Hemodynamic and norepinephrine responses to pacing-induced heart failure in conscious sinoaortic-denervated dogs

MARIAN BRÄNDELE, KAUSHIK P. PATEL, WEI WANG, AND IRVING H. ZUCKER
Department of Physiology and Biophysics, University of Nebraska College of Medicine, Omaha, Nebraska 68198-4575

Brändle, Marian, Kaushik P. Patel, Wei Wang, and Irving H. Zucker. Hemodynamic and norepinephrine responses to pacing-induced heart failure in conscious sinoaortic-denervated dogs. J. Appl. Physiol. 81(4): 1855–1862, 1996.—The present study was undertaken to determine the effects of chronic sinoaortic (baroreceptor) denervation (SAD) on the hemodynamic and sympathetic alterations that occur in the pacing-induced model of congestive heart failure. Two groups of dogs were examined: intact (n = 9) and SAD (n = 9). Both groups of dogs were studied in the control (prepace) state and each week after the initiation of ventricular pacing at 250 beats/min. After the pacemaker was turned off, hemodynamic and plasma norepinephrine levels returned toward control levels in the prepaced state and after 1 and 2 wk of pacing. However, by 3 wk all hemodynamic and norepinephrine levels remained relatively constant over the 10-min observation period with the pacemaker off. With the pacemaker off, left ventricular end-diastolic pressure went from 2.7 ± 1.4 (SE) mmHg during the prepase state to 23.2 ± 2.9 mmHg in the heart failure state in intact dogs (P < 0.01). Left ventricular end-diastolic pressure increased to 27.1 ± 2.2 mmHg from a control level of 4.2 ± 1.9 mmHg in SAD dogs (P < 0.0003). Mean arterial pressure significantly decreased in intact and SAD dogs. Resting heart rate was significantly higher in SAD dogs and increased to 135.8 ± 8.9 beats/min in intact dogs and 136.1 ± 6.5 beats/min in SAD dogs. There were no significant differences in the hemodynamic parameters between intact and SAD dogs after pacing. Plasma norepinephrine was significantly lower in intact than in SAD dogs before pacing (197.7 ± 21.6 vs. 320.6 ± 26.6 pg/ml; P < 0.005). In the heart failure state, plasma norepinephrine increased significantly in both intact (598.3 ± 44.2 pg/ml) and SAD (644.0 ± 64.6 pg/ml) groups. There were no differences in the severity or the magnitude of the developed heart failure state in SAD vs. intact dogs. We conclude from these data that the arterial baroreflex is not the sole mechanism for the increase in sympathetic drive in heart failure.

baroreflex; catecholamines; chronic tachycardia; sympathetic nervous system

CHRONIC CONGESTIVE HEART FAILURE (CHF) is characterized by enhanced neurohumoral drive in both humans and experimental animals (12, 18, 21, 24). Although this adaptive mechanism is beneficial early in the course of the disease, the augmented sympathetic drive and vasoconstrictor tone eventually lead to a further depression of cardiac function and to peripheral organ damage. The mechanisms that lead to the increase in sympathetic and hormonal drive in heart failure are not completely understood. It has been proposed that a depression in both arterial and cardiac reflex sensitivity leads to a loss of central inhibition to sympathetic outflow in the heart failure state (7, 10, 21). Since the early work of Eckberg et al. (9), many investigators (10, 34, 36) have documented a depression in baroreflex function in heart failure. Although a depression in arterial baroreflex sensitivity has been well accepted, a cause-and-effect relationship between this phenomenon and the elevation of sympathetic tone in heart failure has not been established. Experimental models of CHF allow one to determine the role of the arterial baroreflex in the chronic augmentation of sympathetic tone in this disease state. Therefore, the aim of the present study was to investigate the effects of chronic sinoaortic denervation (SAD) on the changes in hemodynamic and sympathetic functions in conscious chronically instrumented dogs before and during the development of severe heart failure.

METHODS

Animals and surgery. All experiments were carried out on healthy adult mongrel dogs of either sex ranging in weight from 19 to 32 kg. Dogs were housed in large indoor runs and were conditioned to a 12:12-h light-dark cycle. They were fed a combination of dry and canned dog food once per day and were allowed water ad libitum.

