Augmented Input From Cardiac Sympathetic Afferents Inhibits Baroreflex in Rats With Heart Failure

Lie Gao, Harold D. Schultz, Kaushik P. Patel, Irving H. Zucker, Wei Wang

Abstract—It has been established that the baroreflex is markedly decreased in chronic heart failure (CHF). Our recent study has indicated that activation of the cardiac sympathetic afferent reflex (CSAR) inhibits the baroreflex in normal rats, and in the rats with CHF the CSAR is significantly enhanced, which is related to augmented central angiotensin II (Ang II) mechanism. Therefore, the hypothesis is that the augmented CSAR in the CHF state tonically inhibits the baroreflex via central AT₁ receptor. To test the hypothesis, the rats with myocardial infarction-induced CHF or sham surgery were anesthetized with α-chloralose and urethane, vagotomized, and recordings were made of the mean arterial pressure (MAP) and renal sympathetic nerve activity (RSNA). We found: (1) left ventricular epicardial application of capsaicin or electrical stimulation of the central end of the left cardiac sympathetic nerve blunted the baroreflex in both sham and CHF rats; (2) left ventricular epicardial application of lidocaine had no significant effects on the baroreflex in sham rats but improved the baroreflex in CHF rats (maximum slope, 1.7 ± 0.3 to 2.9 ± 0.2%/mm Hg; P < 0.01); and (3) intracerebral ventricular injection of losartan had no significant effect on baroreflex in sham rats but improved the baroreflex in CHF rats (maximum slope 1.9 ± 0.2 to 3.1 ± 0.2%/mm Hg; P < 0.01). These results suggest that tonic cardiac sympathetic afferent input plays an important role in the blunted baroreflex associated with CHF, which is mediated by central AT₁ receptors. (Hypertension. 2005;45:1173-1181.)

Key Words: baroreflex ■ cardiac function ■ heart failure ■ reflex ■ renal nerves ■ sympathetic nervous system

Chronic heart failure (CHF) has long been known to be associated with a blunted arterial baroreflex sensitivity.1–5 This is a clinically important phenomenon not only because it contributes to altered moment to moment cardiovascular homeostatic adjustments in the CHF patient but also because it has been directly implicated in an enhanced risk of sudden cardiac death6 and total cardiovascular mortality.7 However, the mechanisms by which the baroreflex is impaired in this disease remain incompletely understood.

In a previous study, we showed that in the CHF state, the cardiac sympathetic afferent reflex (CSAR) was augmented in dogs with CHF8–10 and in rats with CHF.11 The sites at which this reflex is enhanced reside at both the afferent endings10 and in the central nervous system.12 Evidence from this laboratory also suggests that the enhanced gain of the cardiac sympathetic afferent reflex in CHF is related to an enhanced central angiotensin II (Ang II) mechanism.11,13 However, cardiac sympathetic afferent can inhibit baroreflex sensitivity14 and our recent study also demonstrated that in normal rats, electrical and chemical stimulation of the CSAR inhibited the arterial baroreflex control of renal sympathetic nerve activity (RSNA), and that central blockade of AT₁ receptors prevented this inhibition.15 We thus reasoned that in the CHF state, the enhanced CSAR might contribute to impairment of arterial baroreceptor reflex function via central Ang II mechanism. In the present study, we examined the effects of blocking CSAR on this reflex function in the rats with chronic myocardial infarction-induced CHF and explored the role of central Ang II mechanism in this process.

Methods

Male Sprague-Dawley rats weighing 180 to 200 grams were used in these experiments. All experiments were approved by the Institutional Animal Care and Use Committee of the University of Nebraska Medical Center and were performed under the guidelines of the American Physiological Society and the National Institutes of Health Guide for the Care and Use of Laboratory Animals.

