Reduced NO enhances the central gain of cardiac sympathetic afferent reflex in dogs with heart failure

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Ma, Rong, Irving H. Zucker, and Wei Wang. Reduced NO enhances the central gain of cardiac sympathetic afferent reflex in dogs with heart failure. Am. J. Physiol. 276 (Heart Circ. Physiol. 45): H19–H26, 1999.—The aim of the present study was to test the hypothesis that a decrease in central nitric oxide (NO) is involved in the enhancement of the central gain of the cardiac "sympathetic afferent" reflex (CSAR) in dogs with congestive heart failure (CHF). Thirteen dogs with pacing-induced CHF and sixteen sham dogs were anesthetized with α-chloralose and were baroreceptor denervated and vagotomized. The CSAR was evoked by stimulation of the left ventral ansa. A lateral cerebroventricular cannula was inserted to deliver sodium nitroprusside (SNP) and N⁶-nitro-l-arginine methyl ester (L-NAME). Arterial pressure, heart rate, and renal sympathetic nerve activity (RSNA) were recorded at baseline and during elicitation of the CSAR. We found that 1) the responses of RSNA to stimulation were augmented in dogs with CHF, 2) SNP depressed the increase in RSNA induced by the CSAR in CHF dogs but had no effect in sham dogs, and 3) L-NAME potentiated the CSAR-induced increase in RSNA in sham dogs but not in dogs with CHF. We conclude that reduced central NO is involved in the enhanced central gain of the CSAR in CHF dogs.

METHODS
Surgical instrumentation. Twenty-nine mongrel dogs of either sex, weighing between 20 and 30 kg, were used in these experiments. All experiments were approved by the Institutional Animal Care and Use Committee of the University of Nebraska and were carried out under the National Institutes of Health Guide for the Care and Use of Laboratory Animals. In general, all dogs were instrumented using sterile techniques under pentobarbital anesthesia (30 mg/kg iv initially plus one-tenth the dose per h). Through a right thoracotomy (the 5th interspace) catheters were implanted in the left atrium or left ventricle through a branch of a pulmonary vein. A catheter was also implanted in the aorta through the omocervical artery. Catheters were used for measurement of the respective vessel or chamber pressure. An epicardial pacing lead (model 6917–357; Medtronic, Minneapolis, MN) was placed in the myocardium near the base of the right ventricle. Postoperatively, dogs were treated with Tylan 50 (8 mg/kg im for 3 days). Approximately 1 wk was allowed for the dogs to recover from surgery before pacing was begun.

Model of CHF. The rapid ventricular pacing model of CHF was used in this study. In brief, after control measurements were made in the conscious state 1 wk after surgery when these dogs were fully recovered, pacing (right ventricular) was started at 250 beats/min using a Medtronic 8340 pacemaker, which has been modified to pace at this rate. The hemodynamics were measured in the dogs every 3–4 days to monitor the development of CHF. Usually, after 3–4 wk of pacing, the dogs developed decompensated CHF, which was

NEUROHUMORAL EXCITATION is a hallmark of congestive heart failure (CHF) (10). The mechanisms responsible for the neurohumoral activation in CHF are not completely understood. The cardiac sympathetic afferent reflex (CSAR) is a sympathosympathetic excitatory reflex and may contribute to the higher sympathetic tone in the heart failure state (28). The enhancement of this reflex may be attributed to the higher sensitivity of sympathetic afferent endings or to central components of this reflex arc (13, 28). However, the factors and mechanisms that are involved in this enhancement are still unclear. Recent studies have indicated that nitric oxide (NO) in the central nervous system may play an important role in the regulation of sympathetic outflow. General inhibition of central NO synthesis (1, 23) or inhibition of NO synthesis in the regions that are involved in modulation of sympathetic nerve activity, such as the nucleus tractus solitarii (NTS) (8, 23), the rostral ventrolateral medulla (RVLm) (23), and the paraventricular nucleus (PVN) (33), resulted in elevation of renal sympathetic nerve activity (RSNA), mean arterial blood pressure (MAP), heart rate (HR), and plasma norepinephrine concentration. These studies strongly suggested that endogenous NO within the central nervous system regulates sympathetic outflow via inhibitory mechanisms. It has been shown that altered NO mechanisms in peripheral tissues and in the brain may contribute to the pathophysiology of some disease states such as CHF. Studies by Wang et al. (26) indicated that the release of NO from the coronary vasculature was reduced in the dogs with CHF, which was attributed to reduced expression of endothelial NO synthase (NOS) (20). In addition, Zhang and coworkers (17, 34) have shown that the neuronal isoform of NOS (nNOS) is reduced in rats with CHF. These studies suggest that a relationship between central NO and the CSAR may exist. Therefore, the purpose of this study was to test the hypothesis that an abnormal central NO mechanism is involved in the enhancement of the CSAR in dogs with pacing-induced CHF. We reasoned that replacement of central NO by administration of sodium nitroprusside (SNP) would reduce the gain of the CSAR only in dogs with CHF. In control dogs inhibition of NO synthesis with N⁶-nitro-l-arginine methyl ester (L-NAME) on the other hand should enhance the CSAR gain.
indicated by both hemodynamic and clinical changes. The dogs in the sham group were instrumented with the same surgical procedures as in CHF dogs but were not paced.

