Ventricular Mechanoreflex and Chemoreflex Alterations in Chronic Heart Failure

Marian Brändle, Wei Wang, Irving H. Zucker

Abstract Cardiac and arterial baroreflex control of the circulation is abnormal in both human and experimental heart failure. Ventricular vagal afferents mediate mechanical and chemical reflexes, which result in bradycardia and hypotension. The aim of the present study was to evaluate the changes that occur in ventricular mechanoreflexes and chemoreflexes in a conscious canine model of chronic heart failure. Dogs were instrumented for the measurement of left ventricular pressure, left atrial pressure, arterial pressure, and heart rate. Vascular occluders were placed on the ascending thoracic aorta, on the descending thoracic aorta, and on the thoracic inferior vena cava. A chronic left circumflex coronary artery catheter was also implanted. Finally, a pacing lead was secured to the left ventricular free wall. After recovery from surgery (10 to 14 days), the dogs were subjected to complete arterial baroreceptor denervation. The responses to vascular occlusions and intracoronary administration of prostacyclin (PGI1) were carried out before and after heart failure was induced by chronic cardiac pacing at 250 beats per minute. PGI1 was used as a chemical stimulus for ventricular afferents; ascending aortic occlusion was used as a mechanical stimulus. Before chronic pacing, ascending aortic occlusion resulted in a decrease in heart rate of 36.1±12.3 beats per minute (mean±SD, P<.001). After heart failure was induced, the heart rate response to ascending aortic occlusion was almost completely abolished. The slope of the linear relation between pulse interval and left ventricular end-diastolic pressure was reduced by 90.5% from a control value of 11.3±6.9 ms/mm Hg after heart failure had been induced. In three dogs, the bradycardia had returned after cessation of the pacing. On the other hand, there was no change in the response to intracoronary PGI1 after heart failure had been induced. The primary effect was a leftward shift in the PGI1 and heart rate dose-response curve in the heart failure state. At the midrange dose, which averaged 9.5±6.7 ng/kg, heart rate was reduced by 9.6±10.4 beats per minute before pacing versus 36.0±8.9 beats per minute after heart failure (P<.05). Because there were directionally different changes in heart rate evoked by mechanoreflexes and chemoreflexes in heart failure, it is suggested that the change in these reflexes is not mediated by abnormal efferent vagal function but rather by alterations in different types of ventricular vagal afferents. (Circ Res 1994;74:262-270.)

Key Words • cardiac reflex • heart rate • vagus • cardiac pacing • prostaglandins

The myocardium is richly innervated by sensory nerve endings whose axons traverse both vagal and sympathetic pathways. These nerve endings respond to a variety of sensory modalities that can be classified as either mechanically or chemically sensitive. Under some circumstances, endings may respond to both mechanical and chemical stimuli.1 Left ventricular vagal afferents are thought to mediate the Bezold-Jarisch reflex,2-4 which causes a bradycardia and hypotension that are primarily due to cardiac vagal activation and withdrawal of peripheral sympathetic tone.3 It has now been clearly shown that the Bezold-Jarisch reflex can be activated by endogenous substances such as prostaglandins (PGs),5,6 bradykinin,7 and serotonin.8 Activation of ventricular vagal afferents not only results in hypotension and bradycardia but also causes an attenuation of the arterial baroreflex. In studies carried out in this laboratory, we have demonstrated an important and potent effect of cardiac PGs on the expression of the arterial baroreflex under a variety of conditions. In conscious instrumented dogs, we constructed baroreflex curves using implanted vascular occluders. These curves were carried out under control conditions in which a Tris buffer was infused into the left circumflex coronary artery or when either prostacyclin (PGI2), PGE2, or arachidonic acid was infused into the left circumflex coronary artery or into a peripheral vein.9 All three agents caused a significant depression in the maximum heart rate (HR) achieved during inflation of the vena caval occluder as well as a significant decrease in the slope of the arterial pressure (AP)–HR relation. Application of a local anesthetic to the pericoronary area prevented the prostaglandin inhibition of the baroreflex.

Because these reflexes are so potent under normal conditions, it is of interest to determine whether these cardiac reflexes behave differently in states in which the myocardium is either chronically dilated or hypertrophied. Studies carried out in anesthetized dogs with congestive heart failure suggest that the cardiac mechanoreflex is significantly blunted in this state.10-12 These studies were carried out in dogs with all reflexes intact. There have been no studies that have compared cardiac mechanoreflexes with cardiac chemoreflexes in heart failure. In a preliminary report, Hintze et al4 have demonstrated that the intravenous injection of PGI2 caused, in intact conscious dogs, a hypotension and bradycardia that were potentiated by pacing-induced heart failure.6

The aim of the present study was therefore to determine whether the cardiac mechanoreflex and the cardiac chemoreflex are altered in pacing-induced heart
failure in conscious dogs. This question is important because (1) these reflexes may have potent effects on the regulation of sympathetic outflow in heart failure and (2) cardiac chemoreflexes may be activated during coronary ischemia\textsuperscript{13,14} either with or without heart failure. The integrated effects of these two reflexes may determine, in part, the changes in sympathetic outflow that occur in chronic heart failure.

