitory influence of these receptors in heart failure and contribute to sympathetic excitation in heart failure. It also has been hypothesized that excessive activation of cardiac sympathetic afferent fibers might contribute to the sympathoexcitatory state in heart failure. The present study provides substantial evidence against enhanced reflex activation of cardiac sympathetic afferents in heart failure, although we cannot exclude the possible contribution of sympathetic afferents to the resting sympathoexcitatory state.

There are several possible mechanisms for abnormal cardiopulmonary reflexes in heart failure. Zucker et al provided histological evidence of degeneration of unencapsulated atrial receptor endings in dogs with high-output heart failure. However, because these abnormalities can be reversed after correction of heart failure, a functional rather than an anatomic abnormality is more likely to be important in the pathogenesis of reflex abnormalities. These functional abnormalities could be present at the receptor level, in the central nervous system, or in efferent nerve control or transmission. Wang et al provided evidence for excessive Na⁺-K⁺ pump activity as a mechanism for decreased arterial baroreceptor activity. Evidence from studies of humans with heart failure suggests that digoxin normalizes cardiopulmonary reflex control of sympathetic nerve activity and supports the view that impairment of cardiopulmonary reflexes is the result of functional rather than structural changes. It also is conceivable that there are structural abnormalities of baroreceptors that may improve with treatment or reversal of heart failure.

Patients and animals with heart failure have elevated levels of a variety of neurohormones, some of which may have important effects on cardiovascular reflexes. Arginine vasopressin is elevated in heart failure patients. However, arginine vasopressin facilitates cardiopulmonary inhibition of renal sympathetic nerve activity, so it would be expected to oppose the reduced cardiopulmonary control of renal nerve activity observed in the present study. On the other hand, angiotensin II, also elevated in heart failure, has direct cardioaccelerator properties and suppresses baroreflex control of heart rate and sympathetic activity, possibly via central actions on the area postrema. We speculate that the reduced cardiopulmonary control of renal sympathetic nerve activity found in the present study could result in part from the effects of angiotensin II on reflex control.

Hintze and colleagues recently reported that ventricular reflexes elicited by prostacyclin are accentuated in dogs with pacing-induced heart failure. Vagal endings that respond to chemical activation (including bradykinin and prostaglandins) are not particularly sensitive to mechanical stimuli. The present study was an examination of the influence of mechanoreflexes. Our observations along with those of Hintze et al indicate that not all vagal afferents are uniformly depressed in heart failure and that blunted reflex responses may be limited to mechanosensitive rather than chemosensitive afferent fibers.

In a previous study from our laboratory, we showed that despite reduced sensitivity of arterial baroreceptors in this model of heart failure, arterial baroreflex control of renal sympathetic nerve activity was preserved, suggesting there was central augmentation of this reflex. In the present study, we found attenuated reflex control of sympathetic nerve activity by cardiopulmonary mecha-
noreceptors in heart failure. Findings from these two studies suggest that the central augmentation of the arterial baroreflex in heart failure is unable to compensate for abnormalities in the afferent limb of the cardiopulmonary baroreflex.

Acknowledgments

The authors thank David Brands, Kimberly Dailey, and Farhad Forudi for technical help.

References

32. Staszewska-Barczak J: Prostanoids and cardiac reflexes of sympathetic and vagal origin. Am J Cardiol 1983;52:36A–45A
Control of sympathetic nerve activity by vagal mechanoreflexes is blunted in heart failure.

M E Dibner-Dunlap and M D Thames

Circulation. 1992;86:1929-1934
doi: 10.1161/01.CIR.86.6.1929

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1992 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/86/6/1929.citation

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/