Chronic Baroreceptor Activation Enhances Survival in Dogs With Pacing-Induced Heart Failure


Abstract—Much of the current pharmacological therapy for chronic heart failure targets neurohormonal activation. In spite of recent advances in drug therapy, the mortality rate for chronic heart failure remains high. Activation of the carotid baroreceptor (BR) reduces sympathetic outflow and augments vagal tone. We investigated the effect of chronic activation of the carotid BR on hemodynamic and neurohormonal parameters and on mortality in dogs with chronic heart failure. Fifteen dogs were instrumented to record hemodynamics. Electrodes were applied around the carotid sinuses to allow for activation of the BR. After 2 weeks of pacing (250 bpm), electrical carotid BR activation was initiated in 7 dogs and continued for the remainder of the study. The start of BR activation was used as a time reference point for the remaining 8 control dogs that did not receive BR activation. Survival was significantly greater for dogs undergoing carotid BR activation compared with control dogs (68.1±7.4 versus 37.3±3.2 days, respectively; P<0.01), although arterial pressure, resting heart rate, and left ventricular pressure were not different over time in BR-activated versus control dogs. Plasma norepinephrine was lower in dogs receiving BR activation therapy 31 days after the start of BR activation (401.9±151.5 versus 1121.9±389.1 pg/mL in dogs not receiving activation therapy; P<0.05). Plasma angiotensin II increased less in dogs receiving activation therapy (plasma angiotensin II increased by 157.4±58.6 pg/mL in control dogs versus 10.1±14.0 pg/mL in dogs receiving activation therapy; P<0.02). We conclude that chronic activation of the carotid BR improves survival and suppresses neurohormonal activation in chronic heart failure. (Hypertension. 2007;50:904-910.)

Key Words: baroreflex ▪ carotid sinus ▪ sympathetic nerve activity ▪ nerve stimulation

The role of autonomic activation in the setting of chronic heart failure (CHF) is well established and is the target of modern pharmacotherapy of CHF.1–4 Chronic increases in sympathetic function and activation of the renin-angiotensin II (Ang II)-aldosterone system are especially disadvantageous in the setting of CHF. The intense vasoconstrictor tone provided by increases in sympathetic outflow, along with activation of the renin-Ang II-aldosterone system are especially disadvantageous in the setting of CHF. The intense vasoconstrictor tone provided by increases in sympathetic outflow, along with activation of the renin-Ang II-aldosterone system is capable of reducing sympathetic tone in humans and animals.20,21 These studies suggest that augmentation of a depressed baroreflex in the CHF state may be capable of reversing some of the neurohormonal excitation in this syndrome. Recent failures of other pharmacological treatments in CHF22,23 point to an urgent need for the development of other therapies.

Traditionally, it has been well accepted that the BR is involved in short-term regulation and that, with chronic endings have also been shown to be depressed in the CHF state.14–17 There is little doubt that baroreflex function is depressed in CHF.5,10,13 This depression is a function of both baroreceptor abnormalities and changes in central neuronal signal processing.

Interestingly, there is evidence that augmentation of baroreflex function is capable of reducing sympathetic tone in humans with heart failure.18,19 These investigators demonstrated an inotropic independent enhancement in arterial baroreflex function after administration of cardiac glycosides to patients with heart failure. Animal experiments have demonstrated an excitatory effect of cardiac glycosides on baroreceptor discharge in normal and heart failure animals.20,21 These studies suggest that augmentation of a depressed baroreflex in the CHF state may be capable of reversing some of the neurohormonal excitation in this syndrome. Recent failures of other pharmacological treatments in CHF22,23 point to an urgent need for the development of other therapies.
changes in blood pressure, the BR will reset to the prevailing pressure. However, an emerging body of evidence indicates that arterial baroreflexes do not completely reset in response to long-term alterations in arterial pressure. As a result, arterial baroreflexes appear to have a sustained influence on sympathetic activity. Thrasher demonstrated that chronic unloading of the carotid baroreceptors in dogs produced sustained hypertension (7 days) associated with sodium retention and increases in plasma renin activity and heart rate. Such responses indicated sustained increases in sympathetic activity to the heart and kidneys, responses that also occur in CHF. In recent studies the idea of chronic stimulation of the carotid baroreceptors has gained attention as a therapeutic modality for the treatment of drug-resistant hypertension. Earlier studies had evaluated carotid sinus nerve stimulation in humans and animals as a therapy for hypertension and intractable angina. However, chronic baroreflex stimulation has never been evaluated in the setting of CHF. Therefore, in the present study, we hypothesized that chronic carotid sinus stimulation in the setting of CHF would reduce sympathetic outflow and have beneficial effects on cardiac function and survival.