Thoracic surgery was performed under sterile conditions at the University of Nebraska (Omaha) Medical Center Animal Facility. All surgical and experimental procedures were approved by the University of Nebraska Medical Center Institutional Animal Care and Use Committee. In brief, dogs were anesthetized with pentobarbital sodium (30 mg/kg iv; Fort Dodge Laboratories, Fort Dodge, IA) and intubated. They were placed on a positive-pressure respirator (Harvard Apparatus, S. Natick, MA). A left thoracotomy was performed through the fifth intercostal space. A pacing electrode was secured to the left ventricular free wall (Medtronic model 6917T, Minneapolis, MN). Catheters (Tygon) were placed in the descending aorta, left ventricle, and left atrium for hemodynamic monitoring. A catheter was also placed in the right ventricle for blood sampling and as a convenient venous access line. All catheters and wires exited in the midscapular region. The pacing electrode was left under the skin until the pacemaker was implanted. The chest was closed in layers and evacuated. The dogs were placed on an antibiotic regimen of penicillin G and dihydrostreptomycin (Distrycillin, 0.5 ml/kg im; Solvay Veterinary, Princeton, NJ) for 5 days postope-
tive. Experiments were carried out on dogs that were afebrile and eating and drinking normally. The animals were allowed to recover for ~2 wk before the initial experiment or next surgical procedure (see SAD) was performed. During this time, they were trained to lay quietly on a laboratory table in a dimly lit room.

SAD. Ten to fourteen days after the thoracic surgery, one group of dogs (selected at random) underwent a second surgery to completely denervate the arterial baroreceptors. Under pentobarbital sodium anesthesia and with sterile technique, the carotid sinuses and aortic nerves were dissected through a midline cervical incision. The carotid sinuses were stripped of all visible nervous tissue, and the adventitia was stripped from ~1 cm below the carotid bifurcation to ~1 cm above. The carotid sinus nerve was identified, ligated, and cut. The carotid sinuses were then painted with a solution of 10% phenol in ethanol. The vaginal sheath was then opened, and the aortic nerve was identified at its location between the sympathetic trunk and the vagus. It was placed on bipolar platinum-iridium recording electrodes, and the discharge was amplified so that aortic baroreceptor activity could be identified both visually and audibly. The nerve was then sectioned. If baroreceptor activity could still be heard in the vagus, a further dissection was done to find additional baroreceptor fibers. This was done until baroreceptor activity could no longer be identified. The neck was closed, and the dog was allowed to recover for at least 1 wk before any experiments were performed. The effectiveness of baroreceptor denervation was determined by recording the change in heart rate (HR) to bolus injections of nitroglycerin (25 µg/kg) and phenylephrine (10 µg/kg). These doses evoked changes in blood pressure of between 25 and 40 mmHg. Baroreceptor denervation was assumed to be complete if the HR did not change by more than 5 beats/min to both these interventions. Intact vagal afferent and efferent pathways were confirmed by observing a normal bradycardia to a left atrial injection of 1 µg/kg of veratridine. All dogs used in the SAD group met these criteria.

Induction of heart failure. After the dogs recovered from surgery, a pacemaker was implanted for chronic pacing. Dogs were sedated with acepromazine (0.3 mg/kg im; Fort Dodge Laboratories). Under local anesthesia, the pacing lead was retrieved from beneath the skin and attached to a pacemaker (model 5985 or 8329, Medtronic, Minneapolis, MN) that was placed beneath the skin on the back. These pacemakers were modified by us or by Medtronic to pace in the temporary mode at rates substantially higher than they are capable of in the permanent mode. Using a programming unit (model 9710), we determined the minimum voltage and pulse duration for electrical capture of the ventricle. The technique of producing chronic CHF was that originally described by Coleman et al. (5). The pacing rate was set at 250 beats/min, and the dogs were continuously paced for 4 wk, at which time clinical and hemodynamic signs of severe CHF were evident in all dogs.

