Increased cardiac sympathetic nerve activity in heart failure is not due to desensitization of the arterial baroreflex

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Watson AM, Hood SG, Ramchandra R, McAllen RM, May CN. Increased cardiac sympathetic nerve activity in heart failure is not due to desensitization of the arterial baroreflex. Am J Physiol Heart Circ Physiol 293: H798–H804, 2007. First published April 13, 2007; doi:10.1152/ajpheart.00147.2007.—Increased sympathetic drive to the heart worsens prognosis in heart failure, but the level of cardiac sympathetic nerve activity (CSNA) has been assessed only by indirect methods. We directly recorded CSNA in conscious, normal, healthy sheep and in sheep with HF induced by rapid ventricular pacing. We then assessed baroreceptor control of CSNA by measuring heart rate variability. We determined the level of sympathetic drive to the heart because there are no studies in which cardiac sympathetic nerve activity (CSNA) has been recorded directly in HF. Understanding the factors leading to the increased CSNA is increased (9, 28), as is renal norepinephrine spillover in infarction-induced HF, it has also been demonstrated by direct recordings in a sheep model of heart failure thus show that resting CSNA is strikingly increased; but this is not due to defective control by arterial baroreceptors. Desensitized arterial baroreflex control of heart rate has been studied extensively. In HF patients, the sensitivity of the arterial baroreflex control of MSNA in HF patients, and in a recent review (15) it has been argued that the arterial baroreflex control of sympathetic nerve activity is not desensitized even in advanced HF. In experimental animals, preserved arterial baroreflex control of RSNA in HF patients, and without direct recordings of CSNA in HF, it remained unknown whether the arterial baroreflex control of CSNA is desensitized in this state.

To determine the level of sympathetic drive to the heart in HF, we directly recorded CSNA in conscious, normal, healthy sheep and in sheep with HF induced by rapid ventricular pacing. These measures were compared side by side with a commonly used indirect index of sympathetic drive, the low-frequency component of heart rate variability. We then assessed the arterial baroreflex control of CSNA to test whether

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HEART FAILURE (HF) IS CHARACTERIZED by activation of the sympathetic nervous system as demonstrated in patients by increases in circulating norepinephrine (44), total and regional norepinephrine spillover (19), and muscle sympathetic nerve activity (MSNA) (17). In animal models of both pacing- and infarction-induced HF, it has also been demonstrated by direct nerve recording that renal sympathetic nerve activity (RSNA) is increased (9, 28), as is renal norepinephrine spillover in humans with HF (19).

The mechanisms that cause the sympathetic activation in HF are not well understood. This is particularly true for the outflow to the heart, because there are no studies in which cardiac sympathetic nerve activity (CSNA) has been recorded directly in HF. Understanding the factors leading to the increased CSNA in HF is particularly important because it is the increase in CSNA that leads to arrhythmias and sudden death. The detrimental effect of increased CSNA in HF is shown by the strong inverse correlation between cardiac norepinephrine spillover and prognosis (23) and by the beneficial action of β-adrenergic blockers on survival (38).

Studies of cardiac norepinephrine spillover, an indirect, steady-state method, indicate that it is increased more than spillover from other organs in patients with HF (19) and that the cardiac increase occurs earlier in the disease process than in other organs (41). These data imply that in HF there is a preferential activation of CSNA, exposing the heart to higher levels of activation, and for a longer period, than to other organs. On the other hand, changes occur to the cardiac sympathetic nerves in HF that confound the interpretation of indirect functional measures. The sympathetic innervation of the heart progressively rarefies during the development of HF (20), and norepinephrine uptake may be impaired (12, 41). Consequently, the relationship of these indirect measures to the neural drive received by the heart remains unclear.

