Analysis of Baroreflex Control of Heart Rate in Conscious Dogs With Pacing-Induced Heart Failure

Jwo-Sheng Chen, PhD; Wei Wang, MD, PhD; Thomas Bartholet, BS; and Irving H. Zucker, PhD

The autonomic components of the baroreflex control of heart rate were evaluated in conscious mongrel dogs before and after 4–6 weeks of ventricular pacing (250 beats/min). Arterial baroreflex sensitivity (BRS) was determined by the slopes of linear regression of pulse interval versus the preceding systolic arterial pressure in response to bolus injections of either phenylephrine or nitroglycerin. BRS was significantly depressed in the heart failure state [nitroglycerin slope, 5.0±2.7 (mean±SD) versus 16.6±5.1 msec/mm Hg, p<0.005; phenylephrine slope, 15.0±14.8 versus 32.0±26.7 msec/mm Hg, p<0.005]. There was no depression in BRS in dogs that were used as time controls or were acutely paced for 30 minutes. After β1-adrenergic blockade with metoprolol, the resting heart rate in the heart failure state was depressed more than in the normal state (−17.0±5.0% versus −3.2±3.4%, p<0.001). Atropine significantly increased resting heart rate more in the normal state than in the heart failure state (115.8±36.7% versus 25.4±14.5%, p<0.005). Thus, dogs in the heart failure state appear to have high resting cardiac sympathetic tone and low resting vagal tone. For nitroglycerin administration, metoprolol depressed BRS by 47.6±26.3% in the normal state and by 63.6±58.5% in the heart failure state. Atropine decreased the BRS by 86.7±7.8% in the normal state and by 39.5±30.2% in the heart failure state. Although these were significantly different (p<0.05), an analysis of covariance indicates that these differences in response in the normal and heart failure states are largely due to the low resting BRS in the heart failure state. For phenylephrine responses, metoprolol had no significant influence on BRS in either the normal or the heart failure state. In contrast, BRS in both normal and heart failure states was nearly abolished by atropine. There was no difference in the extent of BRS inhibition after atropine between the normal and the heart failure state in response to phenylephrine. These data provide the first description of the autonomic control of heart rate in pacing-induced heart failure. In contrast to other models of heart failure, the primary abnormality is seen during baroreceptor unloading with nitroglycerin. The abnormality is largely manifest by a decrease in sympathetic activation in heart failure when the baroreceptors are unloaded. (Circulation 1991;83:260–267)

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Iterations of baroreflex control of the circulation in both humans and experimental animals with heart failure have been recognized for many years.1–4 It has been suggested that parasympathetic control of heart rate is impaired in patients with heart failure.1,5,6 The muscarinic receptor density of the left ventricular myocardium was significantly decreased in heart failure dogs with chronic experimental aortic stenosis.7 In dogs with right heart failure produced by tricuspid avulsion and pulmonary stenosis, it was found that heart rate responses to direct vagal stimulation or sinus node artery perfusion of acetylcholine were markedly reduced.8 On the other hand, evidence of defects in sympathetic control of the circulation in the heart failure state has also been demonstrated by many investigators.5,8,9 The most common findings of the abnormalities of the sympathetic nervous system in severe heart failure was the increase in circulating catecholamine levels8,9–11 and depletion of catechol-
amine stores. Abnormalities at the adrenergic receptor and subreceptor levels have also been extensively investigated. Downregulation of β₁-adrenergic receptors was found in the failing myocardium. It has also been demonstrated that transmembrane signal transmission of myocardial β-adrenergic receptors may be impaired at the level of the guanine nucleotide regulatory proteins. Faulty sympathetic and parasympathetic control of heart rate in heart failure states is evident. However, the mechanisms that may be responsible for the abnormalities of baroreflex control of the circulation in heart failure remain unclear.