Materials and Methods

Animals and Surgical Preparation

All experiments were carried out on healthy adult mongrel dogs of either sex, averaging 25.3±2.2 kg in weight. Dogs were housed in large indoor runs and were conditioned to a 12-hour light cycle. They were fed a combination of dry and canned dog food once per day and were allowed water ad libitum. The integrated effects and (2) the University of Nebraska Medical Center Animal Facility. All surgical and experimental procedures were approved by the University of Nebraska Medical Center IACUC. These surgical procedures have been previously described in detail.\textsuperscript{15} In brief, dogs were anesthetized with pentobarbital sodium (30 mg/kg IV) and intubated. They were placed on a positive-pressure respirator (Harvard Apparatus). A left thoracotomy was performed through the fifth intercostal space. Instrumentation consisted of placing perivascular occluders on the ascending thoracic aorta just above the aortic valve, on the descending thoracic aorta, and on the thoracic inferior vena cava just above the diaphragm. These occluders were used to alter intracardiac pressures and to test for baroreflex denervation after sinoaortic denervation (SAD). Tygon catheters were implanted in the descending thoracic aorta above the occluder for the measurement of AP, in the left ventricle for the measurement of left ventricular pressure (LVP), and in the left atrium for the measurement of left atrial pressure (LAP). A silastic catheter was placed in the left circumflex coronary artery using a modified technique as described by Herd and Barger.\textsuperscript{16} This catheter was used for the administration of PGs into the coronary circulation. Finally, a pacing electrode was secured to the left ventricular free wall (model 6917T, Medtronic). All catheters and wires exited the chest and were tunneled beneath the skin. The catheters exited in the mid-pectoral region. The pacing electrode was left under the skin until the pacemaker was implanted. The chest was closed in layers and evacuated. Dogs were placed on an antibiotic regimen of Combicotic (0.5 mL/kg) for 5 days after surgery. If, after this time, a fever was evident, the dogs were treated with either Amikin (7.5 mg/kg) or Keflex (1 g) for an additional 5 days. Experiments were carried out on dogs that were eating and drinking normally and had rectal temperatures <103°F. Animals were allowed to recover for ~2 weeks before the initial experiment was performed. During this time, they were trained to lie quietly on a laboratory table in a dimly lit room.

Sinoaortic Denervation

The dogs were anesthetized with pentobarbital sodium (30 mg/kg IV). Under sterile conditions, the carotid sinus nerves were isolated and sectioned. The carotid sinus, common carotid, and internal and external carotid arteries were stripped of their adventitia for ~1 cm above and below the carotid bifurcation. These vessels were then painted with 10% phenol in alcohol to ensure complete denervation. The vagal sheaths were opened, and the sympathetic trunks were separated from the vagi at the level of the nodose ganglia. The aortic depressor nerves were ultimately identified by recording their characteristic activity. The aortic depressor nerves were then sectioned. The neck was then closed, and the dogs were allowed to recover for 7 to 10 days before the next experiment was performed. During this recovery period, the dogs were brought to the laboratory several times to evaluate the completeness of the SAD. The vena caval and descending aortic occluders were inflated to lower and raise pressure in the aortic arch. The change in HR during these maneuvers was used as an index of the adequacy of SAD. Dogs that demonstrated changes in HR in either direction of >10 beats per minute with changes in aortic pressure of 40 to 50 mm Hg were considered not denervated. All dogs in the present study met the above criteria.