Acute experiments. Acute experiments were carried out in dogs which had developed decompensated CHF and sham dogs. At the time of the acute experiment each dog was anesthetized with \( \alpha \)-chloralose (100 mg/kg iv) and intubated. A femoral artery and vein were catheterized for measurement of hemodynamics and administration of supplemental doses of anesthesia (one-tenth of initial dose of \( \alpha \)-chloralose per hour), respectively. Arterial blood gases were measured throughout the experiment and kept within normal limits (pH 7.35–7.45, PCO\(_2\) 30–40 mmHg, PO\(_2\) 85–95 mmHg).

Through a midline incision in the neck the carotid sinus area was exposed bilaterally. Each carotid sinus nerve was identified, ligated, and cut. All other visible nerve fibers in the area of the carotid sinus were cut. The carotid bifurcation and the common carotid arteries were stripped of adventitial tissues from ~1 cm below the bifurcation to 1 cm above. Each vagus was then identified in the neck, tied, and sectioned. The effectiveness of baroreceptor denervation was determined by recording the change in HR to bolus injection of nitroglycerin (25 \( \mu \)g/kg). This dose evoked changes in blood pressure of between 25 and 40 mmHg. Baroreceptor denervation was assumed to be complete if the HR did not change more than 5 beats/min to this intervention.

A midline scalp incision was made, and the skull was exposed. After the bregma was identified, a lateral cerebroventricular cannula was inserted 0.5 cm posterior to bregma and 0.5 cm lateral to midline. The location of the tip of the cerebroventricular cannula was confirmed by outflow of clear cerebrospinal fluid. This cannula was used for central infusion of SNP and saline by a pump that was set at the rate of 1 ml/40 min (Harvard Apparatus, South Natick, MA), and central administration of \( \text{L-NAME} \) (1 mg/kg in 0.3 ml), which was administered as an cerebroventricular bolus.

The chest was opened through the left second intercostal space. The left ventral ansa, which contains cardiac sympathetic afferent nerves, was identified, tied, and cut. A pair of stainless steel stimulating electrodes was placed on the central end of this nerve. Square-wave pulses were delivered by a stimulator (Grass S88) and stimulus isolation unit.

RSNA was recorded using the technique described in our previous study (13). In brief, the discharge was amplified with a Grass DC preamplifier (model P18D; Grass Instrument, Quincy, MA), monitored on a storage oscilloscope (model 121A, Tektronix, Beaverton, OR), and then imported to a computer system with the hemodynamic parameters. Hemodynamics and RSNA were digitized and analyzed by the computer (AcadLab System, ADInstruments; Milford, MA). The RSNA was quantified by setting a window discriminator just above the noise level (the silence between discharge bursts). A rate meter (MacLab) counted spikes above the discriminating level and recorded the frequency.

Experimental protocols. MAP, RSNA, and HR were measured as baseline ~30 min after acute surgery was completed but before any protocol in sham and CHF dogs was started. To compare the central gain of the CSAR between CHF and sham dogs, the percentage increase in RSNA during electrical stimulation of the ventral ansa was determined. The intensity of the stimulus was varied from 5 to 20 V in 5-V increments with a constant frequency of 30 Hz, or the frequency of stimulation was delivered at 1, 5, 10, 20, 30, 40, and 50 Hz at a constant voltage of 20 V. The pulse width was kept at 1 ms, and each stimulus period lasted 30 s.