Chronic rapid cardiac pacing is an experimental heart failure model developed some decades ago and has been used extensively in the past several years. It has been established that this model produces similar clinical symptoms and neurohumoral profiles as observed in heart failure produced by other means, especially in the late stages of heart failure. Abnormal baroreflexes have also been demonstrated in this model. However, to our knowledge, the individual roles of parasympathetic and sympathetic nervous systems in the reflex control of the circulation in this low-output heart failure model have not been previously investigated. The goal of the present study was to analyze the role of the sympathetic and parasympathetic nervous systems in reflex control of heart rate in heart failure produced by rapid ventricular pacing in conscious, instrumented dogs.

**Methods**

**Surgical Preparation**

Twenty-five adult mongrel dogs of either sex (weight, 18–28 kg) were studied. After premedication with acepromazine (0.25 mg/kg i.m.; PromAce, Fort Dodge, Fort Dodge, Iowa), anesthesia was induced with sodium pentobarbital (25–30 mg/kg; Fort Dodge). Supplementary doses were given when needed. A left thoracotomy was performed in the fourth intercostal space using sterile surgical procedures. A screw-type epicardial pacing lead (model 6197-35T, Medtronic) and a pair of stainless-steel ground wires were implanted onto the left ventricle and left atrial appendage, respectively. A Tygon catheter was inserted into the descending thoracic aorta for the measurement of arterial pressure. A Tygon catheter with a Silastic tip was inserted into the left atrium via the left atrial appendage and used for the measurement of left atrial pressure (LAP). In seven dogs, a Konigsberg pressure transducer (P7) was also implanted into the left ventricle through a stab wound in the apex of the heart to measure left ventricular peak systolic pressure (LVSP), left ventricular end-diastolic pressure (LVEDP), and dP/dt max. The pericardium was loosely closed. All of the catheters and pacing leads were brought out of the chest, tunneled subcutaneously, and exited in the midscapular region. The chest was closed and evacuated. The dogs were placed on an antibiotic regimen (cephalexin; Biocraft Laboratories, 500 mg twice a day, p.o.) for the first 5–7 days and allowed to recover for 7–10 days before control studies were conducted. During the recovery period, the dogs were brought into the laboratory several times and trained to lie quietly on a laboratory table for several hours.

**Physiological Measurements**

Arterial pressures and LAP were measured with disposable pressure transducers (model 1270, Hewlett-Packard) calibrated with a mercury manometer. The left ventricular Konigsberg pressure transducer was calibrated in vivo using systolic arterial pressure (SAP) and LAP. The transducer signals were conditioned with bridge amplifiers (model 143, Honeywell Accudata), and heart rate was derived from the pulsatile arterial signal with a cardiotachometer (model 133, Honeywell Accudata). Mean arterial pressure (MAP) was obtained from the electronic mean of the pulsatile arterial pressure. Left ventricular dP/dt was measured with a differentiator (model BL620, Biotronex Laboratories) using the input from left ventricular pressure. These conditioned and derived signals were then directed to an eight-channel strip-chart recorder (model 7758A, Hewlett-Packard) with medium gain amplifiers (model 8802A, Hewlett-Packard) and to a personal computer (model ZBF-3340-EK, Zenith) equipped with an analog-to-digital data-acquisition system (model DA-16, Buxco Electronics) for digitalized signal recording and display. Arterial baroreflex sensitivity (BRS) was determined by the slopes of the linear regression of pulse interval against the preceding SAP (msec/mm Hg; see Figure 2) during the responses to phenylephrine (10–15 μg/kg i.v.; Elkins-Sinn) and nitroglycerin (Nitrostat, 25–40 μg/kg i.v.; Parke-Davis) injections. In most dogs, two baroreflex responses were determined. The slopes from each response were averaged to obtain one value from each dog. The administration of nitroglycerin or phenylephrine was first done in a random fashion. All hemodynamic parameters had returned to baseline for several minutes before the next drug was injected.