Induction of Heart Failure

After the pre–heart failure studies were complete, a pacemaker was implanted for chronic pacing. Dogs were sedated with acepromazine (0.3 mg/kg IM). Under local anesthesia, the pacing lead was retrieved from beneath the skin. It was attached to a Medtronic pacemaker (model 5985 or 8329), which was placed beneath the skin on the back. These pacemakers were modified by us or by Medtronic to pace in the temporary mode at rates substantially higher than their capability in the permanent mode. Using a programming unit (model No. 9710), we determined the minimum voltage and pulse duration for capturing the ventricle. The technique of producing chronic congestive heart failure was that originally described by Coleman et al.\textsuperscript{17} The pacing rate was set at 250 beats per minute, and the dogs were continuously paced until signs of severe congestive heart failure were evident. The dogs were examined daily, and hemodynamic measurements were made weekly. The criteria used for concluding that a dog was in heart failure were a mean LAP and a left ventricular end-diastolic pressure (LVEDP) of >20 mm Hg and a resting HR of >120 beats per minute. In addition, pulmonary edema was assessed by auscultation, and ascites was evaluated by visual inspection. All dogs in heart failure exhibited dyspnea at rest and an exercise intolerance that was determined by a reduced ability of the dogs to walk from the kennel area to the laboratory (~0.5 km) compared with their prepping state. All hemodynamic measurements were made with the pacemaker programmed to the inhibit mode (pacemaker turned off and no pacing artifact) within ~15 minutes after turning the pacemaker off.

Data Acquisition

All pressures were recorded with Hewlett-Packard pressure transducers (model 1270A) attached to Honeywell signal-conditioning amplifiers (model 143) and were recorded on an eight-channel Hewlett-Packard recorder (model 7758 A). HR was derived using a Honeywell cardiostethometer (model 133) that was triggered by the LVP pulse wave. All signals were fed to a Buxco hemodynamics analyzer, where the analog signals were digitized and displayed on a scrolling monitor. All recordings were stored on optical disk and could be played back for later analysis.

Experimental Protocols

Cardiac Mechanoreflex

All experiments were conducted with the pacemaker turned off and in the inhibit mode. Before pacing and with dogs in the SAD state, the ascending aortic occluder was inflated to raise LVP and LAP. The HR response to this intervention was recorded. In addition, the effect of lowering intracardiac pressures during inflation of the vena caval occluder was also examined. The occluders were inflated until AP fell to levels of 20 to 30 mm Hg (~10 seconds), at which time they were rapidly deflated, and pressure immediately returned to near control levels. This maneuver did not appear to cause any signs of significant distress or discomfort to the dogs. This maneuver was repeated at weekly intervals during pacing. In three dogs, the responses to ascending aortic and vena caval occlusion were assessed after discontinuing pacing and allowing the dogs to recover for several weeks. The response to descending aortic occlusion was also determined.
TABLE 1. Baseline Hemodynamics, Body Weight, and Duration of Pacing in Dogs With Sinoaortic Denervation

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Before SAD</th>
<th>After SAD</th>
<th>SAD-HF</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEDP, mm Hg</td>
<td>6.4±3.7</td>
<td>4.9±3.6</td>
<td>31.3±7.2†</td>
</tr>
<tr>
<td>MLAP, mm Hg</td>
<td>5.5±2.0</td>
<td>3.8±2.5</td>
<td>27.2±7.7†</td>
</tr>
<tr>
<td>MAP, mm Hg</td>
<td>99.2±12.9</td>
<td>98.6±21.0</td>
<td>109.8±17.2†</td>
</tr>
<tr>
<td>HR, bpm</td>
<td>67.3±16.4</td>
<td>116.6±20.0*</td>
<td>142.5±24.0†</td>
</tr>
<tr>
<td>LV dp/dt, mm Hg/s</td>
<td>3383±691</td>
<td>3484±591</td>
<td>1828±352†</td>
</tr>
<tr>
<td>Body weight, kg</td>
<td>25.3±2.3</td>
<td>24.7±2.3</td>
<td>24.2±2.7</td>
</tr>
<tr>
<td>Time, d</td>
<td></td>
<td></td>
<td>25.0±9.7</td>
</tr>
</tbody>
</table>

SAD indicates sinoaortic denervation; SAD-HF, heart failure induced in the SAD state; LVEDP, left ventricular end-diastolic pressure; MLAP, mean left atrial pressure; MAP, mean arterial pressure; HR, heart rate; bpm, beats per minute; LV dp/dt, maximum of the first derivative of left ventricular pressure; and time, duration of pacing. Values are mean±SD (n=8).

*P<.05 vs values before SAD.
†P<.05 vs prepared state.

Cardiac Chemoreflex

With the pacemaker turned off, stimulation of left ventricular afferents was carried out by the intracoronary injection of PGI2 in doses that varied between 1 and 100 ng/kg. These doses produced no or very small effects when given intravenously. The effects of these injections on HR and AP were determined when the dogs were in the SAD state before pacing was started and when the dogs were in severe heart failure as determined by the criteria outlined above. In addition, three SAD dogs were sham-operated. These dogs had intracoronary injections of PGI2 separated by 3 to 4 weeks without being paced.