Effect of central infusion of SNP on central gain of CSAR in sham and CHF dogs. Twelve of sixteen sham dogs and nine of thirteen CHF dogs were intracerebroventricularly infused with SNP (0.3 \( \mu \)g/kg) at the rate of 250 \( \mu \)l/min for 40 min after the control RSNA responses to stimulation of cardiac sympathetic afferent nerves were examined. These responses were measured again 20 min after onset of infusion of SNP. The central sensitivity of the CSAR was evaluated and compared before and during infusion of SNP in each group.

Effect of central administration of \( \text{L-NAME} \) on central gain of CSAR in sham and CHF dogs. Ten of sixteen sham dogs (six from the SNP-infusion group) and five of thirteen CHF dogs (one from the SNP-infusion group) were injected with \( \text{L-NAME} \) (1 mg/kg in 0.3 ml iv). In all SNP-infused dogs \( \text{L-NAME} \) was administered at least 20 min after the infusion of SNP was stopped, when all hemodynamics and RSNA had returned to baseline. The effect of \( \text{L-NAME} \) on the central gain of the CSAR was measured 20 min after administration. The RSNA responses to stimulation were examined and compared before and after application of \( \text{L-NAME} \) in each group.

Effect of central administration of saline on central gain of CSAR in sham and CHF dogs. As a control saline was infused intracerebroventricularly in five CHF dogs at the same rate as that used for SNP. Six sham dogs saline was similarly injected intracerebroventricularly at the same volume as that used for \( \text{L-NAME} \). The central gain of the CSAR was examined before and during infusion or after injection of saline.

Statistical analysis. The last 10 s of the RSNA before initiation and termination of the cardiac sympathetic afferent stimulation were sampled and averaged. RSNA was expressed and calculated as the percent change from control (before stimulation). The percent changes in RSNA were plotted against frequencies and voltages to analyze the central sensitivity of the CSAR in sham and CHF dogs. A two-way ANOVA for repeated measures followed by post hoc analysis using the Duncan test was used for determining the level of significance of mean data between the two groups of animals. A paired t-test was used when comparing responses before and after an intervention (administration of SNP and \( \text{L-NAME} \)) in the same animal. Linear regression was used for analyzing responses of RSNA at different voltages and frequencies of stimulation. All statistical analyses were done using computer software (Sigmastat, Jandel). All data are expressed as means ± SE. \( P < 0.05 \) was considered statistically significant.

RESULTS

Hemodynamics of anesthetized, intact sham and heart failure dogs. Systolic arterial pressure, diastolic arterial pressure, MAP, HR, left ventricular systolic pressure, and left ventricular end-diastolic pressure were measured in anesthetized, intact sham and CHF groups 30 min after the pacemaker was turned off. These hemodynamics are shown in Table 1. HR and left ventricular end-diastolic pressure were significantly elevated, whereas other hemodynamics were significantly reduced in dogs with CHF compared with sham dogs. These results are consistent with our previous study (13).

Central gain of CSAR in sham and CHF dogs. The RSNA responses to varying voltages and frequencies of stimulation of the ventral ansa were used to evaluate the central gain of the CSAR. RSNA was increased during stimulation. A significant increase was observed
at 10 V and 30 Hz in sham dogs (Fig. 1). The levels at which significance was reached in the dogs with CHF were 10 V and 20 Hz, respectively (Fig. 1). In most dogs, RSNA increased immediately after stimuli were delivered, usually within 5 s, and reached a maximal level within 10 s.

Figure 1 shows the differences in CSAR-induced RSNA between sham and CHF dogs. Similar to the results of our previous study (13), RSNA responses to stimulation were augmented in the dogs with CHF. The significant difference in these responses between the two groups appeared from 10 to 20 V (Fig. 1, A) and from 30 to 50 Hz (Fig. 1, B). The linear slopes of the RSNA responses to varying voltages and frequencies of stimulation were also significantly different between sham and CHF dogs (Fig. 2).