**Experimental Protocol**

After recovery from surgery, baseline hemodynamics and BRS were determined in the control, normal state. All animals were afebrile, healthy, and vigorous at the time of the initial experiment. On different days, BRS was assessed before and after pharmacological blockade of sympathetic or parasympathetic pathways with intravenous metoprolol (Lopressor 1 mg/kg; CIBA Pharmaceutical) or atropine (atropine methyl bromide 0.1 mg/kg; Sigma Chemical Co., St. Louis, Mo.), respectively. The completeness of blockade was tested with 3–5 μg isoproterenol i.v. (Winthrop) for metoprolol or 80–100 μg acetylcholine i.v. (Sigma) for atropine. Again, the administration of atropine or metoprolol was done in a random fashion. At least 2 days (usually more) were allowed to
elapse before the next blocking drug was given. After the control experiments, the animals were subjected to ventricular pacing at 250 beats/min with an external pacemaker (model 5320, Medtronics) for a period of 4–6 weeks. Postpace hemodynamics and BRS with or without metoprolol or atropine were measured when significant symptoms of heart failure were manifested. Clinical signs of heart failure included ascites, pulmonary congestion, dyspnea, and intolerance to exercise. Hemodynamic criteria were LAP of more than 20 mm Hg, a significant increase in resting heart rate, and a decrease in MAP.

**Time Control and Acute Pacing Studies**

A group of five dogs (included in the original 25) subjected to the same surgical preparation were used as time controls. After recovery from surgery, hemodynamics and BRS were determined. These dogs were then cared for and housed in the same manner as the paced dogs, but they were not paced. After 4 weeks, hemodynamics and BRS were again determined in these dogs.

To examine the influence of short-term table training and acute rapid ventricular pacing on baseline hemodynamics and BRS, the following experimental protocol was also carried out in these five dogs after time control studies. Hemodynamics and BRS were measured when the dogs were on the laboratory table for 10 minutes, again after 40 minutes, and 10 minutes after 30 minutes of ventricular pacing at 250 beats/min. Although this latter procedure does not simulate chronic pacing, it does address the issue of the effects of short-term, acute pacing per se on hemodynamics and BRS.

**Statistical Analysis**

The analysis of the difference in baseline hemodynamic parameters between the prepping and post-pacing states was done using a paired t analysis. The effects of autonomic blockade on resting heart rate, arterial pressure, and BRS was determined using an analysis of covariance with the absolute resting values as the covariate and the absolute differences as the dependent variable. The data were analyzed using the general linear model procedure from the SAS Institute and the method of multiple comparisons using the least-squares means. A probability value of less than 0.05 was considered statistically significant. Data are given as mean±SD.

**Results**

**General Effects of Rapid Ventricular Pacing**

General clinical signs of heart failure such as intolerance to exercise, dyspnea, ascites, and pulmonary congestion were observed in all dogs after 4–6 weeks of rapid ventricular pacing. The average duration of pacing in these dogs was 34±9.5 days. Various degrees of pulmonary congestion or ascites were also confirmed at autopsy. The hemodynamic characteristics of heart failure were present in these dogs and are summarized in Table 1. Because some dogs died before the heart failure state and some had instrumentation failure, Table 1 does not reflect the data for each parameter for all 20 dogs entered into the study. LVEDP and LAP were significantly increased after chronic pacing (4.6±3.4 and 2.8±3.5 to 21.5±6.6 and 22.6±5.5 mm Hg, respectively; p<0.005). Left ventricular dP/dt max was significantly depressed (2,250±272 to 1,534±447 mm Hg/sec, p<0.01). Resting MAP was decreased in the heart failure state (96.8±7.6 to 80.8±7.6 mm Hg, p<0.005), whereas resting heart rate was increased (77.1±10.8 to 124.3±13.0 beats/min, p<0.005). Pulse pressure was also less in the heart failure state (40.9±6.5 to 32.6±6.3 mm Hg, p<0.005). Figure 1 shows the blood pressure and heart rate responses of one dog before and after heart failure in response to intravenous injections of nitroglycerin and phenylephrine. Representative plots of pulse interval versus the preceding SAP during the responses to intravenous phenylephrine and nitroglycerin injections are shown in Figure 2. The slopes (BRS) of the regression lines were lower after 4–6 weeks of pacing for both the phenylephrine and the nitroglycerin responses. The average BRS (Table 1) was significantly depressed after chronic ventricular pacing by 70% for nitroglycerin (16.6±5.1 to 5.0±2.7 msec/mm Hg, p<0.005) and by 53% for phenylephrine (32.0±26.7 to 15.0±14.8 msec/mm Hg, p<0.005; n=13 dogs).