Data Analysis

For mechanoreflex responses, the maximum change in HR in response to each occlusion was determined directly from the strip-chart recordings. In addition, the relation between LVEDP and the change in HR (plotted as pulse interval) during ascending aortic occlusion was determined on a beat-to-beat basis during the occlusion from the stored data.

For chemoreflex responses, the maximum changes in HR and AP were determined from the strip-chart recordings. Each dog seemed to operate on a slightly different dose-response curve for PGI2. Therefore, the doses were classified as high, medium, or low according to whether they were maximal, midrange, or threshold responses, respectively. The response to the average dose at each level was plotted as the log dose versus the maximum change in HR.

The change in HR in response to vascular occlusions was analyzed by a two-way ANOVA in which the changes to occlusions were determined in both the prepared and postpaced states. A similar analysis was performed for the PGI2 dose-response curves. When statistical significance was found, post hoc analysis was performed by use of the Newman-Keuls test. The change in hemodynamic parameters after induction of heart failure was analyzed using a paired t-test. Statistical significance was assumed at P < .05. All data are presented as mean±SD.

Results

Hemodynamics in Heart Failure and Sinoaortic Denervation

A total of eight dogs were studied before pacing and after pacing-induced heart failure. The average duration of pacing was 25.0±9.7 days. Table 1 shows hemodynamic variables taken at rest before and after heart failure. Baseline HR tended to be higher after SAD. Although mean arterial pressure (MAP) was not significantly increased after SAD, HR was significantly elevated to 116.6±20.0 beats per minute. Before SAD, these dogs had HRs averaging 87.3±16.4 beats per minute. After heart failure was induced, HR was observed to increase to 142.6±24.0 beats per minute. SAD did not alter any other hemodynamic parameter. The variability in AP as indicated by the standard error of the mean was greater in the SAD state. There was a significant increase in LVEDP, LAP, and MAP after pacing in these SAD dogs. Left ventricular dp/dt max was reduced by 47.5% after pacing. In addition to the hemodynamic changes, clinical signs of heart failure were evident after pacing. These included pulmonary edema, ascites, and exercise intolerance, although all signs did not appear in every animal.

Mechanoreceptor Stimulation

Fig 1 shows a representative recording of the response to ascending aortic occlusion in one dog before and after heart failure. Before SAD, ascending aortic occlusion resulted in a marked fall in AP and an increase in LVP and LAP. HR increased initially and then returned toward the control value. After SAD, ascending aortic occlusion caused a frank reduction in HR. In this particular SAD dog, HR fell by ~35 beats per minute from a control value of 145 beats per minute. After the induction of heart failure, ascending aortic occlusion caused similar changes in AP, LVEDP, and LAP but did not evoke bradycardia.

The relation between LVEDP and the change in HR in the control and heart failure states is shown in Figs 2 and 3. Fig 2 shows that the response to ascending aortic occlusion is variable. The responses from two SAD dogs before and after induction of heart failure are shown in this figure. In the top panel, ascending aortic occlusion evoked an increase in pulse interval on a beat-to-beat basis starting from an LVEDP of 5 mm Hg up to almost 25 mm Hg. The slope of this regression line was 21.7 ms/mm Hg, with a correlation coefficient of 0.98. Three of the eight dogs responded in this manner. However, the dog shown in the bottom panel of Fig 2 responded differently. There was no change in HR until an LVEDP of ~20 mm Hg was reached; then a linear decrease in HR was observed. The slope of the regression line describing the bradycardia in this dog was 17.6 ms/mm Hg, with a correlation coefficient of 0.98. Five of the eight dogs responded in this fashion. After heart failure was induced (right panels of Fig 2), elevating LVEDP to extremely high levels failed to alter HR. Fig 3 shows the individual and mean data for the slope of the linear portion of the relation between LVEDP and pulse interval. The average slope decreased in the heart failure state by 90.5% from a control value of 11.3±6.9 ms/mm Hg (P<.001). Although it is generally assumed that this mechanoreflex is evoked only at extremely high LVPs, it can be seen from Fig 2 that bradycardia could be evoked at lower LVEDPs in the SAD state in some dogs. The mean data from the occlusion experiments are shown in Fig 4. The responses to ascending and descending aortic occlusions and to vena caval occlusions are shown before SAD, after SAD, and after heart failure was induced with dogs in the SAD state. Before SAD, vena caval occlusion evoked a strong tachy-
cardiac response that was undoubtedly due to baroreceptor unloading. HR increased by an average of 95.8±41.3 beats per minute, whereas MAP decreased by 45.4±7.3 mm Hg. Likewise, descending aortic occlusion evoked a significant bradycardia (decrease of 25.5±26.1 beats per minute). The response to ascending aortic occlusion before SAD is divided into two phases, the initial tachycardia (phase 1) and the return toward baseline (phase 2). HR increased by 47.7±22.5 beats per minute when MAP was reduced by 22.8±7.5 mm Hg. As MAP continued to fall and LAP continued to increase, HR fell (phase 2) toward control levels. This second phase was highly variable: some dogs showed a return toward the control value, whereas others showed a frank bradycardia. After SAD but before chronic pacing was begun, vena caval and descending aortic occlusions failed to change HR despite large changes in AP, confirming the effectiveness of the SAD. Ascending aortic occlusion, on the other hand, evoked a pronounced and significant bradycardia. HR fell by