Influences of central administration of SNP and L-NAME on hemodynamics of sham and CHF dogs. The changes in baseline hemodynamics elicited by administration of SNP and L-NAME are shown in Fig. 3. SNP depressed MAP significantly in both sham and CHF dogs. RSNA was also reduced significantly in the sham group but not in the CHF group. Administration of L-NAME resulted in a significant elevation of MAP in both groups and RSNA in sham dogs. However, neither SNP nor L-NAME elicited significant changes in HR in sham or CHF dogs.

Effect of central infusion of SNP on RSNA responses to stimulation in sham and CHF dogs. As shown in Fig. 4, central infusion of SNP attenuated the augmented RSNA responses to varying intensities of stimulation in the dogs with CHF. The significant inhibition appeared from 30 to 50 Hz and from 10 to 20 V. The slope of the RSNA response to varying voltages of stimulation was also depressed significantly in this group (Fig. 5). However, this inhibition was not seen in sham dogs (Figs. 4 and 5).

Effect of central administration of L-NAME on central gain of CSAR in sham and CHF dogs. L-NAME, administered intracerebroventricularly, elicited clear enhancement of RSNA responses to stimulation in the sham group (Fig. 6). The slope of RSNA response to stimulation was also increased significantly in this group (Fig. 7). However, L-NAME did not affect the RSNA responses elicited by stimulation of the ventral ansa in dogs with CHF. These responses had a tendency to increase after administration of L-NAME in CHF dogs; however, it did not reach a significant level (P > 0.05; Figs. 6 and 7).

### Table 1. Baseline hemodynamics in sham dogs and dogs with CHF

<table>
<thead>
<tr>
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<th>Sham</th>
<th>CHF</th>
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<tr>
<td>SAP, mmHg</td>
<td>141.2 ± 6.6</td>
<td>115.1 ± 4.5*</td>
</tr>
<tr>
<td>DAP, mmHg</td>
<td>97.4 ± 3.8</td>
<td>80.7 ± 3.5*</td>
</tr>
<tr>
<td>MAP, mmHg</td>
<td>110.2 ± 4.0</td>
<td>91.8 ± 3.4†</td>
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<tr>
<td>HR, beats/min</td>
<td>116.5 ± 5.3</td>
<td>135.1 ± 5.0*</td>
</tr>
<tr>
<td>LVSP, mmHg</td>
<td>135.1 ± 4.5</td>
<td>117.3 ± 3.8*</td>
</tr>
<tr>
<td>LVEDP, mmHg</td>
<td>3.0 ± 0.5</td>
<td>22.8 ± 2.3†</td>
</tr>
</tbody>
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Values are means ± SE; n = 16 sham and 13 congestive heart failure (CHF) dogs. SAP, systolic arterial pressure; DAP, diastolic arterial pressure; MAP, mean arterial pressure; HR, heart rate; LVSP, left ventricular systolic pressure; LVEDP, left ventricular end-diastolic pressure. *P < 0.05 and †P < 0.01 compared with sham dogs.
Effect of central administration of saline on central gain of CSAR in sham and CHF dogs. As a vehicle control the same volume of saline as that of SNP and L-NAME was administered intracerebroventricularly in 5 CHF and 6 sham dogs. As shown in Fig. 8 RSNA responses to different intensities of stimulation were not affected by central application of saline in either group of dogs.

DISCUSSION

It is generally acknowledged that the decreased sensitivity of the arterial baroreflex control of autonomic nerve activity plays a role in the elevation in sympathetic tone in humans and animals with CHF (27). However, in a study by Brändle et al. (2) it was shown that hemodynamic parameters and plasma noradrenaline levels were not different in sinoaortic denervated and intact dogs with CHF, suggesting that the arterial baroreflex is not the sole mechanism for the increase in sympathetic drive in CHF. Recent studies from this laboratory suggested that the CSAR was enhanced in dogs with CHF (13, 28). This enhancement was attributed to an increase in the sensitivity of both afferent endings and the central components of this reflex. We proposed that this reflex may contribute to the sustained higher sympathetic tone in CHF (13, 28).

As was expected, stimulation of cardiac sympathetic afferent nerves elicited significantly greater increases in RSNA in CHF dogs in the present study. These results confirm our previous conclusion that the central gain of the CSAR is enhanced in CHF dogs (13). Thus one important question is, What are the mechanisms responsible for this enhancement? Little information exists that would provide answers to this question. Providing evidence for a central mechanism was the main goal of this study. Many factors may be involved in the elevated central gain of this reflex. We only examined the possible role of one candidate, NO, in the alteration of the CSAR in CHF dogs in the present study.