**Autonomic Blockade**

The influences of metoprolol and atropine on resting heart rate and MAP are presented in Figure 3. In eight dogs, atropine significantly increased resting heart rate in both normal (80.0±14.1 to 167.5±6.3 beats/min, 115.8±36.7%, p<0.001) and

| Table 1: Resting Hemodynamics and Baroreflex Sensitivity Before and After 4–6 Weeks of Left Ventricular Pacing |
|-------------------------------------------------|-------------------------------------------------|
| Prepping                                        | Postpacing                                       |
| LVSP (mm Hg)                                    |                                                 |
| 116.0±18.3 (7)                                  | 105.9±9.5*                                      |
| LVEDP (mm Hg)                                   |                                                 |
| 4.6±3.4 (7)                                     | 21.5±6.6†                                       |
| dP/dt max (mm Hg/sec)                           |                                                 |
| 2,250±272 (7)                                   | 1,534±447†                                     |
| SAP (mm Hg)                                     |                                                 |
| 121.9±8.3 (13)                                  | 101.4±8.3†                                     |
| DAP (mm Hg)                                     |                                                 |
| 80.9±7.6 (13)                                   | 68.8±7.9†                                      |
| PP (mm Hg)                                      |                                                 |
| 40.9±6.5 (13)                                   | 32.6±6.3†                                      |
| MAP (mm Hg)                                     |                                                 |
| 96.8±7.6 (13)                                   | 80.8±7.6†                                      |
| LAP (mm Hg)                                     |                                                 |
| 2.8±3.5 (12)                                    | 22.2±5.5†                                      |
| HR (beats/min)                                  |                                                 |
| 77.1±10.8 (13)                                  | 124.3±13.0†                                    |
| BRS-PE (msec/mm Hg)                             |                                                 |
| 32.0±26.7 (13)                                  | 15.0±14.8†                                     |
| BRS-NG (msec/mm Hg)                             |                                                 |
| 16.6±5.1 (13)                                   | 5.0±2.7†                                       |

LVSP, left ventricular peak systolic pressure; LVEDP, left ventricular end-diastolic pressure; dP/dt max, maximum of the first differentiation of left ventricular pressure; SAP, peak systolic arterial pressure; DAP, diastolic arterial pressure; PP, pulse pressure; MAP, mean arterial pressure; LAP, mean left atrial pressure; HR, heart rate; BRS-PE or BRS-NG, baroreflex sensitivities in response to phenylephrine or nitroglycerin injections, respectively.

Data are given as mean±SD (n dogs).

*p<0.05, †p<0.005, ‡p<0.01 compared with prepping.
heart failure states (112.5±11.1 to 140.0±12.6 beats/min, 25.4±14.5%, p<0.01). However, the increase in heart rate in the normal state was significantly higher than in the heart failure state (p<0.005). Analysis of covariance indicated that the higher increase in the normal state was largely due to the increase in the resting heart rate in the heart failure state. The effect of metoprolol on heart rate was insignificant in the normal state. However, in the heart failure state, heart rate was significantly decreased by metoprolol (120.0±11.2 to 99.5±10.8 beats/min, 17.0±4.5%, p<0.001). This difference was significant compared with the normal state (p<0.001). Again, the different behaviors in the normal and heart failure states were due to the increase in resting heart rate in the heart failure state. In no case did metoprolol decrease heart rate to the level of the normal state. When the heart rate data are expressed as pulse interval, the same relation exists. Metoprolol did not evoke a change in interval in the normal state (791.8±120.6 versus 822.1±152.2 msec) but significantly increased interval in the heart failure state (504.4±52.0 versus 609.6±65.9 msec, p<0.001). Atropine decreased interval in both normal and heart failure states (777.3±172.2 versus 358±15.4 msec in the normal state, p<0.001; 539.3±66.4 versus 432.0±42.9 msec in the heart failure state, p<0.01).