Methods

Animals
All of the experiments were carried out on male dogs weighing between 21 and 25 kg. All of the procedures were approved by the University of Nebraska Medical Center Institutional Animal Care and Use Committee and conformed to the National Institutes of Health Guide for the Care and Use of Laboratory Animals. Animals were housed in runs and subjected to a 12-hour light cycle. They were fed 2 cans of food per day (738 g; 0.21% sodium; 0.20% potassium) and allowed water ad libitum.

Heart Failure Model
The model of chronic tachycardia as described in previous studies from this laboratory was used to produce CHF. Dogs were instrumented with a left ventricular pacing electrode secured to an external pacing unit. At the same time, a Data Sciences Inc. instrumented with a left ventricular pacing electrode secured to an external pacing unit. At the same time, a Data Sciences Inc. radio telemetry transducer was implanted (Model TL 11 M3-D70 PCTP) from this laboratory was used to produce CHF.8,33,34 Dogs were fed 2 cans of food per day (738 g; 0.21% sodium; 0.20% potassium) and allowed water ad libitum.

Carotid Sinus Stimulation
Stimulation of the carotid sinus baroreceptors was carried out as previously described. Two weeks after the thoracic instrumentation, stimulating electrodes were implanted circumferentially around both carotid sinuses. The electrodes were tunneled beneath the skin and attached to a programmable carotid sinus stimulator (Rheos, CVRx, Inc.). The efficacy of the stimulation and proper placement of the electrodes were confirmed by the blood pressure– and heart rate–lowering responses during activation at the time of surgery. Several days after recovery from surgery, the response to carotid sinus stimulation was again determined in the conscious state. This was done several times over the subsequent week to insure a stable response. It has been shown that there is a linear stimulus response relationship between stimulus amplitude (voltage) and the fall in arterial pressure over the range of 4.5 to 7.5 volts. However, because there is some variability in the sensitivity to stimulation because of electrode placement or intrinsic differences in the carotid sinus architecture, we tested each dog for its sensitivity beginning at 1 week after electrode implantation. Over a 2- to 3-day period, we established the level of stimulation necessary to decrease arterial pressure by 10 to 15 mm Hg. We stimulated each dog at the predetermined voltage with 0.5- to 1.0-msec wave pulses at 50 to 100 Hz. The duty cycle for stimulation included continuous trains of pulses for 9 minutes and then off for 1 minute. This duty cycle was chosen to avoid the possibility that baroreceptors may undergo chronic resetting without a short period in which they were not stimulated. Figure S1 (see online supplemental data at http://hyper.ahajournals.org) shows a representative tracing of the arterial pressure and heart rate responses to bilateral carotid sinus stimulation in a conscious dog 2 weeks after electrode implantation.

Echocardiography
With the dogs lying on their left side on a laboratory table in a quiet, dimly lit room, echocardiographic measurements were made with an Acuson Sequoia 512 C echocardiograph using a 5-MHz probe. Left ventricular function was determined by the measurement of LV end diastolic diameter and end systolic diameter. Derived parameters were diastolic volume, systolic volume, fractional shortening, and ejection fraction.

Plasma Ang II and Norepinephrine
The protocol for Ang II extraction from plasma samples was essentially similar to that described by Raff et al; however, we have modified the protocols for final sample preparation and the assay, which has resulted in a significant improvement of the assay. The protocol has been optimized and verified by spiking plasma samples with known and unknown amounts of pure Ang II. The sensitivity of the assay is 2 pg per tube.

Plasma norepinephrine was measured using the radioenzymatic technique as described by Peuler and Johnson and obtained in kit form (Amersham Biosciences). The technicians carrying out these assays were blinded to the animals that they were obtained from.