NOS has been shown to be distributed discretely within the brain, including several brain regions involved in regulating cardiovascular function (3, 6). Recent studies have indicated that NO in the central nervous system may contribute to the regulation of the cardiovascular system through inhibition of the sympathetic nervous system and the modulation of the arterial baroreflex (8, 21–23, 32). It has been found that endothelial NOS is reduced in CHF dogs (20). By using the NADPH-diaphorase staining technique, Patel and co-workers (17, 33) found that nNOS activity was also reduced in several brain sites, such as the hypothalamus, in CHF rats.

Central infusion of SNP caused a significant reduction of MAP in both sham and CHF dogs and a reduction of RSNA in sham dogs. This supports the data from other laboratories, suggesting that central NO possesses sympathoinhibitory effects. However, a significant change in HR was not seen in either group after application of SNP. This can be attributed to the surgical intervention before the experiment. The animals used in this study have been vagotomized bilaterally and sympathectomized unilaterally (left). Therefore, the neural control to the heart has been almost completely removed. More importantly, in this set of experiments central infusion of SNP attenuated the enhanced RSNA responses to stimulation in dogs with CHF but did not affect these responses in sham dogs. This may indicate that exogenous NO does not play a role in the central control of the CSAR in the normal state but does in the CHF state. We postulate that the normal level of central endogenous NO may provide an intense inhibition of the CSAR. Hence, application of additional NO into the central nervous system in normal dogs is not capable of inhibiting this reflex. If central NO is reduced in CHF dogs and this reduction results in a loss of the inhibition of the CSAR, it may contribute to the enhancement of the CSAR in CHF dogs. If the hypothesis discussed above is correct, inhibition of central NO should have a greater effect on the CSAR in sham dogs than that in the dogs with CHF, because NO in the latter case is already reduced. The results of central administration of the NOS inhibitor
L-NAME support this conclusion. First, L-NAME administered into the brain elicited significant increases in baseline MAP in both groups and RSNA in the sham group. Second, RSNA responses to stimulation were increased after application of L-NAME in sham dogs but not in CHF dogs. These data suggest that endogenous NO in the brain inhibits sympathetic outflow. With regard to the CSAR, this reflex is also depressed by NO, but this inhibition was attenuated in the CHF state. Therefore, removal of this inhibitory effect by administration of L-NAME resulted in a greater augmentation of the CSAR in sham dogs than that in CHF dogs.

Central administration of saline at the same rate and volume as those for infusion of SNP and L-NAME had no effect on the CSAR. This confirms that the changes in the CSAR observed in this study are elicited by alterations in central NO levels in both groups of dogs.

The central pathway of the CSAR is unclear. Several regions may be involved, such as the spinal cord, the brain stem, and the hypothalamus. NO may act on one or all of these sites to modulate this reflex. Even though the exact site(s) of NO action cannot be determined from this study, the RVLM may be a major candidate. As shown by several studies, inhibitory effects are consistently evoked by NO within the RVLM. Microinjection of NO donors in the RVLM elicited a reduction in baseline and reflex-activated sympathetic nerve activity (19, 31). Similarly, microinjection of the NO precursor, L-arginine, into the RVLM also evoked a dose-dependent depressor and bradycardiac effect and inhibition of RSNA (23). The PVN in the hypothalamus is another potential site for NO action in the present study. The PVN contains a high density of NOS neurons (3). Microinjection of L-NAME into the PVN elicited an increase in RSNA, MAP, and HR, and these effects were reversed by L-arginine (33). Furthermore, microinjection of SNP into the PVN elicited a significant decrease in RSNA, MAP, and HR (11, 33). More importantly it was found that nNOS mRNA levels in the hypothalamus were significantly decreased in rats with CHF. This decreased nNOS gene expression may lead to the increased sympathetic drive seen in CHF (17). Data from several groups have shown that NO has a potent excitatory action on the sympathetic preganglionic neurons in the spinal cord (7, 12). However, the findings in this study suggest that central NO has an inhibitory effect on sympathetic outflow. This indicates...
that the spinal cord may not be the primary site that mediates the action of NO on the CSAR in this study. Although the NTS is a critical site on which NO may modulate sympathetic control of cardiovascular activity (8, 21), it is probably not the primary site mediating the effect of NO on the CSAR, because all dogs were subjected to sinoaortic denervation (SAD) and vagotomized, removing the main inputs to the NTS. The central site(s) at which NO modulates the CSAR remain to be determined.