The arterial baroreflex is a potent inhibitory reflex with dominant control over resting sympathetic nerve activity, and its role in the activation of noncardiac sympathetic outflow in HF has been studied extensively. In HF patients, the sensitivity of the baroreflex control of MSNA has been reported to be reduced (17, 25, 31), with similar changes in the baroreflex control of RSNA reported in conscious rabbits with pacing-induced HF (26) and in rats with HF induced by coronary occlusion (9). Other studies (6), however, have found preserved arterial baroreflex control of MSNA in HF patients, and in a recent review (15) it has been argued that the arterial baroreflex control of sympathetic nerve activity is not desensitized even in advanced HF. In experimental animals, preserved baroreflex control of RSNA was found in anaesthetized dogs with HF induced by pacing or an aortovenacaval fistula (7, 48). Desensitized arterial baroreflex control of heart rate has been reported widely in HF (11, 14, 17), so it seemed reasonable to propose that the reduced heart-rate changes in response to pressor and depressor stimuli depended not only on the well-established attenuation of parasympathetic control (3, 10, 11, 40) but also on impaired cardiac sympathetic responses. Without direct recordings of CSNA in HF, it remained unknown whether the arterial baroreflex control of CSNA is desensitized in this state.

To determine the level of sympathetic drive to the heart in HF, we directly recorded CSNA in conscious, normal, healthy sheep and in sheep with HF induced by rapid ventricular pacing. These measures were compared side by side with a commonly used indirect index of sympathetic drive, the low-frequency component of heart rate variability. We then assessed the arterial baroreflex control of CSNA to test whether

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it was desensitized in HF. Importantly, the studies were conducted on untreated, conscious animals, thus avoiding the confounding actions of drugs or of anesthesia, which has a particularly potent depressive effect on CSNA (32).

MATERIALS AND METHODS

Adult merino ewes were housed in individual metabolism cages in association with other sheep. Experiments were conducted on conscious sheep standing in their home cages and were not started until they were accustomed to laboratory conditions and human contact. Sheep were fed a diet of oaten chaff (800 g/day), and water was offered ad libitum. All experiments were approved by the Animal Experimentation Ethics Committee of the Howard Florey Institute.

Surgical procedures. Before the studies, sheep underwent two or three aseptic surgical procedures, each separated by 2-wk recovery. Anesthesia was induced with intravenous sodium thiopental (15 mg/kg) and following intubation was maintained with 1.5–2.0% isoflurane/O2. In the first stage, 16 sheep were prepared with a carotid arterial loop and a jugular vein for the measurement of arterial pressure and a basal measurement was made before the start of ventricular pacing, at 200–220 beats/min. Echocardiography was performed weekly with the pacing switched off. Sheep were placed on the operating table, the thoracic cardiac nerves were identified, and the fascia over the fourth rib, the periosteum was opened, and the rib was removed. The thoracic cardiac nerves were exteriorized through the skin was used as a ground. Animals were treated with atropine, methohexital, and fentanyl.

The thoracic cardiac nerves were identified, and the facia over the nerves was removed. Up to five electrodes were pressed obliquely through the nerve sheath, ensuring that the tip was positioned in the center of the nerve (47). Electrodes were fixed in place with cyanoacrylate glue, the implantation site was covered with a layer of Kwik-Sil (WPI, Glen Waverly, Vic, Australia), and the wires were exteriorized next to the sutured wound. A stainless-steel suture looped through the skin was used as a ground. Animals were treated with antibiotics (Ilum Prophen; procaine penicillin, Troy Laboratories, Smithfield, NSW, Australia) at the start of surgery and then for 2 days postoperatively. Postsurgical analgesia was maintained with intramuscular injection of flunixin meglumine (1 mg/kg; Troy Laboratories) at the start of surgery, then 4 and 16 h after surgery. To minimize any effect of surgical stress, experiments were not started until the third day after implantation of the electrodes. On the day before implantation of recording electrodes, cannulae were implanted into the carotid artery loop and a jugular vein for the measurement of arterial pressure and for intravenous infusion (47).

Experimental protocols. The development of HF was assessed by measurement of ejection fraction by using short axis M-echo-echocardiography on conscious sheep lying on their right side. Following placement of ventricular pacing leads, a basal measurement was made before the start of ventricular pacing, at 200–220 beats/min. Echocardiography was performed weekly with the pacing switched off. Sheep were considered to be in HF when ejection fraction had fallen to <40%. All experiments were conducted with the pacing switched off.