Protocol
Figure 1 summarizes the experimental protocol used in these studies. In brief, after recovery from the carotid electrode and stimulator surgery, baseline hemodynamic measurements and plasma samples were taken with the dogs lying quietly on a laboratory table in the conscious state. On day −14, cardiac pacing was initiated at a rate of 250 bpm. Pacing continued until the demise of the dogs. After 2 weeks (day 0) of pacing, dogs were divided into 2 groups. In one group, carotid sinus stimulation was initiated. The other group was treated in a similar fashion, but no carotid sinus stimulation was carried out. Hemodynamic measurements and blood sampling were then carried out twice per week for the remainder of the experiment. All of the hemodynamic measurements and blood sampling took the following form...
place after the cardiac pacemaker had been turned off for ≥20 minutes.

Statistical Analysis
All of the data are expressed at mean ± SEM. Group differences were determined with a Student’s t test. Differences within a group across time were determined with a 1-way ANOVA for repeated measures when the numbers were similar. A P < 0.05 was assumed to be statistically significant.

Results
Baseline Parameters
Seventeen dogs were included in this study. One dog in the stimulated group was eliminated from the data after carotid sinus stimulation, because we could not confirm continuous carotid sinus stimulation. However, this dog’s baseline data have been included. Because the survival of dogs in each group was different, the numbers for various time points are different, being greatest in the earlier time periods. The Table shows baseline hemodynamic parameters measured in the conscious state before either chronic pacing or carotid stimulation was initiated. The only significant difference was a slightly higher mean arterial pressure in the stimulated group. The changes in ejection fraction and fractional shortening are shown in Figure 4. As was the case for the other parameters, these echo-based parameters were also not different between stimulated and nonstimulated groups over time. Left ventricular diameters and volumes progressively increased equivalently in both groups (data not shown).

Plasma Norepinephrine
Baseline plasma norepinephrine averaged 288.5 ± 75.5 pg/mL in 7 dogs from the nonstimulated group and 338.0 ± 104.0 pg/mL in 7 dogs from the nonstimulated group and 338.0 ± 104.0 pg/mL.

Table. Baseline Hemodynamic and Postmortem Heart Weights

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Nonstimulated</th>
<th>Stimulated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight, kg</td>
<td>24.4 ± 1.2 (8)</td>
<td>24.9 ± 0.8 (9)</td>
</tr>
<tr>
<td>Heart weight, g</td>
<td>218.6 ± 15.4 (8)</td>
<td>215.6 ± 9.5 (9)</td>
</tr>
<tr>
<td>LV weight, g</td>
<td>124.1 ± 9.6 (8)</td>
<td>114.5 ± 4.0 (9)</td>
</tr>
<tr>
<td>Heart weight/body weight, g/kg</td>
<td>8.9 ± 0.3 (8)</td>
<td>8.6 ± 0.2 (9)</td>
</tr>
<tr>
<td>LV weight/body weight, g/kg</td>
<td>5.1 ± 0.2 (8)</td>
<td>4.6 ± 0.1 (9)</td>
</tr>
<tr>
<td>LVEDP, mm Hg</td>
<td>3.0 ± 2.1 (7)</td>
<td>2.2 ± 1.2 (6)</td>
</tr>
<tr>
<td>LVSP, mm Hg</td>
<td>114.9 ± 3.5 (7)</td>
<td>119.6 ± 3.9 (6)</td>
</tr>
<tr>
<td>dp/dtmax, mm Hg/s</td>
<td>3467 ± 392 (7)</td>
<td>3638 ± 395 (6)</td>
</tr>
<tr>
<td>MAP, mm Hg</td>
<td>93.8 ± 4.1 (8)</td>
<td>106.8 ± 2.5 (9)*</td>
</tr>
<tr>
<td>HR, bpm</td>
<td>95.8 ± 5.1 (8)</td>
<td>103.9 ± 6.5 (9)</td>
</tr>
</tbody>
</table>

LV indicates left ventricle; LVEDP, left ventricular end diastolic pressure; LVSP, left ventricular systolic pressure; MAP, mean arterial pressure; HR, heart rate. Numbers in parentheses denote the number of dogs that the data are based on.