Model of Chronic Heart Failure

CHF was produced by coronary artery ligation as previously described.16,17 All rats were anesthetized with ketamine (100 mg/kg, intraperitoneally), intubated, and mechanically ventilated. A left thoracotomy was performed through the fifth intercostal space, the pericardium was opened, the heart was exteriorized, and the left anterior descending coronary artery was ligated. Sham-operated rats were prepared in the same manner but did not undergo coronary artery ligation. All the rats survived the sham surgery. However, ~68% of rats survived coronary artery ligation surgery.
Acute Experiments

General Animal Preparation

Seven to 9 weeks after coronary ligation, each rat was anesthetized with urethane (800 mg/kg intraperitoneally) and \(1/10\) chloralose (40 mg/kg intraperitoneally). A midline incision in the neck was made, and the trachea was cannulated to facilitate mechanical ventilation. Each vagus was then identified, tied, and sectioned, and the right common carotid artery was catheterized with a Millar transducer (model SPR-524; Millar Instruments) for measurement of mean arterial pressure (MAP). Heart rate (HR) was derived from the arterial pressure pulse using the cardiotachometer function of the PowerLab (model 16S; ADInstruments). A femoral vein was cannulated with a polyethylene catheter (PE20) for administration of drugs.

### TABLE 1. Body Weight, Heart Weight, Lung Weight, Infarct Size, and Hemodynamics in the Anesthetized Rats Subjected to Either Coronary Ligation or Sham Operation

<table>
<thead>
<tr>
<th>Measurements</th>
<th>Sham</th>
<th>CHF</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>12</td>
<td>10</td>
</tr>
<tr>
<td>Body weight, g</td>
<td>406.7±16.9</td>
<td>378.9±10.1</td>
</tr>
<tr>
<td>Wet whole heart weight, g</td>
<td>1.9±0.2</td>
<td>2.7±0.2†</td>
</tr>
<tr>
<td>Wet whole heart weight/body weight, mg/g</td>
<td>4.7±0.3</td>
<td>7.1±0.4‡</td>
</tr>
<tr>
<td>Wet lung weight, g</td>
<td>2.2±0.1</td>
<td>4.1±0.3‡</td>
</tr>
<tr>
<td>Wet lung weight/body weight, mg/g</td>
<td>5.4±0.4</td>
<td>10.8±0.7‡</td>
</tr>
<tr>
<td>IS, %LV area</td>
<td>47.5±5.4</td>
<td></td>
</tr>
<tr>
<td>SAP, mm Hg</td>
<td>111.9±9.3</td>
<td>96.5±7.4*</td>
</tr>
<tr>
<td>DAP, mm Hg</td>
<td>82.4±5.9</td>
<td>79.3±6.1</td>
</tr>
<tr>
<td>MAP, mm Hg</td>
<td>89.5±4.4</td>
<td>85.9±7.6</td>
</tr>
<tr>
<td>HR, bpm</td>
<td>322.8±10.9</td>
<td>347.6±17.3</td>
</tr>
<tr>
<td>LVESP, mm Hg</td>
<td>119.5±6.6</td>
<td>99.7±10.1*</td>
</tr>
<tr>
<td>LVEDP, mm Hg</td>
<td>0.2±0.5</td>
<td>13.9±2.6‡</td>
</tr>
</tbody>
</table>

DAP indicates diastolic arterial pressure; HR, heart rate; IS, infarct size; LVEDP, left ventricular end-diastolic pressure; LVSP, left ventricular peak systolic pressure; MAP, mean arterial pressure; SAP, systolic pressure.

*\(P<0.05\), †\(P<0.01\), and ‡\(P<0.001\) compared with sham group.