CSNA was recorded differentially between the pair of electrodes with the best signal-to-noise ratio. The signal was amplified (×100,000) and filtered (band pass 300–1,000 Hz), displayed on an oscilloscope, and passed through an audio amplifier and a loud speaker. Sympathetic nerve activity (5,000 Hz) and arterial blood pressure (100 Hz) were recorded on a computer using a CED micro 1401 interface and Spike 2 software (Cambridge Electronic Design).

At 3 days after surgical implantation of cardiac sympathetic nerve electrodes, a 5-min recording of resting CSNA and arterial pressure was made in conscious sheep in the normal state and in HF. Following this, baroreflex curves were generated by measuring the CSNA and heart-rate responses to increases and decreases in arterial pressure induced by intravenous administration of incremental doses of phenylephrine and sodium nitroprusside. Phenylephrine hydrochloride (33, 67, 133, and 330 mg/min; NeoSynephrine, Abbott Australasia, Kurnell, NSW, Australia) and sodium nitroprusside (42, 83, 167, and 417 mg/min; David Bull Laboratories, Mulgrave, Vic, Australia) were infused at 0.5, 1.0, 2.0, 5.0 ml/min for 1–2 min at each dose, with treatments given in random order.

Data analysis. Data were analyzed on a beat-to-beat basis by using custom-written routines in the Spike 2 program. For each heartbeat the program determined diastolic, systolic, and mean arterial blood pressures, heart period, and the number of discriminated spikes above threshold between the following diastolic pressures, a measure of burst size. The threshold was set just above background so that spikes from small bursts were counted. The background noise was taken as the spikes per second during the highest dose of phenylephrine when CSNA was abolished, and this was subtracted from the data collected on that day.

As a measure of CSNA, the spikes over threshold minus the background were calculated for each heartbeat. Burst frequency was calculated as the percentage of heartbeats that included spikes above background. The accuracy of burst determination was checked by eye over the 5-min control data for each sheep. Post hoc analysis of data was conducted by using custom-written scripts for Spike 2, and data were exported to a spreadsheet for further analysis.

Baroreceptor relations were constructed from data collected during infusion of phenylephrine and nitroprusside. The burst size, determined as the number of discriminated spikes between successive diastolic pressures, was divided by the heart period. The relation between CSNA and diastolic blood pressure was determined because, on a beat-to-beat basis, diastolic pressure has a closer correlation to sympathetic activity than either systolic or mean arterial pressures (43). To correct for natural variation in CSNA levels between sheep, spike counts were expressed as a percentage of the mean activity recorded during the 5-min control period. The data were then sorted by diastolic pressure. The mean values of groups of 10 data points were used to plot the burst size against diastolic pressure by using a four-parameter sigmoidal logistic equation to fit the data (SigmaPlot v. 8.0; SPSS) (16). The CSNA data were normalized by using the top and bottom plateaus that represent the maximum level during sodium nitroprusside and zero activity during phenylephrine, respectively. Normalized CSNA was plotted against diastolic pressure by using the four-parameter sigmoidal logistic equation. Heart rate was plotted against systolic blood pressure because changes in vagal activity are the primary cause of changes in heart rate in response to increases and decreases in arterial pressure, and vagal tone is more closely correlated with systolic than with diastolic blood pressure. Variables from the equations of all the graphs were grouped for the normal and HF animals, and average baroreflex relations were plotted.

Power-spectral density was calculated for both the normal and the HF sheep for the heart rate and the CSNA signals by using custom-written routines in Spike 2. For the CSNA signal, the raw nerve activity was full-wave rectified and integrated with a time constant of 10 ms. The threshold was set just above background so that spikes from small bursts were counted. The background noise was taken as the spikes per second during the highest dose of phenylephrine when CSNA was abolished, and this was subtracted from the data collected on that day.

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Data are expressed as means ± SE and were analyzed by using unpaired Student’s t-tests (SigmaStat, Access Softek, ver 2.03). P < 0.05 was considered statistically significant.