*P < 0.05.
pg/mL in 7 dogs from the stimulated group, and they were not significantly different from each other. As shown in Figure 5, the changes in plasma norepinephrine after chronic pacing were marked in the nonstimulated group but remained low in the stimulated group until almost 10 weeks of pacing. After pacing in the nonstimulated group, norepinephrine was highly variable but increased to a peak of 1121.9±389.1 pg/mL at 31 days after the initiation of pacing. The changes in plasma norepinephrine at days 24 to 42 in the stimulated group were significantly lower compared with the nonstimulated group.

Plasma Ang II
Baseline plasma Ang II taken before ventricular pacing was initiated at an average of 43.3±14.5 pg/mL in the nonstimulated group and 60.0±14.5 pg/mL in the stimulated group. These differences were not significantly different from each other. Figure 6 shows the changes in plasma Ang II on a weekly basis after the initiation of chronic pacing in each group. As was the case for norepinephrine, Ang II remained at baseline in the carotid sinus–stimulated group until very late in the course of pacing, whereas it increased significantly at 35 days of pacing in the nonstimulated group, reaching 198.4±63.0 pg/mL at this time point.

Survival
Dogs in both groups were paced until they either died or they were moribund (eg, would not stand, eat, drink, etc) and were euthanized. Two dogs in the nonstimulated group and 1 dog in the stimulated group were euthanized. The mean survival rate after the initiation of pacing was 37.3±3.2 days in the nonstimulated group versus 68.1±7.4 days in the stimulated group (P<0.01). A Kaplan-Meier plot of the percentage of survival versus time is shown in Figure 7. Nonstimulated dogs started to die as early as 22 days after pacing compared with the stimulated group, where the first dog died at 37 days. In the nonstimulated group, no dogs survived past 49 days.
after ventricular pacing. The longest survivor in the stimulated group was 91 days. For those dogs that succumbed to their heart failure, the exact cause of death cannot easily be determined. Hemodynamic parameters but not waveform data were recorded continuously; therefore, it is difficult to determine whether an arrhythmia or pump failure with resulting pulmonary edema caused their demise. On postmortem inspection, all of the dogs showed signs of pulmonary edema and ascites.

**Discussion**

Short-term regulation of sympathetic outflow is determined to a large degree by the arterial baroreflex. There is, however, a good deal of controversy as to the role of the arterial baroreflex in regulating chronic changes in sympathetic outflow, especially in disease states, such as hypertension and heart failure,26,27,37,38 where sympathoexcitation is an important component.39,40 Although disagreement remains as to the long-term contribution of abnormal baroreflex function in CHF,12,33,41 there is a general consensus that arterial baroreflex function is depressed in the setting of CHF.6,11,13 Because the arterial baroreflex is a sympathoinhibitory negative feedback system, it was of interest to determine the effects of augmentation of baroreflex function in CHF. In the current study we observed significant reductions in sympathetic function and a dramatic enhancement in survival in a canine model of pacing-induced CHF. Survival was increased in spite of the fact that ventricular function did not appear to be enhanced in dogs subjected to chronic stimulation of the carotid baroreceptors.

The use of carotid sinus nerve stimulation for the treatment of hypertension and intractable angina was described in humans and animals 40 years ago.79,42–44 Although these early studies demonstrated the efficacy of this technique, it was abandoned because of limitations of implantable medical devices of that era, as well as because of improved pharmacological therapy becoming widely available. A renewed interest in carotid sinus stimulation has been generated by the development of a programmable device currently being tested for treatment of severe drug-resistant hypertension in humans. Using this device (Rheos System, CVRx, Inc), arterial pressure was chronically lowered in normotensive dogs with various forms of chronic hypertension. Lohmeier et al45,46 showed a sustained suppression of plasma norepinephrine, renin, and arterial pressure during 1 week of carotid sinus stimulation in both normal and hypertensive dogs. It is of interest to speculate why the carotid sinus–stimulated dogs in this study did not exhibit a further fall in arterial pressure compared with their nonstimulated counterparts. The model used in these experiments is substantially different than the normal or hypertensive models used by Lohmeier et al.45,46 One characteristic of the pacing model is hypotension as a result of a decrease in cardiac function. This occurred equally in both stimulated and nonstimulated dogs. Most likely it is difficult to observe a further decrease in arterial pressure, which would be superimposed on a hypotensive phenomenon. Furthermore, it must be remembered that the data obtained by Lohmeier et al45,46 were obtained during carotid sinus stimulation, whereas in our data, the stimulus was turned off during data acquisition. Sato et al47 demonstrated the use of a servo control system to regulate sympathetic outflow and arterial pressure in rats with baroreflex dysfunction in CHF. Therefore, because these neurohumoral changes would typically result in a favorable response to treatment in CHF, we set out to determine whether baroreceptor stimulation was effective in reducing mortality in the CHF state. Our data clearly demonstrate an improved survival in the group receiving carotid sinus stimulation in this pacing model of CHF.