Hemodynamic monitoring. Arterial pressure, left atrial pressure (Pla), and left ventricular pressure were recorded with the dog resting quietly on its right side in a dimly lit room. The appropriate catheters were attached to pressure transducers (model 6199, Utah Medical Products, Midvale, UT) and zeroed at the level of the supraspinous process. Honeywell (Denver, CO) 143 signal-conditioning amplifiers were used to process the signals that were displayed on a recorder (model 7758A, Hewlett-Packard, Andover, MA). HR was determined with a Honeywell cardiotachometer (model 133) that was triggered by the left ventricular pulse. All signals were also fed into a hemodynamics analyzer (Buxco, Sharon, CT) that digitized the waveforms and stored them on disk for later analysis.

Measurement of plasma norepinephrine (NE). Liquid chromatography in combination with electrochemical detection was used to determine the plasma levels of NE. Venous blood samples (2.5 ml) were collected from an indwelling right ventricular catheter, with a minimum amount of arousal of the dog, and placed into chilled centrifuge tubes containing 20 µl of heparin (1,000 U/ml). A hexamethonium extraction and quantitation of plasma NE were carried out as previously described and modified by Robie and Duspin (30).

Protocol. Each dog was studied before pacing and at weekly intervals after the initiation of pacing for up to 4 wk. Before chronic pacing was started (i.e., in the control state), each dog was paced at 250 beats/min for at least 15 min. When all hemodynamic variables were stable and the dog was resting comfortably, a venous blood sample (right ventricular or peripheral venous) was drawn for the determination of plasma NE, and a 1-min average of all hemodynamics was obtained. No differences were seen between sites of blood sampling. Five minutes later, a second hemodynamic average and blood sample were taken. Five minutes after the second control sample, the pacemaker was turned off (placed in the inhibit mode), and a blood sample and hemodynamic average were taken immediately. Two more blood samples and hemodynamic averages were taken 5 and 10 min after cessation of pacing. The pacemaker was then reprogrammed to 250 beats/min, and the dog was returned to the kennel. This protocol was repeated in a subset of dogs after the administration of 10 mg/kg of hexamethonium. Hexamethonium was given as an intravenous infusion (1 mg·kg−1·min−1 for 10 min) after the pacemaker was turned off. A time-course study was not done in these dogs. The effects of hexamethonium were only investigated before pacing and after 4 wk of pacing. Once again, samples were taken 10 min after cessation of pacing. In preliminary experiments, it was determined that this dose of hexamethonium completely inhibited renal sympathetic nerve activity.

Data analysis. All values are expressed as means ± SE. A repeated-measures two-way analysis of variance followed by Duncan’s multiple range test was used to determine significant differences between groups and time periods before and after induction of heart failure. The analysis of plasma NE levels in intact and SAD dogs was analyzed both in absolute terms and after a log transformation of the data. Significance levels were the same with either method. P < 0.05 was considered statistically significant.

RESULTS
All dogs in this study developed clinical signs of CHF. This included pulmonary edema, ascites, and exercise intolerance as assessed by a reduction in their capacity to walk briskly from the kennel area to the laboratory (~0.3 km). All of these symptoms were not necessarily present in each dog, however.

Hemodynamic and NE changes in intact (n = 9) and SAD (n = 9) dogs. Table 1 shows the baseline hemodynamics in intact and SAD dogs before and after chronic pacing. Before pacing, baseline mean arterial pressure (MAP) was slightly but not significantly higher in the SAD dogs compared with the intact dogs (100.6 ± 4.7 and 118.3 ± 7.3 mmHg for intact and SAD dogs, respectively). After the establishment of heart failure, the MAP fell significantly in both groups of dogs. In the intact dogs, the MAP fell to 84.2 ± 3.8 mmHg. In the
SAD dogs, the MAP fell to 88.0 ± 6.6 mmHg. There was no significant difference between the two groups in the heart failure state. Mean Pla was similar in both groups of dogs before initiation of pacing (2.4 ± 0.9 and 2.6 ± 1.2 mmHg in intact and SAD dogs, respectively). In the heart failure state, the Pla increased to similar levels in both groups of dogs (20.0 ± 2.5 and 18.9 ± 1.6 mmHg in intact and SAD dogs, respectively). HR was significantly higher in the SAD dogs before pacing (94.1 ± 7.0 and 118.6 ± 7.8 beats/min in intact and SAD dogs, respectively; \( P < 0.05 \)). However, with the pacemaker turned off, the HR increased to similar levels in the heart failure state in both groups of dogs (135.8 ± 8.9 and 136.1 ± 6.5 beats/min in intact and SAD dogs, respectively).