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Table 1. Resting points of normal animals and animals in heart failure from 5 min of control data

<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th>Heart Failure</th>
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<tbody>
<tr>
<td>Burst frequency, %</td>
<td>46 ± 6</td>
<td>89 ± 3***</td>
</tr>
<tr>
<td>CSNA, %maximum</td>
<td>22.5 ± 3.3</td>
<td>61.2 ± 6.5***</td>
</tr>
<tr>
<td>CSNA, spikes/s</td>
<td>13.9 ± 4.2</td>
<td>44.6 ± 7.9**</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>69.9 ± 4.9</td>
<td>87.1 ± 3.1*</td>
</tr>
<tr>
<td>Diastolic BP, mmHg</td>
<td>74.9 ± 2.0</td>
<td>69.4 ± 1.8</td>
</tr>
<tr>
<td>Systolic BP, mmHg</td>
<td>101.5 ± 2.8</td>
<td>93.3 ± 3.2</td>
</tr>
<tr>
<td>Mean arterial pressure, mmHg</td>
<td>83.7 ± 2.1</td>
<td>77.2 ± 2.2</td>
</tr>
<tr>
<td>Pulse pressure, mmHg</td>
<td>26.5 ± 1.4</td>
<td>24.0 ± 1.6</td>
</tr>
<tr>
<td>SD of RR interval, ms</td>
<td>57.4 ± 7.5</td>
<td>32.8 ± 7.3**</td>
</tr>
</tbody>
</table>

Values are means ± SE; n = 8 both groups. CSNA, cardiac sympathetic nerve activity; BP, blood pressure; RR interval, interbeat interval. *P < 0.05, **P < 0.01, and ***P < 0.001 vs. normal sheep.

RESULTS

Resting hemodynamics and heart rate variability. Left-ventricular ejection fraction and fractional shortening, measured in conscious sheep by echocardiography, gradually decreased over 4–6 wk of rapid ventricular pacing at 200–220 beats/min. At 1–2 days before implantation of cardiac sympathetic recording electrodes, HF animals had an ejection fraction of 36 ± 2%, compared with 82 ± 3% before pacing (P < 0.001). Fractional shortening was decreased from 48 ± 2 to 19 ± 1% (P < 0.001), and there were increases in end-diastolic diameter (from 3.5 ± 0.1 to 4.4 ± 0.2 cm; P = 0.015) and end-systolic diameter (from 1.9 ± 0.1 to 3.5 ± 0.2 cm; P = 0.001). An increase in pericardial fluid was visible by echocardiography in 5 of the HF sheep, and at surgery HF animals had 100 to 500 ml of pleural effusion. Systolic blood pressure (P = 0.073), diastolic blood pressure (P = 0.065), and mean arterial pressure (P = 0.055) all tended to be lower in HF sheep, although these differences did not reach significance (Table 1). Animals in HF had a significantly higher mean heart rate than normal animals and lower heart rate variability, as measured by the standard deviation of the interbeat interval (Table 1). Spectral analysis of heart-rate variability showed no difference in the proportion of low-frequency spectral power between normal and HF sheep (40.6 ± 8 vs. 40.2 ± 6% of total power, respectively; Fig. 2) and no difference in the ratio of low-frequency to mid-frequency spectral power (3.4 ± 1.2 in normal sheep vs. 3.1 ± 0.9 in HF).

CSNA measurements. Like the activity in other sympathetic nerves, CSNA occurred in arterial pulse-synchronous bursts. This was true in both normal and HF sheep (Fig. 1). In four of the normal sheep, we demonstrated that CSNA was blocked by ganglion blockade with hexamethonium, indicating that the recordings from these nerves were of postganglionic, efferent sympathetic nerve activity (data not shown). The resting burst incidence of CSNA in eight HF sheep was 89 ± 3% (range 80–100%), compared with 46 ± 6% (range 20–70%) in eight normal animals (P < 0.001; Table 1). The resting CSNA burst rate, expressed as a percentage of its maximum level during infusion of sodium nitroprusside, was also significantly higher in the HF sheep (61.2 ± 6.5%) compared with the normal sheep (22.5 ± 3.3%; P < 0.001; n = 8 in each group). Comparisons of raw nerve activity in different animals have to be interpreted cautiously, because the absolute size of the signal is affected by physical factors such as nerve fascicle size and electrode placement. Nevertheless, the measured raw CSNA spike count was substantially greater in the HF sheep (44.6 ± 7.98 spikes/s) than in normal sheep (13.9 ± 4.2 spikes/s; P < 0.01; Table 1). Spectral analysis of the CSNA signal showed that 22.9 ± 1.6% of total power was present in the low-frequency range in normal animals, which fell to 14.6 ± 1.35% in the HF group (P < 0.01; Fig. 2). The ratio of low-frequency to mid-frequency power was also reduced in the HF group (1.0 ± 0.1% in normal animals vs. 0.6 ± 0.1% in HF; P < 0.05).