### TABLE 2. Effects of Epicardial Application of Capsaicin and Electrical Stimulation of Cardiac Sympathetic Afferents on MAP, HR, and RSNA

<table>
<thead>
<tr>
<th>Groups</th>
<th>Treatment</th>
<th>MAP, mm Hg</th>
<th>HR, bpm</th>
<th>RSNA, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sham</td>
<td>Before cap</td>
<td>90.3±5.5</td>
<td>314.7±19.9</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>During cap</td>
<td>105.4±4.9*</td>
<td>392.5±23.7*</td>
<td>178.7±17.6†</td>
</tr>
<tr>
<td></td>
<td>Before ele</td>
<td>91.3±6.1</td>
<td>326.6±18.7</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>During ele</td>
<td>109.4±7.5‡</td>
<td>414.4±31.8‡</td>
<td>192.2±21.3§</td>
</tr>
<tr>
<td>CHF</td>
<td>Before cap</td>
<td>85.3±6.6</td>
<td>339.6±21.4</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>During cap</td>
<td>116.1±9.3*</td>
<td>424.4±18.7*</td>
<td>251.9±19.6†</td>
</tr>
<tr>
<td></td>
<td>Before ele</td>
<td>84.9±8.8</td>
<td>341.5±27.6</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>During ele</td>
<td>116.6±7.9‡</td>
<td>451.8±32.6‡</td>
<td>227.7±21.3§</td>
</tr>
</tbody>
</table>

Cap indicates capsaicin; ele, electrical stimulation; RSNA, renal sympathetic nerve activity.

\(^*P<0.05\) and †\(^P<0.01\) compared with before capsaicin.

\(^‡P<0.05\) and §\(^P<0.01\) compared with before electrical stimulation.

Figure 1. Top panels show original recordings of arterial blood pressure changes induced by phenylephrine injection (10 \(\mu\)g intravenously; starting at the nadir of arterial pressure fall after administration of nitroglycerin) and attendant RSNA reflex responses in a CHF rat before (left) and during (right) epicardial application of capsaicin (A) and electrical stimulation of cardiac sympathetic afferents (C). Bottom panels show the composite arterial baroreflex curves from a group of CHF rats (\(^*P<0.05\), \(n=10\)).
Recording of RSNA

The left renal sympathetic nerves were placed on a pair of platinum–iridium recording electrodes and then were covered with a fast-setting silicone (Kwik-Sil; World Precision Instruments). The amplified discharge was monitored on a storage oscilloscope (model 121 N; Tektronix), imported to a computer system with other parameters, and then stored on disk until analyzed.

Epicardial Application of Capsaicin or Lidocaine

The chest was opened through the fourth intercostal space. The pericardium was removed to expose the left ventricle. A 2-mm piece of filter paper containing capsaicin (0.4 μg in 2 μL) or lidocaine (2% in 20 μL) was applied to the anterior surface of the left ventricle. Each drug was applied for ~2 minutes until the end of a baroreflex test.

Electrical Stimulation of Cardiac Sympathetic Afferent Nerves

The chest was opened through the left second intercostal space. The pericardium was removed to expose the left ventricle. The pericardium was removed to expose the left ventricle. A 2-mm piece of filter paper containing capsaicin (0.4 μg in 2 μL) or lidocaine (2% in 20 μL) was applied to the anterior surface of the left ventricle. Each drug was applied for ~2 minutes until the end of a baroreflex test.

Figure 2. Cardiac sympathetic afferent stimulation impairs baroreflex control of renal sympathetic nerve activity in both sham and CHF rats. Epicardial application of capsaicin (left panels) or electrical cardiac sympathetic afferent stimulation (right panels) reduced the average slope (A and E) and Gainmax (B and F), and increased the minimum RSNA (C and G). *P<0.05 and **P<0.01 compared with before capsaicin or electrical stimulation; †P<0.05 compared with sham group before capsaicin or electrical stimulation; ‡P<0.05 compared with sham group during capsaicin or electrical stimulation. Sham rats, n=12; CHF rats, n=10.
The stimulus (7 V, 1 ms, 20 Hz) was delivered with a stimulator (Grass S88; Astro-Med) and a stimulus isolation unit.