![Fig 1](https://circres.ahajournals.org/)

**Fig 1.** An original strip-chart recording of the response to an ascending aortic occlusion in a dog before sinoaortic denervation (SAD), after SAD, during pacing (heart failure [HF]), and after recovery from pacing. The tracings from top to bottom are as follows: left ventricular pressure (LVP), heart rate (HR), arterial blood pressure (ABP), and left atrial pressure (LAP). The LAP tracing after SAD before pacing is a pulsatile tracing; the other left atrial tracings are mean LAP. Note that ascending aortic occlusion increases LAP and LVP while reducing ABP. The effects on HR vary depending on the state of the dog. The arrows indicate the time the occlusion was started; bpm, beats per minute.

![Fig 2](https://circres.ahajournals.org/)

**Fig 2.** Graphs showing the heart rate (pulse interval) response to occlusion of the ascending aorta in two dogs with sinoaortic denervation before (○) and after (●) heart failure was induced by pacing. Pulse interval is plotted against left ventricular end-diastolic pressure (LVEDP) on a beat-to-beat basis. Note that two types of response patterns were observed. The dog represented in the top panels shows a linear decrease in heart rate as LVEDP is increased. This dog also shows a low threshold for this response. The dog represented in the bottom panels shows a high threshold for the bradycardia in response to aortic occlusion. In this dog, heart rate did not change until LVEDP was ~20 mm Hg. In both dogs, there was no response to aortic occlusion after heart failure was induced.

![Fig 3](https://circres.ahajournals.org/)

**Fig 3.** Graph showing mean and individual slopes of the linear portion of the relation between left ventricular end-diastolic pressure and pulse interval before (○) and after (●) heart failure. In all but one dog, the slope was reduced to zero after heart failure was induced. The error bars denote ±1 SD. *P < .05 vs control.
36.1±12.3 beats per minute during ascending aortic occlusion despite a significant fall in AP and a large increase in LAP. After pacing, when the dogs were in stable heart failure, ascending aortic occlusion failed to evoke a significant change in HR. The response to ascending aortic occlusion was abolished at week 1 (early period) and remained blunted until the final heart failure experiment was carried out. Table 2 shows baseline HR, MAP, and LAP before and at each stage of pacing. Note that HR and LAP increased progressively over this time, whereas MAP was maintained. In the three dogs in which the pacemaker was turned off and recovery was allowed, the response to ascending aortic occlusion (i.e., the bradycardia) returned, even though the LAP and LVEDP had not returned to control levels. In three SAD nonpaced dogs, ascending aortic occlusion evoked bradycardia, which was not changed over a 4-week period.

**Stimulation of Chemosensitive Receptors**

Fig 5 shows a strip-chart recording of the response to intracoronary PGI$_2$. The left panel shows the responses to 2.5 ng/kg in a SAD dog before pacing. This dose represents a low dose for this particular dog. The right panel shows the responses to this same dose of PGI$_2$ after 30 days of ventricular pacing. PGI$_2$ evoked a hypotension and bradycardia in both control and heart failure states. The HR response was greater after pacing. The mean data for the responses to PGI$_2$ are shown in Fig 6. Because each dog operated on a different dose-response curve, the data are expressed as the mean change in HR and MAP versus the log of the mean dose of PGI$_2$ used at the threshold, midrange, and maximum doses. The change in HR was significantly greater at the threshold and midrange doses. The difference between the pre- and post–heart failure states at the maximum dose did not reach significance. Although the slopes of the linear regression curves through the mean data shown in Fig 6 are not different (−14.3 before pacing versus −16.6 after pacing), the y intercepts indicate a parallel shift of the dose-response curve toward a greater bradycardia in the postpacing state (+3.2 beats per minute before pacing versus −10.8 beats per minute after pacing). In contrast to the change in HR, the change in MAP was not significantly different in the control and heart failure states. The HR responses to intracoronary PGI$_2$ (50 ng/kg) were examined in three sham-operated SAD dogs that were not paced. The responses were separated by 3 to 4 weeks. PGI$_2$ evoked a decrease in HR of 22.3±5.4% from a control value of 113.6±8.5 beats per minute for the first response and a decrease in HR of 26.6±8.4% from a control value of 101.9±20.1 beats per minute for the second response. These were not significantly different from each other.