For blood pressure responses, metoprolol slightly decreased MAP in the heart failure state (79.1±9.0 to 74.3±12.4 mm Hg, 6.7±7.4%, p<0.05) but did not alter pressure in the normal state. On the other hand, atropine significantly increased MAP in the normal state (93.3±4.7 to 106.3±12.5 mm Hg, 13.7±9.4%, p<0.05) but did not alter pressure after heart failure.

The influences of metoprolol and atropine on BRS before and after heart failure are illustrated in Figure 4. For nitroglycerin responses (reflex tachycardia), metoprolol depressed the BRS by 47.6±26.3% (14.3±5.2 to 7.2±3.9 msec/mm Hg, p<0.005) in the normal state and by 63.6±58.5% (5.3±2.3 to 2.2±1.5, p<0.01) in the heart failure state. However, an analysis of covariance using the absolute changes in BRS after metoprolol in both states indicates that although the control BRS was reduced in the heart failure state compared with control, the reduction after metoprolol after correction for the lower control value was significantly less in the heart failure state. On the other hand, atropine decreased the BRS by 86.7±7.8% (16.1±5.0 to 2.0±1.0 msec/mm Hg, p<0.001) in the normal state and by only 39.5±30.2% (4.3±0.8 to 2.5±1.4 msec/mm Hg, p<0.05) in the heart failure state. In this case, the differences in the atropine responses are primarily related to the depressed basal BRS (i.e., before
atropine). The BRS after atropine in the heart failure state was not significantly different from that in the normal state. Taken together, these data indicate that for the reflex tachycardia, sympathetic activation contributes a slightly smaller influence than vagal withdrawal in this model of heart failure.

For phenylephrine responses (reflex bradycardia), metoprolol had no significant effect on BRS in either the normal or the HF state. Atropine almost completely suppressed the BRS in both the normal (97.9±2.8%) and the heart failure (95.1±13.6%) states. The suppression of BRS by atropine was not different in the normal and the heart failure states; this indicates that vagal activation contributes exclusively to the bradycardia and to an equal extent in both normal and heart failure states.

Time Control and Acute Pacing Studies

Resting hemodynamics and BRS measured in week 1 and 4 of time control studies are listed in Table 2. These parameters are comparable to those observed in the experimental groups. No significant differences were found between the data of week 1 and those of week 4. The effects of acute pacing and acute training on BRS are presented in Table 3. There was no difference between control and 30 minutes of acute pacing or 30 minutes of training. In addition, the resting arterial pressure and heart rate were not significantly changed by acute pacing.

Discussion

The results of the present study demonstrate that there is a depression of arterial baroreflex control of heart rate in dogs with chronic ventricular pacing-induced heart failure. In the studies involving autonomic blockade (Figure 3), the heart rate increase by atropine was significantly greater in the normal state than in the heart failure state, whereas the heart rate decrease by metoprolol was less in the normal state.
than in the heart failure state. Therefore, these data suggest that there is a high vagal tone and low sympathetic tone to the heart in normal, conscious dogs. In heart failure, however, there is an alteration in the pattern of autonomic control of the heart in the resting state such that sympathetic tone is high and parasympathetic tone is low. This confirms the results of the recent study by Porter et al. Based on both pharmacological and direct neural recording data, these investigators found that patients with class II–IV heart failure had a low level of parasympathetic tone and high resting sympathetic tone.

Our data agree with the results reported by others that baroreflex-mediated cardiac slowing during phenylephrine in the normal state in humans is primarily due to vagal activation and that the role of sympathetic withdrawal is negligible. More than 95% of the reflex bradycardia could be blocked by administration of atropine, whereas BRS was unaffected by metoprolol (Figure 4). Atropine reduced BRS in response to phenylephrine in both normal and heart failure states. The change in BRS (either as absolute or percent change) in response to phenylephrine after atropine is less in the heart failure state. However, as indicated by the analysis of covariance (using the control value as the covariate), this apparent reduction in vagal activation is because the control BRS is reduced in the heart failure state. It should be noted that the resting heart rate after atropine was 167.5 ± 2.6 beats/min in the normal state and 140.0 ± 5.1 beats/min in the heart failure state. Although atropine has been shown to result in a higher heart rate than simply vagal block would predict, this “excess tachycardia” is approximately 26 beats/min, resulting in an absolute heart rate of

![Figure 3](http://circ.ahajournals.org/)

**Figure 3.** Bar graphs of baseline heart rate (HR) (left) and arterial blood pressure (ABP) (right) responses to autonomic blocking agents metoprolol and atropine in normal and heart failure dogs. *p < 0.05, **p < 0.01, ***p < 0.001 compared with preautonomic blockade. Data are given as mean ± SD.