Limitations of this study. Several limitations of this study need to be addressed. First, our experiments were carried out in SAD and vagotomized dogs. This animal model raises a crucial question, i.e., what influence did this intervention have on the CSAR? Baroreceptor reflexes interact with the CSAR (14). Although the central mechanism for this interaction is not known, it is logical to speculate that the baroreceptor reflexes inhibit the expression of the CSAR. Therefore, removal of the inhibitory action from baroreceptor reflexes by SAD in this study should increase the sensitivity of the CSAR. Because the baroreceptor reflexes are attenuated in the CHF state (5), SAD should have a greater influence on the CSAR in the normal dog than in the CHF dog. Even under these conditions, the RSNA responses to stimulation of cardiac sympathetic afferent nerves were significantly greater in CHF. Second, because it has been known that NOS is widely distributed in the peripheral nervous system (3), and the renal sympathetic nerves recorded from in this study are postganglionic, the changes in the CSAR-induced RSNA may be attributed to a peripheral effect of NO. Indeed, we cannot rule out this possibility completely. However, the data from other studies suggest that inhibition of NO synthesis does not affect ganglionic transduction (30). Third, because the RSNA responses to stimulation have been used to indicate the central gain of the CSAR in this study, the question that may be asked is, How representative is

Fig. 6. Effect of central administration of L-NAME on RSNA responses to varying frequency and voltage stimulation of cardiac sympathetic afferent nerves in CHF (n = 5, A) and sham dogs (n = 10, B). *P < 0.05 and **P < 0.01 compared with before administration.

Fig. 7. Effect of central administration of L-NAME on slope of RSNA response to varying voltage stimulation of cardiac sympathetic afferent nerves in CHF and sham dogs. *P < 0.05 compared with before administration.
the RSNA of the sympathetic nervous system in general in CHF? Several physiological indicators, such as arterial pressure, HR, plasma norepinephrine, and efferent sympathetic nerve activity have been used as an index of the level of sympathetic outflow. RSNA has been shown to mimic changes in sympathetic outflow evoked by various cardiovascular reflexes in normal and pathological states (15, 29). We and others have used RSNA as the efferent indicator of the CSAR. Although there have been several studies showing heterogeneity in sympathetic outflow to various vascular beds in both normal and disease states (9, 24, 25), there are also several important papers that have shown a close relationship between RSNA and plasma norepinephrine (4, 16). Not only is the RSNA relatively easy to measure, but the responses are relevant to changes in renal function that may occur in the heart failure state. Finally, it can be inferred that the effect of central administration of SNP and L-NAME on RSNA might be due to cerebral vasodilation or vasoconstriction. We do not have direct evidence to refute this possibility. However, Sakuma et al. (18) found that the intravenous administration of the NOS inhibitor N\(^\text{G}\)-methyl-L-arginine did not alter cerebral blood flow as measured by laser-Doppler flowmetry. In addition, we observed the effect of central hydralazine, which is a non-NO dependent vasodilator, on the CSAR in two additional dogs. The dose of hydralazine was adjusted to cause equivalent depressor effects as SNP. No effect of hydralazine on the CSAR was found. This indirect information provides evidence that the effects of SNP and L-NAME on the CSAR obtained in this study are most likely not mediated by alterations of cerebral blood flow. Nevertheless, it remains to be ascertained whether SNP and L-NAME can alter cerebral blood flow and whether such changes in cerebral vessel tone can affect neuronal activity, which may contribute to the SNP and L-NAME effects on the CSAR.

In summary, dogs with CHF exhibited enhanced RSNA responses to electrical stimulation of the cardiac sympathetic afferent nerves. Central infusion of SNP attenuated these responses in the CHF group but not in the sham group. Whereas central administration of L-NAME augmented these responses in the sham dogs, there was no significant effect in dogs with CHF. These results indicate that the central gain of the CSAR is enhanced in CHF and that central NO has an inhibitory effect on the CSAR. Furthermore, the reduction of central NO that occurs in the CHF state may contribute significantly to the elevated central sensitivity of the CSAR in CHF dogs.

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