**Discussion**

It is a generally assumed that cardiac reflexes are attenuated in heart failure. This is based, in part, on data from atrial reflexes. Based solely on the response of atrial receptors or the reflex responses to interventions such as acute volume expansion, this notion is not justified.$^{10-12,18}$ Since ventricular reflexes may behave differently if they are subserved by different types of afferent endings. In addition to mechanoreflexes emanating from ventricular afferents, chemically sensitive

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**Table 2. Baseline Hemodynamics Early and Late in the Course of Pacing and Recovery From Heart Failure**

<table>
<thead>
<tr>
<th></th>
<th>Before SAD</th>
<th>After SAD</th>
<th>Pacing (n=8)</th>
<th>Recovery (n=3)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Early</td>
<td>Late</td>
<td>Early</td>
<td>Late</td>
</tr>
<tr>
<td>MLAP, mm Hg</td>
<td>5.5±2.0</td>
<td>3.8±2.5</td>
<td>11.8±6.6*</td>
<td>27.2±7.7*</td>
</tr>
<tr>
<td>MAP, mm Hg</td>
<td>99.2±12.9</td>
<td>98.6±21</td>
<td>105.6±20</td>
<td>109.8±17</td>
</tr>
<tr>
<td>HR, bpm</td>
<td>87.3±16.4</td>
<td>116.6±20</td>
<td>134.0±23*</td>
<td>142.6±24*</td>
</tr>
<tr>
<td>Time, d</td>
<td>.</td>
<td>.</td>
<td>7.2±0.4</td>
<td>25.0±9.7</td>
</tr>
</tbody>
</table>

SAD indicates sinoaortic denervation; MLAP, mean left atrial pressure; MAP, mean arterial pressure; HR, heart rate; bpm, beats per minute; and time, duration of pacing or recovery. Values are mean±SD.

*P<.05 vs control values.
endings in the ventricles mediate reflexes that are similar to the Bezold-Jarisch reflex. These chemosensitive endings are activated by a variety of endogenous and exogenous substances that include PGs, bradykinin, serotonin, and veratridine. Chemosensitive ventricular reflexes not only mediate hypotension and bradycardia but also inhibit the arterial baroreflex control of both HR and sympathetic nerve activity.9,20

The data presented in the present are, to our knowledge, the first to demonstrate abnormalities in cardiac reflexes in conscious dogs after SAD. Mechanoreflex responses (ie, the HR response to ascending aortic occlusion) were almost completely abolished after 1 week of ventricular pacing. The mechanism for the recovery response is not completely clear. Although, in the three dogs that were allowed to recover, the LAP was 10.7±1.2 mm Hg, which was significantly higher than in the paced group (3.8±2.5 mm Hg), it was also significantly lower than in the paced group (27.2±7.7 mm Hg). It is possible that the LAP and the LVEDP were slightly elevated during recovery because of sustained ventricular remodeling21 but that heart size returned to near normal. On the other hand, the HR response to intracoronary injection of PGI2 was not attenuated. Although the AP responses to intracoronary PGI2 were not different in the heart failure state, this is difficult to interpret because of direct vascular effects of PGI2 and the fact that vascular reactivity is altered in heart failure.22,23

**Efferent Pathways Mediating Changes in Heart Rate During Cardiac Receptor Stimulation**

The bradycardia in response to elevation of LVP is mediated by activation of the efferent vagus. This fact has been demonstrated in intact dogs by the abolition of the bradycardia to increased LVP after atropine admin-
istration.24 Although atropine was not given in the present study, several animal and human studies have shown that bradycardia in response to interventions that increase LVEDP can be blocked or blunted by atropine.15,24 Likewise, the HR response to the administration of PGI₂ is mediated to a large extent by the efferent vagus.9 Eckberg et al²⁵ have shown a poor vagal response to baroreflex activation with phenylephrine in patients with cardiac dysfunction. A similar mechanism has been proposed in dogs with high-output heart failure due to an aortocaval fistula.2⁶ In studies from this laboratory using the pacing model of heart failure, we observed abnormalities in both vagal and sympathetic arms of baroreflex function in response to hypotension, although the vagal response to phenylephrine administration remained intact.2⁷ In addition, we have previously shown that the bradycardia in response to intracoronary administration of veratridine was normal in this model of heart failure.2⁸ These data would suggest that both efferent vagal and sinoatrial nodal function is normal in this model of heart failure. The blunted ventricular mechanoreflex shown in the present study is not likely due to the failure of the efferent vagus to turn on or to activate the sinoatrial node, since the response to intracoronary PGI₂ was maintained. This would suggest a specific afferent abnormality to account for the blunted mechanoreflex.