**Mechanisms for Enhanced Survival During Baroreflex Stimulation**

Although the present study cannot definitively determine the mechanisms for enhanced survival in CHF dogs subjected to carotid sinus stimulation, several potential possibilities may be put forth. First, chronic increases in sympathetic outflow, especially to the heart and kidneys, can impair organ function.38,48 Indeed, cardiac sympathetic function is a prime target for therapy in the use of β-adrenergic blockers in heart failure. However, in the present study, there were no differences in cardiac function between the stimulated and nonstimulated dogs. Therefore, it is unlikely that the beneficial effect of carotid sinus stimulation was mediated by a major influence of reducing cardiac sympathetic nerve activity or enhancing cardiac vagal outflow. It should be noted however, that Sabbah et al49 have recently reported an increase in ejection fraction after prolonged BR activation in a coronary embolization model. In this model, ejection fraction was reduced to ≈25% compared with ≈40% using the pacing model described in the current study. The lack of an effect of BR activation on ventricular function in the present study suggests that, at least in this model of CHF, the beneficial effects of this intervention may be mediated by important peripheral adjustments. If we assume that the maintenance of low levels of plasma norepinephrine in stimulated dogs reflects a global reduction in sympathetic outflow, then it is possible that peripheral organ function is maintained for a longer period of time in the stimulated dogs (eg, maintenance of renal function).

Another potential mechanism for the beneficial effects of this therapy is a reduction in plasma Ang II. Although there was a good deal of variability in these data, in general Ang II increased at an earlier time point in nonstimulated dogs than in the stimulated dogs. This coincided with the survival profiles of the nonstimulated dogs compared with the carotid-stimulated dogs. Again, suppression of Ang II generation and Ang II receptor blockade has become mainstream therapy for the treatment of patients with CHF. Providing a stimulus that keeps Ang II low should contribute to a reduction in vascular resistance and extracellular volume and should reduce the mitogenic effects of Ang II, which may attenuate the remodeling process.50,51 What is not clear from these studies is whether the prevention of Ang II from rising in the stimulated dogs depends on a reduction in renal sympathetic nerve activity or whether the reduction in Ang II contributes to the reduced central sympathetic outflow, a phenomenon for which a large amount of evidence exists.52–55
Finally, there may be additional neurohumoral and peripheral mechanisms involved in the salutary effects of carotid sinus stimulation. For instance, it is theoretically possible that a reduction in plasma norepinephrine and Ang II would lead to enhanced endothelial function, thus enhancing regional perfusion to critical vascular beds.

**Limitations of Carotid Sinus Stimulation**

Because arterial baroreflex function is impaired in CHF, it is widely accepted that this depression contributes at some point to neurohumoral activation. In the present study, baroreceptor activation was performed using field stimulation of the carotid sinus wall. Although this technique avoids dissection and direct stimulation of the carotid sinus nerve, it could potentially activate chemoreceptors. Because the response to carotid sinus stimulation is acutely dominated by a fall in blood pressure and heart rate, it is unlikely that chemoreceptor stimulation contributed in a major way to the effects of carotid sinus stimulation in these experiments. Ventilation was not measured.