The mean plasma NE values are shown in Fig. 1 in the control (prepaced) and heart failure (postpaced) states. Plasma NE averaged 197.7 ± 21.6 pg/ml in the intact group before pacing. After pacing and the establishment of the heart failure state, plasma NE increased to 598.3 ± 44.2 pg/ml (\( P < 0.05 \)). Plasma NE before pacing averaged 320.5 ± 26.6 pg/ml in the SAD group. After pacing into heart failure, the plasma NE increased in the SAD group in a similar fashion as in the intact group. Plasma NE increased to 644.0 ± 64.6 pg/ml in the SAD group. There was no significant difference between the heart failure values in the intact and SAD groups; however, the NE values before pacing were significantly higher in the SAD group (\( P < 0.005 \)). Furthermore, the absolute differences were not statistically different between the intact and SAD groups before and after pacing (400.6 ± 49.3 pg/ml for intact group; 323.4 ± 60.7 pg/ml for SAD group).

Time course of hemodynamic and NE changes. Figures 2–5 show the time courses of the mean data for the changes in HR, MAP, Pla, and plasma NE in intact and SAD dogs over 4 wk of pacing. The HR changes to acute cessation of pacing in the control state and each week during pacing are shown in Fig. 2. In both the intact and SAD groups, termination of pacing resulted in a rapid decrease in HR. In the control state, HR was reduced from its pacing rate of 250 beats/min to 94.2 ± 7.4 beats/min 10 min after the pacemaker was turned off in the intact group. The SAD group declined to 116.9 ± 7.6 beats/min at the 10-min period. There was a progressive increase in resting HR over the 4 wk of pacing in both groups.

With the pacemaker on, control MAP averaged 103.8 ± 4.2 mmHg in the intact dogs and 90.8 ± 5.2 mmHg in the SAD dogs (Fig. 3). These values were not statistically different. In the intact dogs, MAP did not change when the pacemaker was turned off. There was a progressive reduction in MAP during the development of CHF so that by 4 wk the 10-min off-pace
measurement had fallen to 85.8 ± 3.3 mmHg in the intact dogs (P < 0.05). The pattern of changes in MAP was quite different in the SAD dogs. During the control state, 10 min after the pacemaker was turned off, MAP increased to 117.2 ± 7.0 mmHg. However, MAP fell during the course of pacing. At 4 wk, the MAP was significantly reduced to 92.6 ± 5.6 mmHg in this group of dogs. Furthermore, the increase in MAP on turning off of the pacemaker in the SAD group was abolished at 3 and 4 wk of pacing.

The time course for the changes in Pla (Fig. 4) were similar in intact and SAD dogs. During pacing, the control Pla values were 8.8 ± 1.1 and 6.4 ± 1.4 mmHg in intact and SAD dogs, respectively. These values were not significantly different from each other. On turning off of the pacemaker, Pla fell in the control state and at weeks 1 and 2 in intact and SAD dogs. However, by 3 weeks of pacing, Pla remained at the paced level when the pacemaker was turned off in the intact and SAD dogs. Pla increased progressively over the 4 wk of pacing in both groups of dogs. The 10-min off-pace data increased to 20.5 ± 6.0 mmHg after 4 wk of pacing (P < 0.001) in the intact group. Similarly, the 10-min off-pace data increased to 17.7 ± 6.0 mmHg (P < 0.001) in the SAD group.

Figure 5 shows the time course of the mean NE data in intact and SAD dogs. With the pacemaker on, baseline NE was not significantly different in intact and SAD dogs during the control state, averaging 264.9 ± 19.2 pg/ml in the intact dogs and 305.9 ± 22.7 pg/ml in the SAD dogs. In the prepaced state, 10 min after the pacemaker was turned off, plasma NE fell slightly in the intact dogs and rose slightly in the SAD dogs. This resulted in a slight but significant difference between the two groups (198.1 ± 20.4 pg/ml in intact dogs and 314.5 ± 28.8 pg/ml in SAD dogs; P < 0.005). There was a clear fall in plasma NE in the intact dogs after the pacemaker was turned off at weeks 1–3 of pacing. By week 4, however, plasma NE remained relatively constant in the intact group. On the other hand, there was very little change in plasma NE in the SAD group after the cessation of pacing. As can be seen in Fig. 5, there was a progressive increase in plasma NE over the 4-wk pacing regimen. At 4 wk, the 10-min off-pace data averaged 745.6 ± 211.7 pg/ml in the intact group and 583.4 ± 60.0 pg/ml in the SAD group. The large SE in the intact group results from one dog in which the plasma NE increased to 1,449.5 pg/ml 10 min after the cessation of pacing. Removal of this dog from
the data results in a mean value of 644.8 ± 32.1 pg/ml, even closer to the value obtained in the SAD group. In neither case were these values significantly different from each other. The increase in plasma NE from the prepace state (10-min off-pace data) to 4 wk of pacing was significant for both groups of dogs.