**Afferent Pathways Mediating the Heart Rate Changes During Cardiac Receptor Stimulation**

Since it has been shown that abnormalities in cardiovascular sensory transduction exist in heart failure,1⁸,2⁹ it would not be surprising that ventricular mechanoreceptor abnormalities also exist. For the mechanoreflex, the receptors could reside in the left ventricle, the left atrium, or the pulmonary vascular bed, since occlusion of the ascending aorta increases pressure at all of these sites. Two pieces of evidence argue against the site of the receptors being in the left atrium or in the pulmonary bed. First, left atrial receptor stimulation evokes tachycardia, not bradycardia.²⁰ Second, Mark et al.³¹ have shown that patients with severe aortic stenosis exhibit forearm vasodilation and syncpe when subjected to bicycle exercise. However, this was not seen in patients with mitral stenosis. In a companion study by Mark et al.,³² it was shown that left ventricular outflow obstruction resulted in peripheral vasodilation. These data would suggest that left ventricular afferents mediate this response. Although we cannot definitively rule out a contribution of pulmonary afferents in this response, the basis of the two studies cited above, it does not appear that stimulation of pulmonary afferents is necessary for evoking reflex bradycardia during cardiac distension.

Chemically sensitive afferents have been described throughout the left ventricular myocardium.¹,³⁴ PGs have been shown to stimulate these endings and to reverse the tachyphylaxis to bradykinin.²⁶ Direct left circumflex coronary artery administration of PGI₂ evokes a reflex bradycardia and sympathoinhibition by stimulation of left ventricular afferents.⁹,²⁰ This reflex is mediated by an afferent vagal pathway, since application of lidocaine to the pericoronary nerves results in abolition of the reflex.⁹,²⁰ It is highly likely that the bradycardia evoked in the present study in response to intracoronary PGI₂ was mediated by vagal C fiber afferents. Although other chemical stimuli such as veratridine show enhanced reflex responses in heart failure,²⁸ the response to this agent is more difficult to interpret than the response to PGI₂, since veratridine may stimulate both chemically and mechanically sensitive afferents.³⁰

Ventricular mechanoreflexes have been attributed to changes in systolic ventricular pressure, end-diastolic ventricular pressure, and myocardial contractility.³⁴,³⁶ Clearly, there are changes in all of these parameters in the heart failure state (Table 1). The increase in LVEDP during ascending aortic occlusion was similar in the normal and heart failure states. In fact, the absolute LVEDP evoked by ascending aortic occlusion was substantially greater in the heart failure state, since the baseline pressure was higher. On the other hand, left ventricular systolic pressure could not be increased to the same degree in the heart failure state. The mechanism of the blunted ventricular mechanoreflex in heart failure may be related to a decrease in left ventricular systolic pressure or contractility or to resetting of ventricular mechanoreceptors due to a prolonged period of elevated LVEDP. It is unlikely that the blunting of the ventricular mechanoreflex is due to differences in left ventricular systolic pressure or contractility. Afferent recording experiments have shown a good relation between LVEDP and afferent discharge during aortic occlusion;³⁴,³⁶,³⁷; however, increases in left ventricular systolic pressure alone are not sufficient to increase the discharge of ventricular afferents. Thoren and Gupta and Thames have demonstrated that enhancement of the inotropic state in cats increases the firing of ventricular afferents at a given end-diastolic pressure. Although afferent recordings have not been made in the dog during enhancement of the inotropic state, data from this laboratory have shown that enhancement of the inotropic state in the conscious SAD dog by intracoronary infusion of epinephrine did not augment the HR response to ascending aortic occlusion. Finally, mechanoreceptors from a wide variety of systems have been shown to exhibit resetting, loss of sensitivity, or both during a sustained stimulus.³⁸ The only stimulus known to activate left ventricular mechanoreceptors that is chronically increased in the heart failure state is LVEDP. This could result in blunting of the afferent discharge sensitivity or resetting of the pressure-discharge relation much the same as has been shown to occur for atrial receptors.³⁹ Recent data from our laboratory have shown that the depression of carotid sinus baroreceptor discharge in pacing-induced heart failure is likely due to augmentation of Na⁺, K⁺-ATPase activity.³⁹ Although we cannot provide evidence for this, it is possible that a similar mechanism may be operating to blunt ventricular mechanoreceptor discharge sensitivity in heart failure.