Baroreflex control of heart rate and CSNA. Composite baroreflex relations between heart rate and systolic BP in eight normal sheep and in eight sheep with HF are shown in Fig. 3. The maximum gain of the relation in HF animals (−3.29 ± 0.56 beats·min⁻¹·mmHg⁻¹) was less than that in normal animals (−5.34 ± 0.66 beats·min⁻¹·mmHg⁻¹; P < 0.05), confirming observations in humans and other species (11, 14, 17). The upper plateau of heart rate was also significantly lower in the HF group (117.1 ± 4.3 beats/min) compared with normal sheep (162.0 ± 11.4 beats/min; P < 0.01), whereas the
Similar findings were obtained if baroreflex relations between heart rate and diastolic blood pressure were calculated. In the normal and HF groups, respectively, the maximum gains were 5.20 ± 0.76 and 2.26 ± 0.36 beats·min⁻¹·mmHg⁻¹ (P < 0.05), the upper plateaus were 163.0 ± 8.5 and 118.8 ± 5.6 beats/min (P < 0.001), and the bottom plateaus were 49.5 ± 5.7 and 51.8 ± 3.1 beats/min.

In contrast, the gains of the baroreflex relations between diastolic blood pressure and normalized CSNA were not significantly different in the HF (6.33 ± 1.06%max/mmHg) compared with the normal group (6.03 ± 0.95%max/mmHg; Table 2).

The baroreflex relationship between diastolic blood pressure and raw CSNA spike counts showed a nonsignificant tendency toward an increased gain and upper plateau in HF sheep (Table 2).

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<thead>
<tr>
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<th>Normal</th>
<th>Heart Failure</th>
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<tr>
<td>sBP vs. HR</td>
<td></td>
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<tr>
<td>Maximum gain,</td>
<td>-5.34±0.66</td>
<td>-3.29±0.56*</td>
</tr>
<tr>
<td>Top plateau, beats/min</td>
<td>162.0±11.44</td>
<td>117.1±4.3***</td>
</tr>
<tr>
<td>Bottom plateau, beats/min</td>
<td>52.6±4.3</td>
<td>58.2±1.8</td>
</tr>
<tr>
<td>dBP vs. normalized CSNA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maximum gain, %max/mmHg</td>
<td>-6.03±0.95</td>
<td>-6.33±1.06</td>
</tr>
<tr>
<td>dBP vs. CSNA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maximum gain, spikes·s⁻¹·mmHg⁻¹</td>
<td>-2.30±0.41</td>
<td>-5.51±1.60</td>
</tr>
<tr>
<td>Top plateau, spikes/s</td>
<td>43.8±9.9</td>
<td>76.8±14.5</td>
</tr>
<tr>
<td>Bottom plateau, spikes/s</td>
<td>-2.47±3.5</td>
<td>-3.0±2.2</td>
</tr>
</tbody>
</table>

Values are means ± SE; n = 8 both groups. dBP, Diastolic BP; HR, heart rate. *P < 0.05 and ***P < 0.001 vs. normal sheep.
normal sheep. As expected from observations in humans and other species (11, 14, 17), in HF there was a desensitization of the relation between heart rate and arterial pressure; but, crucially, there was no blunting of the arterial baroreflex control of CSNA.