Effects of hexamethonium on hemodynamics and plasma NE in intact (n = 8) and SAD dogs (n = 4). To confirm that changes in plasma NE were, indeed, mediated by sympathetic nervous activity in heart failure, we examined the hemodynamics and plasma NE after the administration of hexamethonium. Table 2 presents the mean data for MAP, HR, Pla, measured 10 min after the pacemaker was turned off. Hexamethonium caused a significant decrease in MAP both before and after pacing in intact and SAD dogs. The decrease in MAP was greater, however, in the SAD dogs compared with the intact dogs (P < 0.05) in the prepace state. Pla was significantly reduced by hexamethonium in both groups of dogs in the prepace state. In the postpace state, Pla was significantly reduced by hexamethonium only in the intact group. HR was significantly elevated after hexamethonium in the intact prepace group only. In fact, in the postpace state, there was a tendency for HR to fall in both groups after hexamethonium; however, this did not reach statistical significance. Figure 6 shows the plasma NE changes in each group after hexamethonium. Hexamethonium had a dramatic effect on plasma NE. As can be seen, plasma NE was reduced to very low levels in both groups in both the prepace and postpace states.

**DISCUSSION**

The present study has demonstrated significant alterations in cardiovascular and sympathetic nervous functions in conscious SAD dogs with pacing-induced heart failure. MAP, HR, Pla, and plasma NE changed to similar degrees in SAD and intact dogs over the duration of pacing. These data strongly suggest that mechanisms other than, and perhaps in addition to, depressed arterial baroreceptor function contribute to the sympathoexcitation of heart failure. An additional interpretation of these data is that the baroreflex is ineffective in modulating sympathetic outflow in heart failure. Therefore, removal of the baroreceptors has little effect on this response.

A second issue related to the pacing model of heart failure was demonstrated in this study. For the first...
time, both hemodynamic and sympathetic nervous functions were assessed within minutes of turning off the pacemaker during the development of heart failure in intact and SAD animals. A rapid return of these parameters occurs in the first 2 wk of pacing; however, by 3 wk of pacing, hemodynamic and sympathetic functions remained stable after cessation of pacing. This fact is important to determine when, in the course of the development of heart failure, short-term experiments can be carried out. Although we only examined the changes in hemodynamics and plasma NE over a 15-min period after turning off the pacemaker, our experience has shown that after 3 wk of pacing, and certainly after 4 wk of pacing, these animals have stable parameters for several hours after the pacemaker was turned off. The remainder of this discussion will focus on 1) the role of arterial baroreflexes in modulation of sympathetic tone in heart failure and 2) other possible mediators of sympathetic outflow in heart failure.

Arterial baroreflex in heart failure. Numerous studies have documented a depression in the arterial baroreflex control of HR and sympathetic nerve activity in heart failure (7, 9, 15, 34, 36). In fact, this observation has become so prevalent that there is a tacit assumption that the depressed arterial baroreflex leads to the characteristic augmentation of sympathetic tone in heart failure (21). Very few studies have focused on the issue of whether these associated phenomena represent a cause-and-effect relationship. One approach to answering this question is to evaluate the sensitivity of the baroreflex during the development of heart failure to determine whether decreases in sensitivity precede the augmentation of sympathetic tone. Using the pacing model of heart failure, a study by Grima et al. (15) showed that the arterial pressure-to-HR relationship in response to nitroprusside (baroreceptor unloading) was depressed very early in the course of pacing (1 wk), whereas the response to phenylephrine (baroreceptor unloading) was not depressed until overt heart failure developed (3–5 wk). A study from this laboratory (3) has confirmed this finding. In a study by Moe et al. (24), plasma NE was significantly elevated by 1 wk of pacing, a time when the nitroprusside slope was depressed but the phenylephrine slope was normal. On the other hand, a study by Riegger and Liebau (29) did not show an increase in plasma NE until 2 wk of pacing.