Since the HR response to intracoronary PGI₂ was maintained or enhanced in heart failure, it is unlikely that there was a generalized depression of receptor sensitivity. It is not clear why the response to PGI₂ was enhanced in the heart failure state. We can speculate that there may be additional substances released in heart failure that can potentiate the response to PGI₂. For instance, in the atrioventricular fistula model of heart failure, there are increased levels of PGI₂ in the pericardial effusate.³⁹ Since
the model we used has been characterized histologically as being consistent with chronic ischemia, there may be several substances that are released by the myocardium that potentiate the response to PGI₁, such as potassium and bradykinin. In an important study by Mapp et al., it was shown that the ability of PGI₁ to contract guinea pig isolated bronchi was mediated by capsaicin-sensitive afferents. A selective inhibitor of NK-2-tachykinin receptors decreased the PGI₁ contractions. Therefore, the effects of PGI₁ could be due to tachykinin release, which may be enhanced in heart failure. We cannot, of course, rule out a direct neuronal membrane effect that may be responsible for enhancement of the PGI₁ response in heart failure. For instance, Pritchford and Levine have recently shown that PGI₁ acts to enhance current flow in response to capsaicin in nociceptors. cAMP was shown to be a second messenger in this response. These investigators concluded that PGI₁ sensitizes nociceptors.

Another possibility that could explain the enhanced response to intracoronary PGI₁ in heart failure is that a reduction in coronary blood flow may have caused an increase in the effective concentration of PGI₁ at the receptor level. We do not believe this to be a likely possibility for two reasons. First, we measured left circumflex coronary blood flow (Doppler technique) in one dog before and after pacing-induced heart failure. We found no change in blood flow after pacing (38.4 mL/min before pacing versus 32.4 mL/min after pacing). More importantly, PGI₁ increased coronary blood flow in both states; however, there was a greater increase after pacing (+21.6% before pacing versus +56.8% after pacing). This greater increase in flow after pacing would, if anything, reduce the concentration of PGI₁ reaching the receptor. Second, in three normal anesthetized dogs we reduced coronary blood flow by 30% and recorded the renal sympathetic inhibitory response to PGI₁ in the control state and after reduction of coronary flow. In the control state, renal nerve activity was inhibited by 20.6 ± 5.0%, and in the reduced-flow state, renal nerve activity was inhibited by 22.8 ± 5.9%.

Implications of Altered Cardiac Reflexes in Heart Failure

As eluded to above, a good deal of evidence has accrued showing that activation of these reflexes not only results in frank bradycardia and hypotension but, more importantly, modulates the expression of the arterial baroreflex. In a recent study, Thames and Minis showed that the HR response (bradycardia) to left circumflex coronary artery occlusion could be abolished by cyclooxygenase inhibition in anesthetized SAD dogs. On the other hand, in a relevant study by Mukharji et al., it was shown that an intracoronary injection of radiocontrast agent evoked a bradycardia that was blunted in patients with heart failure and abolished after cardiac transplantation. The differences between this study and the present study are not readily apparent. One possible difference is the stimulus used in the two studies. Radiocontrast agents tend to be hyperosmotic and may stimulate both chemosensitive and mechanosensitive receptors, whereas PGI₁ primarily stimulates chemosensitive afferents.

Although it is certainly possible that the blunted ventricular mechanoreflex, along with the blunted arterial baroreflex, contributes to the elevation in sympathetic tone in heart failure, this may be offset to some degree by the augmented chemoreflex. It is clear that sympathetic nerve activity is elevated in heart failure. Although baroreflex function is depressed in this disease state, there are no definitive data to link these two findings to a cause and effect relation. If the blunted baroreflex is, indeed, a cause for the altered sympathetic tone in heart failure, then the ventricular mechanoreflex may contribute to this phenomenon. Alternatively, “sympathetic afferent” reflexes are also stimulated by prostanooids. It is possible that augmentation of these reflexes contributes to increases in sympathetic tone in heart failure. The physiological significance of the responses reported here is of some concern. The weight of the evidence suggests that reflexes emanating from ventricular chemoreceptors and mechanoreceptors do not operate as sensitive controllers of cardiovascular or humoral function. It appears that these reflexes are called into play during pathological conditions such as severe cardiac distension, ischemia, or heart failure. Although we could demonstrate bradycardia in response to ascending aortic occlusion at relatively low levels of LVEDP (Fig 2), most of the animals showed responses when LVEDP was raised beyond the physiological range.

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