**Intracerebroventricular Losartan**

The rats were placed in a stereotaxic head-holder (Stoelting) and the skull was exposed through an incision on the midline of the scalp. An intracerebroventricular cannula (outer diameter 0.5 mm and inner diameter 0.1 mm) connected to a microsyringe (model 7001 Hamilton) was implanted into the right cerebral ventricle. The coordinates were determined from the Paxinos and Watson rat atlas\(^1\), which are 0.8 mm posterior, 1.4 mm lateral to the bregma, and 3.8 mm ventral to the zero level. Losartan was given as 500 nmol in 1/\(H_9\) artificial cerebrospinal fluid (aCSF). At the end of the experiment, the cannula tip placement was confirmed by microinjection of Fast Green (1/\(H_9\)).

**Measurement of Left Ventricle End-Diastolic Pressure, Left Ventricle Systolic Pressure, and Cardiac Infarct Size, and the Verification of Central Microinjection Site**

At the end of each experiment, the Millar catheter was advanced through the carotid artery into the left ventricle (LV) to determine LV end-diastolic pressure and LV systolic pressure, which were obtained from a 7- to 9-beat average. The rats were then euthanized with an overdose of anesthetic (pentobarbital sodium 100 mg/kg, intravenous). The hearts were removed from the chests, sectioned, photographed with a digital camera, and the ratio of the infarct area to whole LV minus septum was measured using SigmaScan Pro 5 software. The brains were removed from the skull, placed in 10% formalin, and sectioned, and the microinjection site was verified.

**Construction of Arterial Baroreflex Curves and Statistical Analysis**

Baroreflex curves were generated by measuring the RSNA responses to decreases and then increases in arterial pressure by intravenous administration of nitroglycerin (25 μg) followed by phenylephrine (10 μg). The RSNA response was normalized as percentile of baseline. A sigmoid logistic function was fit to the data using a nonlinear regression program (Sigma Plot; SPSS). Four parameters were derived from the equation: \(\% \text{RSNA} = A/[1 + \exp(B (\text{MAP} - C))] + D\), in which \(A\) is percent RSNA range, \(B\) is the slope coefficient, \(C\) is the pressure at the midpoint of the RSNA range (BP\(_{50}\)), and \(D\) is minimum RSNA.\(^9\) The peak slope (or maximum gain) was determined by taking the first derivative of the baroreflex curve described by the equation.

The sympathetic afferent stimulation induced increases in RSNA and arterial pressure reached their maximal responses at 5 to 10 seconds and then gradually declined to the baseline, which lasted \(\sim 3\) to 4 minutes. Baroreflex function was tested when the RSNA and arterial pressure reached their peak (during 5 to 10 seconds after stimulation of cardiac sympathetic afferents), and the testing lasted \(\sim 20\) to 30 seconds. In CHF rats, epicardial application of lidocaine or intracerebroventricular losartan induced a decrease in RSNA. In this case, the baroreflex function testing was performed when the RSNA reached its nadir (\(\sim 40\) to 60 seconds after the treatment of lidocaine or losartan).

The baseline MAP and RSNA were averaged over a 20-second period before any treatment. The maximum MAP and RSNA responses to the sympathetic afferent stimulation, lidocaine, or losartan were measured over 10 seconds. However, the change of

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**Figure 3.** A, Original recording of arterial blood pressure changes induced by phenylephrine injection (10 μg intravenous; starting at the nadir of arterial pressure decline after administration of nitroglycerin) and attendant RSNA reflex responses in a CHF rat before (left) and during (right) epicardial application of lidocaine. B, Composite arterial baroreflex curves from a group of CHF rats (*P<0.05, n=10).*
MAP and RSNA during baroreflex testing was averaged for each for 1 second to obtain smooth baroreflex function curves, which were generated from data collected as pressure increased on administration of phenylephrine beginning at the nadir of arterial pressure after nitroglycerin administration.

All values are expressed as mean ± SE. We constructed composite baroreflex curves by averaging the 4 parameters of the logistic equation for all curves and using the mean parameters to construct a single curve. A 1-way analysis of variance followed with the Newman-Keuls test for post-hoc analysis was used when multiple comparisons were made. A value of P<0.05 was considered statistically significant.