Another approach to this problem is to remove the arterial baroreceptors and determine the sympathetic response to pacing until the state of heart failure is achieved. In the present study, we found similar increases in plasma NE in paced intact and SAD dogs.

At the time of measurement, SAD dogs had higher resting levels of plasma NE, indicating an elevation in sympathetic tone. The fact that hexamethonium reduced plasma NE levels to extremely low levels both before and after pacing indicates that enhanced sympathetic neuronal activity contributed in a major way to these levels. Although baseline plasma NE was significantly higher in SAD dogs compared with intact dogs, the levels achieved after pacing (i.e., in the heart failure state) were similar in both groups. Several studies (2, 6) have shown that the average values for most neurohumoral and hemodynamic parameters are not different in the chronic SAD state. However, the lability of these parameters is increased after SAD (1). In fact, the sharp increase in MAP after cessation of pacing at 1 and 2 wk in SAD dogs (Fig. 3) most likely reflects this lability. It is, therefore, highly likely that because of the short duration of recording, the increased plasma NE levels in the present study reflect this enhanced variability in sympathetic nervous function. Baseline MAP was not significantly elevated in the SAD state before pacing (Table 1). This may suggest that plasma NE is a more sensitive marker of sympathetic drive than MAP and that other factors are responsible for determining the MAP in the SAD state.

Other possible mediators of sympathetic outflow in heart failure. Although SAD does not appear to attenuate or otherwise alter the degree of sympathetic outflow in heart failure, there are at least two other cardiovascular reflex mechanisms that may play an important role in the modulation of sympathetic outflow in this disease state. First, there are the cardiopulmonary reflexes that have been shown to be attenuated in heart failure (25). In a recent study by Kinugawa et al. (16), it was shown that the cardiopulmonary reflex is blunted in dogs with pacing-induced cardiac dysfunction without heart failure at a time when the arterial baroreflex sensitivity was normal. These data along with those cited above (15, 24, 25) may suggest that an early impairment of cardiopulmonary reflexes contributes to augmented neurohumoral drive in heart failure. The data of Kinugawa et al. (16) are consistent with the observation that plasma NE levels return to control levels after 2 wk of pacing in the intact dogs but were sustained after 3–4 wk of pacing or after as little as 1 wk of pacing in the SAD dogs. It is possible that early impairment of vagal cardiac mechanoreflexes is responsible for the failure of plasma NE to return toward the control level in SAD dogs after 1 wk of pacing.

Cardiac vagal mechanoreceptors and chemosensitive receptors normally inhibit sympathetic outflow. However, the effect on the reflex sensitivity of stimulation of these two afferent pathways may be different in heart failure. There is good evidence that cardiac mechanoreceptors and mechanoreflexes are blunted in heart failure (4, 25); however, this may not necessarily be the case for the chemosensitive afferents and their reflexes. Recent data from this laboratory (4) suggest that chemosensitive reflexes are actually enhanced in the canine pacing model of heart failure. Therefore, the net effect of changes in the input from vagal cardiac afferents on sympathetic outflow is not clear. On the other hand, a highly relevant study by Levett et al. (19) failed to show a change in plasma NE in dogs with cardiac denervation paced into heart failure. These data would suggest that cardiac afferents are not responsible for initiating the increase in sympathetic outflow in heart failure. The crucial experiment of combined SAD and cardiac denervation has not yet been performed.
In addition to cardiac vagal afferents, "sympathetic afferents" can modulate sympathetic outflow (20). These afferent fibers can be stimulated by a variety of endogenous substances such as bradykinin and prostaglandins (31, 32). Although no data exist on the contribution of cardiac sympathetic afferents to the regulation of sympathetic tone in heart failure, one could speculate that these fibers may be tonically stimulated by the local release of such endogenous substances as bradykinin, prostaglandins, and potassium (33). Once again, the study by Levett et al. (19) would seem to rule out this possibility. This would require an examination of the electrophysiological properties of cardiac sympathetic afferents in heart failure to determine whether these fibers are modulated by these substances. A recent study from this laboratory is relevant in this regard. Wang and Zucker (35) have shown an enhanced cardiac sympathetic afferent reflex control of renal nerve activity in dogs with pacing-induced heart failure. In this study, topical epicardial application of lidocaine in vagotomized SAD dogs reduced renal nerve activity in the heart failure state but had little effect in normal dogs.