Earlier studies in humans and animals in which the carotid sinus nerve was stimulated showed repeated hypertensive effects for periods of up to several years. In animal experiments, Lohmeier et al showed sustained hypotensive, norepinephrine, and renin effects over a stimulation period of 1 week using the same Rheos system as that used in the present study. Based on the suppression of plasma norepinephrine in carotid sinus–stimulated dogs, the present study provides evidence of sustained baroreflex augmentation for periods of up to 3 months.

The efficacy of this technique in humans with CHF will have to wait for appropriate clinical trials. However, this device has been implanted in patients with drug-resistant hypertension in clinical trials in Europe (DeBut-HF) and North America (Rheos). In these studies, the device evoked reductions in arterial pressure for prolonged periods of time. Although implantation of this device involves a surgical procedure, it is more robust and less invasive than the device reported in the late 1960s and early 1970s, where carotid sinus nerve dissection was necessary. It remains to be seen whether unilateral stimulation is as effective as bilateral stimulation. If so, this would further enhance the acceptability of this device as an adjunctive therapy for CHF.

**Perspectives**

Chronic carotid sinus stimulation in dogs with pacing-induced CHF-reduced neurohumoral excitation and dramatically increased survival. This occurred in spite of little change in ventricular function. Although targeting sympathetic nerve activity in CHF appears to be logical and is, to a large degree, mainstream therapy, it remains unclear whether suppression of sympathetic support in CHF is beneficial. For instance, in the Moxonidine Congestive Heart Failure Trial, which was designed to evaluate the role of central imidazoline receptor stimulation with moxonidine on survival, a surprise increase in mortality was observed. This was associated with an 18.8% decrease in plasma norepinephrine. This suppression of plasma norepinephrine may have been larger than is therapeutically necessary. In the present study, plasma norepinephrine was prevented from rising during ventricular pacing and the development of CHF but never went below baseline. Although the 2 situations are not completely comparable, the use of BR activation may provide significant advantages in the control of the level of sympathoinhibition. These data suggest that the beneficial effects of carotid sinus stimulation may be attributable more to peripheral vascular and/or neurohumoral inhibition than to cardiac benefits. Furthermore, they suggest that carotid sinus stimulation may be a beneficial therapy for patients with CHF in addition to patients with drug-resistant hypertension.

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**Disclosures**

I.H.Z. is a member of the scientific advisory board of CVRx, Inc. The remaining authors report no conflicts.

**References**

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Table S1. Baseline Echocardiographic Parameters

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<thead>
<tr>
<th>Parameter</th>
<th>Non Stimulated</th>
<th>Stimulated</th>
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<tr>
<td>LVIDd (mm)</td>
<td>32.3±1.2 (6)</td>
<td>34.6±2.4 (7)</td>
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<tr>
<td>LVIDs (mm)</td>
<td>18.4±1.9 (6)</td>
<td>20.6±1.9 (7)</td>
</tr>
<tr>
<td>IVSd (mm)</td>
<td>11.0±0.5 (6)</td>
<td>11.3±1.0 (7)</td>
</tr>
<tr>
<td>IVSs (mm)</td>
<td>15.1±1.1 (6)</td>
<td>14.8±1.3 (7)</td>
</tr>
<tr>
<td>LVVd (ml)</td>
<td>43.3±5.9 (6)</td>
<td>52.3±8.5 (7)</td>
</tr>
<tr>
<td>LVVs (ml)</td>
<td>11.4±5.9 (6)</td>
<td>15.6±3.5 (7)</td>
</tr>
<tr>
<td>EF (%)</td>
<td>69.9±5.1 (6)</td>
<td>67.1±4.4 (7)</td>
</tr>
<tr>
<td>FS (%)</td>
<td>42.4±2.7 (6)</td>
<td>41.1±2.2 (7)</td>
</tr>
</tbody>
</table>

LVIDd, left ventricular internal diameter in diastole; LVIDs, left ventricular internal diameter in systole; IVSd, intraventricular septum in diastole; IVSs, intraventricular septum in systole; LVVd, left ventricular volume in diastole; LVVs, left ventricular volume in systole; EF, ejection fraction; FS, fractional shortening.
Figure S1. An original recording of the response to bilateral carotid sinus stimulation in a conscious dog 2 weeks following carotid sinus electrode implantation prior to initiation of chronic pacing. Dashed vertical lines indicate the start and stop of stimulation.