## Results

### Body Weight, Heart Weight, Lung Weight, and Baseline Hemodynamics

Table 1 summarizes the hemodynamic characteristics of sham and CHF rats. In the rats with CHF, gross examination revealed a dense scar in the anterior ventricular wall and the mean infarct area was 47.3±5.4% of the LV area. No infarcts were evident in sham-operated rats. The body weight was similar in the 2 groups. However, both the heart weight and heart-to-body weight ratio were higher in CHF rats compared with sham-operated rats. Both the lung weight and the lung-to-body weight ratio were higher in CHF rats compared with sham-operated rats, thus documenting the occurrence of substantial pulmonary congestion. Pleural fluid and ascites were found in the 10 CHF rats compared with none in the 12 sham-operated rats.

There were no statistically significant differences in baseline MAP, diastolic arterial pressure, and HR between the sham-operated rats and CHF rats. However, the systolic arterial pressure and peak LV systolic pressure were decreased, and the LV end-diastolic pressure was significantly increased in CHF rats compared with sham-operated rats.

### Effects of Chemical and Electrical Stimulation of Cardiac Sympathetic Afferents on Arterial Baroreflex Function

In both sham and CHF rats, HR, MAP, and RSNA were significantly higher during epicardial application of capsaicin or electrical stimulation of cardiac sympathetic afferents compared with those before treatment (Table 2). Figure 1 (upper panels) show original recordings of arterial blood pressure changes induced by phenylephrine and attendant RSNA reflex responses before and during epicardial application of capsaicin (Figure 1A) and electrical stimulation of cardiac sympathetic afferents (Figure 1C) in 1 CHF rat. The reduced reflex sympatho-inhibition to phenylephrine in CHF rats was further impaired by these treatments. These patterns were further reduced in CHF rats. Epicardial application of lidocaine increased the average slope (A) and Gainmax (B), and decreased the minimum RSNA (C) only in CHF rats. *P<0.05 compared with before lidocaine; †P<0.05 compared with sham rats. Sham rats, n=12; CHF rats, n=10.
were confirmed by the average group data shown in Figure 1 (bottom panels). Both chemical and electrical stimulation significantly reduced the average slope and \( \text{Gain}_{\text{max}} \) and increased the minimum RSNA of baroreflex curve in both sham and CHF groups (Figure 2).

**Effects of Epicardial Application of Lidocaine on Arterial Baroreflex Function**

In the rats with CHF, the baseline RSNA was significantly lower during epicardial application of lidocaine (from 100 to 81.8 \( \pm \) 6.5%; \( P < 0.05 \)). In addition, lidocaine significantly increased the average slope and \( \text{Gain}_{\text{max}} \), and decreased the minimum RSNA of baroreflex curve (Figures 3 and 4).

In contrast to the CHF rats, lidocaine had no significant effects on baseline RSNA, or on the average slope, \( \text{Gain}_{\text{max}} \), and minimum RSNA of the arterial baroreflex curve in sham rats (Figure 4).

**Effects of Intracerebroventricular Losartan on Arterial Baroreflex Function**

Figure 5A shows an original recording of arterial blood pressure changes induced by phenylephrine injection (10 \( \mu \)g intravenous) starting at the nadir of arterial pressure decline after administration of nitroglycerin and attendant RSNA reflex responses before and after intracerebroventricular losartan in a CHF rat. The reflex RSNA response to phenylephrine is enhanced after intracerebroventricular losartan. This pattern was confirmed by the average group data reported in Figure 5B. Figure 6A shows an original recording of arterial blood pressure changes induced by phenylephrine and attendant RSNA reflex responses before and during electrical stimulation of cardiac sympathetic afferents after intracerebroventricular losartan in rats with CHF. In this setting, electrical cardiac sympathetic afferent stimulation failed to blunt the reflex RSNA response to phenylephrine after intracerebroventricular losartan. This pattern was confirmed by the average group data shown in Figure 6B. Although there were no significant differences in HR and MAP, baseline RSNA was significantly lower after intracerebroventricular losartan (from 100 to 76.8 \( \pm \) 9.5%; \( P < 0.01 \)). In addition, losartan significantly increased the average slope, \( \text{Gain}_{\text{max}} \), and range of the RSNA response (Figure 7), and decreased the minimum RSNA. It can be seen from the Figure 7 that intracerebroventricular losartan prevented the electrical stimulation of cardiac sympathetic afferents from lowering the average slope, \( \text{Gain}_{\text{max}} \), and range of the RSNA response of the arterial baroreflex curve in both sham and CHF rats.