The majority of direct information on the control of sympathetic nerve activity in HF has been obtained from measurement of RSNA in animals and MSNA in humans, and in both cases large increases in activity have been found in HF (9, 14, 17, 28). Due to the heterogeneity of control of sympathetic outflow, the changes in resting activity and baroreflex control of CSNA cannot be predicted from the measurement of other sympathetic outflows. For example, in the normal state the bursting pattern of CSNA is not identical to that of other sympathetic nerves (37), the time course of the response to behavioral stimuli differs (37), activation of left atrial receptors stimulates CSNA but decreases RSNA (21), and anesthesia has a greater depressant effect on CSNA compared with RSNA (32). Furthermore, we have demonstrated that central infusion of angiotensin II had opposite effects on CSNA compared with RSNA (21). The observation that CSNA retained its pulse-synchronous character in HF indicates that the arterial baroreflex was still functional. Testing the full range of responses to arterial pressure changes showed clearly that the control of CSNA by arterial baroreflexes was not only present in HF sheep but was at least as powerful as in normal animals. Although this conclusion contrasts with reports of desensitized baroreflex control of MSNA in HF patients (14, 17, 25) and of RSNA in experimental animals (9, 26), preserved arterial baroreflex control of these sympathetic nerves has been reported by others (6, 7, 48). Crucially, these observations tell us that although CSNA was strongly activated in this model of HF, the activation could not have been due to dysfunctional baroreflex control.

A consistent finding in studies of HF is that the baroreflex control of heart rate is desensitized (5, 11, 14). Numerous studies have shown that vagal tone and parasympathetic nervous control of the heart are depressed in HF (3, 10, 11, 40), and this is likely to be the major reason that baroreflex control of heart rate is blunted. Indeed our finding that heart-rate variability was significantly decreased indicates that vagal tone was reduced in the paced sheep. Although it is possible that abnormal baroreflex control of CSNA could be a contributing factor to the blunted heart rate response to hypotension, the present findings do not support such a view. It is likely that factors such as the downregulation of cardiac β-receptors in HF, uncoupling of cardiac β-receptors from second-messenger systems (29), and reduced density of cardiac sympathetic noradrenalin neurons in HF (20) contribute to this blunted response.

Previous studies using spectral analysis of heart-rate variability have suggested that the low-frequency power in heart rate is a good index of cardiac sympathetic tone in the normal state (30, 39). Our recordings of CSNA in normal and HF sheep allowed us to test directly whether the difference in CSNA between the two states is reflected in the low-frequency component of heart-rate variability. Our data showed clearly that it was not a useful measure of the changes in CSNA that occur in HF, confirming the conclusions from previous studies using MSNA (24). Interestingly, we observed a reduction in the low-frequency spectral power in CSNA during HF (Fig. 2). This is in accord with previous studies that have observed a reduction in the low-frequency spectral power in MSNA in HF patients (1, 45).

Limitations. The sheep used in these studies had ejection fractions of 35–40%, so we cannot exclude the possibility that in more severe HF (e.g., with ejection fraction ~20%), recruitment of further mechanisms might lead to desensitization of the baroreflex control of CSNA. What we can say, however, is that desensitization of the arterial baroreflex was not a causative factor in the large increases in CSNA seen at this stage of HF in our experiments. It is also evident that reflexes from arterial baroreceptors cannot be the sole drive to increase sympathetic nerve activity in HF, because sinoaortic denervation has been found not to reduce the increased plasma nor-

![Graph](image_url)
epinephrine in dogs with pacing-induced HF (4). Other mechanisms that may stimulate CSNA in HF include cardiac mechanoreceptors and chemoreflexes (2, 22, 36, 42), increased circulating levels of hormones such as angiotensin II and endothelin (8, 27, 35), and altered central mechanisms that may act to amplify the effects ofafferent inputs (8, 49). Further studies are required to determine the relative importance of these mechanisms as causes of the increased CSNA in HF.

In conclusion, we have found that in conscious sheep with HF induced by rapid ventricular pacing, directly recorded CSNA was greatly increased compared with that in normal sheep. Although the baroreflex control of heart rate was desensitized in sheep with HF compared with that in normal animals, the baroreflex control of CSNA was not significantly changed. These data indicate that the increased CSNA in HF is not dependent on depressed arterial baroreflex control of CSNA.

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REFERENCES