![Figure 4](http://circ.ahajournals.org/)

**Figure 4.** Bar graphs of baroreflex responses (BRS) to metoprolol and atropine in normal and heart failure dogs during nitroglycerin-induced hypotension (top) and phenylephrine-induced hypertension (bottom). Baroreflex sensitivity is given in msec/mm Hg. *p < 0.05, **p < 0.01, ***p < 0.001 compared with preautonomic blockade. #p < 0.05, ###p < 0.001 compared with normal dogs. Data are given as mean ± SD.

### Table 2. Resting Hemodynamics and Baroreflex Sensitivity of Time Control Dogs

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Week 1</th>
<th>Week 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAP (mm Hg)</td>
<td>121.4±7.4</td>
<td>115.4±4.3</td>
</tr>
<tr>
<td>DAP (mm Hg)</td>
<td>79.6±8.5</td>
<td>74.7±11.2</td>
</tr>
<tr>
<td>PP (mm Hg)</td>
<td>41.7±8.1</td>
<td>40.5±7.8</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>95.1±6.5</td>
<td>92.2±6.9</td>
</tr>
<tr>
<td>LAP (mm Hg)</td>
<td>2.9±2.0</td>
<td>1.7±2.0</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>74.8±7.6</td>
<td>80.2±3.4</td>
</tr>
<tr>
<td>BRS-PE (msec/mm Hg)</td>
<td>33.5±13.6</td>
<td>38.2±19.9</td>
</tr>
<tr>
<td>BRS-NG (msec/mm Hg)</td>
<td>16.8±8.3</td>
<td>17.5±8.1</td>
</tr>
</tbody>
</table>

SAP, peak systolic arterial pressure; DAP, diastolic arterial pressure; PP, pulse pressure; MAP, mean arterial pressure; LAP, mean left atrial pressure; HR, heart rate; BRS-PE, baroreflex sensitivity to phenylephrine; BRS-NG, baroreflex sensitivity to nitroglycerin.

Data are given as mean ± SD (n = 5 dogs).
approximately 200 beats/min. Therefore, it is unlikely that excess tachycardia contributed to the BRS seen after atropine in the present experiments. Although depressed sinus node responsiveness to direct vagal stimulation or sinus node artery infusion of acetylcholine in heart failure dogs has been demonstrated, these studies were carried out in a different model of heart failure. However, based on the results of the present study, it is difficult to conclude that there is a depressed activation of the vagi in response to baroreceptor activation with phenylephrine.