In sham-operated rats, however, intracerebroventricular losartan had no significant effects on the average slope, \( \text{Gain}_{\text{max}} \), and range of the arterial baroreflex curve in both sham and CHF rats.

**Discussion**

It has been well established that arterial baroreceptor reflex function is markedly decreased\(^{20–22}\) and the cardiac sympa-
thetic afferent reflex is augmented\textsuperscript{8–10} in chronic heart failure. However, it is not clear what relationship exists between the aforementioned 2 cardiovascular reflexes in this state. The cardiac sympathetic afferent reflex is a sympatho-excitatory reflex\textsuperscript{23} and contributes to the elevation in sympathetic tone.\textsuperscript{24} Increases in sympathetic nerve activity can antagonize baroreflex function\textsuperscript{25–27} in the heart failure state. Therefore, it is possible that the augmented cardiac sympathetic afferent reflex might impair arterial baroreflex function via its sympatho-excitatory effects. In the present study, we found that in anesthetized rats with CHF, LV epicardial application of lidocaine decreased the baseline RSNA and improved the impaired baroreflex control of RSNA (see Figures 3 and 4), suggesting that blockade of cardiac sympathetic afferent input partially normalized the impaired baroreflex function seen in the heart failure state. To our knowledge, this is first demonstration that tonic cardiac sympathetic afferent input plays an important role in blunting the baroreflex in CHF. This phenomenon appears to be specific to heart failure states because in sham-operated rats, we failed to find any change of RSNA and baroreflex parameters during epicardial application of lidocaine, indicating that there is little, if any, tonic cardiac sympathetic afferent input in the regulation of sympathetic nerve activity in the normal rats. However, in the normal cats, Gnecchi-Ruscone et al demonstrated that tonic sympathetic afferent activity inhibited baroreflex function,\textsuperscript{14} which differs from our findings in the current study. The different anesthetics, species, and the methods to block sympathetic afferent nerves used in the 2 experiments might account for this inconsistency. In addition, the potential differences in baroreflex control of RSNA and HR also might play some role in the contravention.

The exact mechanisms by which arterial baroreflex function is impaired by tonic cardiac sympathetic afferent input in rats with CHF are not completely clear. Our previous studies showed that the Ang II concentration in the cerebrospinal fluid was increased in the dogs with pacing induced heart failure,\textsuperscript{24} and Wang et al demonstrated the prevention of sympathetic and cardiac dysfunction induced by myocardial infarction in transgenic rats deficient in brain angiotensinogen.\textsuperscript{28} Evidence from our laboratory also suggests that the augmented central Ang II mechanism was involved in the enhanced CSAR in the heart failure state. For instance, central administration of losartan normalized the enhanced CSAR in the dogs with pacing-induced heart failure,\textsuperscript{12} and intracerebroventricular administration of losartan normalized the enhanced CSAR evoked by epicardial application of both bradykinin and capsaicin in rats with CHF.\textsuperscript{11} In a recent study in normal rats,\textsuperscript{15} we found that intracerebroventricular administration of losartan normalized the enhanced RSNA induced by electrical stimulation of cardiac sympathetic afferents. In addition, losartan also prevented this electrical stimulation
from impairing arterial baroreflex function. These results suggested that central Ang II is the key mediator in the inhibitory effect of CSAR evoked by the electrical stimulation on the arterial baroreflex function in normal state. In the present study, we confirmed that central administration of losartan normalized the enhanced RSNA and improved the impaired arterial baroreflex control of RSNA in rats with CHF (Figures 5 and 6), a result similar to that found by DiBona et al.29 These results imply elevated central Ang II as playing an important role in the inhibitory effects of tonic cardiac sympathetic afferent input on arterial baroreflex control of RSNA in the heart failure state. In contrast, in the sham-operated rats, we failed to find any change in RSNA and baroreflex parameters after intracerebroventricular administration of losartan, indicating that in the normal state, central Ang II does not tonically inhibit arterial baroreflex function.