Finally, the possibility exists that cardiovascular afferent pathways of any type are not responsible for the increased sympathetic drive in heart failure. A humoral link between the periphery and the central nervous system may be responsible for sympathetic activation. This notion suggests that a central abnormality is responsible for the sympathoexcitation of heart failure. For instance, it is well documented that angiotensin II can stimulate sympathetic nerve activity and that this peptide binds to those brain stem areas that regulate sympathetic outflow (8, 28). In addition, angiotensin II can potentiate the presynaptic release of NE (14), which could account for the increase in plasma NE seen in the present study. As further evidence for a role of the renin-angiotensin system in the modulation of sympathetic nerve activity in heart failure, it has been shown that angiotensin-converting enzyme inhibitors not only reduce angiotensin II levels but also reduce both sympathetic nerve activity and plasma NE levels (26, 27).

Limitations of the study. There are several limitations to this study that should be discussed. First, we are using plasma NE as an index of global sympathetic function. It is well known that plasma NE is dependent on neuronal release, binding to receptors, reuptake, and clearance by several tissues. It could be argued that the increase in plasma NE observed in this study after the development of heart failure was due to a reduction in the clearance of NE as the cardiac output falls, as indicated by Esler et al. (11). However, there are several lines of evidence to indicate that this concept may not be correct. More recent data from Esler's laboratory (23) found that increased NE spillover from the heart of patients with heart failure was largely due to increased neuronal activity rather than an abnormal reuptake mechanism. It has also been shown by several investigators (12, 27) that directly recorded sympathetic nerve activity correlates with both plasma NE and NE spillover in both humans and animals and in both normal and heart failure states. On the basis of this evidence, it seems highly likely that plasma NE measurements in heart failure reflect changes in sympathetic neuronal activity. Second, several hemodynamic and humoral responses were not measured in the dogs in this study. We did not determine cardiac output or total peripheral responses and, therefore, cannot assess the contribution of these changes to arterial pressure in intact and SAD dogs. Because cardiac output has been assessed by others (17), its measurement would not provide sufficient new information relevant to the aims of this study. Third, we did not measure such substances as vasopressin and angiotensin II. Both hormones may influence sympathetic function. Although it is important to determine the involvement of these substances in the sympathetic modulation of heart failure, this aspect of reflex function was beyond the scope of this study and will await future work. Fourth, as indicated above (11), the measurement of plasma NE is a global determination of sympathetic function. It is not known whether regional sympathetic function would show differences in heart failure that are baroreflex dependent. Fifth, it is possible that the arterial baroreceptors play some role in sympathoexcitation early in the development of the heart failure state; however, the data presented here strongly suggest that they are not responsible for the maintenance of the sympathoexcitation in the chronic phase of heart failure. Last, it could be argued that these findings only pertain to the pacing-induced model of heart failure. Although this is possible, we feel that it is highly unlikely because the hemodynamic and plasma NE changes are similar to those that have been described in other animal models of heart failure and in human heart failure (13, 22).

The authors thank Joan H. Hackley, Pamela Curry and John Goering for expert technical assistance.

This work was supported by National Heart, Lung, and Blood Institute Grant HL-38690 and by a Fellowship to M. Brändle from the American Heart Association, Nebraska Affiliate.

Present address of M. Brändle: Universitätsklinikum Essen, Zentrum für Innere Medizin, Abteilung für Pathophysiologie, Hufelandstr. 55, 45122 Essen, Germany.

Address for reprint requests: I. H. Zucker, Dept. of Physiology and Biophysics, Univ. of Nebraska College of Medicine, 600 S. 42nd St., Omaha, NE 68198-4575.

Received 21 December 1995; accepted in final form 16 July 1996.

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