On the other hand, reflex tachycardia during nitroglycerin has been shown to be dependent on both vagal withdrawal and sympathetic activation in either normal or heart failure states. The change in BRS after atropine is less in the heart failure state (Figure 4); however, this is primarily due to the reduction in control BRS in heart failure. After metoprolol, the absolute change in BRS was less in the heart failure state. This decrease is not dependent on the control BRS even though metoprolol reduced it. These data suggest that the autonomic control of resting heart rate in dogs with heart failure is different than the autonomic control of heart rate during baroreflex activation and withdrawal. Both high sympathetic and low vagal tone contribute to the increase in resting heart rate in heart failure, but reduced sympathetic activation contributes to the decreased BRS when the baroreceptors are unloaded. The apparent failure of the vagus to withdraw during baroreceptor unloading is due primarily to a reduced control BRS in the heart failure state. In a recent study by Dibner-Dunlap and Thames of a similar model of low-output heart failure, it was observed that the baroreflex control of RR interval was depressed. Based on the normally accepted assumption that the bradycardia in response to phenylephrine is vagally mediated and the tachycardia in response to nitroglycerin is primarily sympathetic in origin, these investigators concluded that pacing-induced heart failure results in a preferential reduction in vagal activation in this model of heart failure when arterial pressure is increased with phenylephrine. Although these conclusions differ from those of the present study, there may be several explanations for these discrepancies. First, the dogs studied by Dibner-Dunlap and Thames were anesthetized and subjected to recent surgery, whereas our dogs were awake and resting in the laboratory. Although the resting heart rates of the dogs in the study of Dibner-Dunlap and Thames were not reported, the arterial pressure indicates that the sham dogs were markedly hypertensive (MAP, 146±11 mm Hg compared with 88±6 mm Hg for the heart failure dogs). Second, the reported baroreflex slopes were quite low for both sham and heart failure groups compared with those in our study and in other studies of conscious dogs in heart failure. Last, the lack of autonomic receptor-blocking data makes it difficult to be confident that the reduction in BRS in response to phenylephrine was due to a lack of vagal activation in these dogs. It is possible that anesthesia accounts for the majority of these differences. On the other hand, the data from studies on humans reported by Eckberg et al suggest that a vagal defect is responsible for the baroreflex inhibition to phenylephrine in patients with cardiac dysfunction of various types. These investigators did not examine the response to a hypotensive stimulus.

In addition to a defect in efferent reflex control of heart rate, abnormalities at the arterial baroreceptor level or in the central integration of the baroreflex in the heart failure state cannot be ruled out based on the results of the present study. Recent data from this laboratory showed that the peak discharge and the slope of the carotid sinus baroreceptors were depressed in dogs with heart failure produced by chronic ventricular pacing. It has also been demonstrated that the baroreceptor sensitivity to static pressure steps was depressed in heart failure dogs with aortocaval fistulas. Thus, the afferent limb of the reflex arc is also abnormal in heart failure. Furthermore, the results from the study by Dibner-Dunlap and Thames and from this laboratory indicate that the central baroreflex control of renal sympathetic nerve activity is normal in dogs with pacing-induced heart failure. Therefore, the central integration for the reflex control of sympathetic efferent activity to the heart may be normal in the heart failure state.

It should be noted that resting MAP was significantly lower in the heart failure state. Resetting of baroreceptors and of the baroreflex may have occurred. However, resetting is generally thought to result in a shift in the baroreflex curve without affecting gain. Therefore, the depression of BRS in the heart failure state observed in the present experiments cannot be completely accounted for by resetting the baroreceptors to a lower arterial pressure. In the experiments in which acute ventricular pacing was performed, MAP and heart rate remained unchanged 10 minutes after 30 minutes of acute pacing compared to baseline. Therefore, these results do not support a resetting mechanism as the cause of the baroreflex depression in heart failure.
with controls (Table 3). In addition, hemodynamic parameters were not significantly changed during the 30-minute period of acute pacing. This is different from the observation by Redfield et al.30 There is no clear explanation for this discrepancy except that the animals of Redfield et al were studied in the standing position compared with the supine posture of our animals. Postural differences may have resulted in changes in arterial pressure during pacing. In addition, in the present study, left rather than right ventricular pacing was used.

In summary, the data presented here are the first to describe the change in autonomic control of both resting heart rate and baroreflex-mediated changes in heartrate in the rapid ventricular pacing model of heart failure. The general observation of low sympathetic tone and high vagal tone in conscious dogs was reversed in the heart failure state, in which the sensitivity of the baroreflex control of heart rate during both hypotension and hypertension was significantly depressed. In contrast to other models of heart failure, a significant reduction in the sympathetic component to heart rate control during activation of the baroreflex was noted.

Acknowledgments

The authors would like to thank Ms. Johnnie F. Hackley and Dr. Kahlil J. Haiderzad for their expert technical assistance. We are indebted to Dr. Kashinath Patil and to Mr. Thomas Reardon for help with the statistical analysis.

References


Key Words • vagus • sympathetic nerves • autonomic blockade • chronic pacing • heart failure
Analysis of baroreflex control of heart rate in conscious dogs with pacing-induced heart failure.
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Circulation. 1991;83:260-267
doi: 10.1161/01.CIR.83.1.260
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1991 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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