In the present study, we noticed that intracerebroventricular losartan improved the blunted arterial baroreflex sensitivity of CHF via increasing both the average slope and range of RSNA response of the arterial baroreflex curve, but left epicardial application of lidocaine partially improved the impaired arterial baroreflex function of CHF only via changing the average slope. This difference implies that increased central Ang II level mediates not only the responses to augmented input from cardiac sympathetic afferents but also some other yet unknown pathways to impair the arterial baroreflex function in heart failure state.

As expected, in the sham-operated rats of the present study, we confirmed that both epicardial application of capsaicin and electrical stimulation of cardiac sympathetic afferents inhibited the arterial baroreflex control of RSNA, and that intracerebroventricular losartan attenuated the inhibitory effect of electrical stimulation of cardiac sympathetic afferents on arterial baroreflex function.15 However, in the present study, we also found that in the rats with CHF, both epicardial application of capsaicin and electrical stimulation of cardiac sympathetic afferents increased MAP and RSNA and further reduced the average slope and Gainmax of the arterial baroreflex. These results suggest that in this heart failure model, the augmented cardiac sympathetic afferent reflex was not maximal and could still be enhanced. However, these results also imply that at least in the present CHF model, the arterial baroreceptor reflex, even though blunted, can still control RSNA over a limited range and could be further impaired when the cardiac sympathetic afferents were chemically and electrically stimulated.

In conclusion, the results of the present study suggest that tonic cardiac sympathetic afferent input plays an important role in the blunted baroreflex associated with CHF, which is mediated by central AT1 receptors.

**Perspectives**

In this study, we found that blockade of cardiac sympathetic afferents partially normalized the decreased arterial baroreflex in the rats with chronic myocardial infarction-induced CHF. Consequently, these findings indicate that in the heart failure state, the tonic cardiac sympathetic afferent input plays an important role in impairing arterial baroreflex function. These results suggest a new mechanism by which arterial baroreflex function is impaired in the heart failure state and provide a new potential therapy to this disease. For instance, blockade of the cardiac sympathetic afferent reflex might benefit the CHF patient via improvement of the impaired arterial baroreflex function.

**Acknowledgments**

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In an article by L. Gao et al in the June 2005 issue of *Hypertension* (Gao L, Schultz HD, Patel KP, Zucker IH, Wang W. Augmented input from cardiac sympathetic afferents inhibits baroreflex in rats with heart failure. *Hypertension*. 2005;45:1173–1181), the authors mistakenly omitted a relevant reference. In a study by L Mircoli et al (Mircoli L, Fedele L, Benetti M, Bolla GB, Radaelli A, Perlini S, Ferrari AU. Preservation of the baroreceptor heart rate reflex by chemical sympathectomy in experimental heart failure. *Circulation*. 2002;106:866–872) these authors showed that chronic chemical sympathectomy normalized arterial baroreflex function in rats with myocardial infarctions. Whereas the authors’ study focused on cardiac sympathetic afferent function in chronic heart failure, the study by Mircoli et al clearly suggests that interruption of sympathetic function may be a novel strategy for normalization of baroreflex function and perhaps myocardial function in an early stage of myocardial infarction. The authors apologize for this oversight.