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# Enalaprilat Augments Arterial and Cardiopulmonary Baroreflex Control of Sympathetic Nerve Activity in Patients With Heart Failure

MARK E. DIBNER-DUNLAP, MD, FACC, MICHAEL L. SMITH, PHD, TORU KINUGAWA, MD, MARC D. THAMES, MD, FACC

*Cleveland, Ohio*

***Objectives.*** **This study sought to determine the effects of enalaprilat on reflex control of sympathetic nerve activity.**

***Background.*** **Angiotensin-converting enzyme inhibitors decrease mortality in patients with congestive heart failure. Their efficacy appears to be related importantly to antiadrenergic effects, the mechanism for which has not been determined. Because baroreflexes tonically inhibit sympathetic outflow, and baroreflexes are blunted in heart failure, we hypothesized that these agents reduce sympathetic activity by augmenting baroreflexes.**

***Methods.*** **We assessed baroreflex control of sympathetic nerve activity and heart rate in patients with congestive heart failure and in control subjects before and after enalaprilat (0.02 mg/kg body weight intravenously). Arterial baroreflexes were perturbed by bolus administration of sodium nitroprusside and phenylephrine. Cardiopulmonary baroreflexes were perturbed by lower body negative pressure and head-down tilt. Muscle sympathetic nerve activity was recorded by microneurography.**

***Results.*** **Enalaprilat decreased systolic blood pressure in patients with heart failure and control subjects. Sympathetic nerve activity increased in control subjects but decreased in patients with heart failure after enalaprilat despite reductions in central venous pressure in this group. Baroreflex control of sympathetic nerve activity was unchanged by enalaprilat in control subjects. In patients with heart failure, both arterial and cardiopulmonary baroreflex control of sympathetic nerve activity was enhanced by enalaprilat. Baroreflex control of heart rate was unchanged by enalaprilat in either group.**

***Conclusions.*** **Enalaprilat augments both arterial and cardiopulmonary baroreflex control of sympathetic activity in heart failure. These augmented inhibitory influences are associated with a reduction in sympathetic outflow and may contribute to the beneficial effects of angiotensin-converting enzyme inhibitors in heart failure.**

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Congestive heart failure is one of the leading causes of morbidity and mortality in the United States today. Although several classes of drugs have been shown to exert beneficial hemodynamic effects in patients with heart failure, the only class of drugs that has been approved by the Food and Drug Administration to reduce mortality in patients with heart failure is the angiotensin-converting enzyme inhibitors. The reason for this beneficial effect on mortality still is not clear. The hemodynamic effects of long-term administration of these agents are modest at best. In the second Vasodilator–Heart Failure Veterans Affairs Cooperative Study Group trial (VHeFT-II) (1), the vasodilator combination hydralazine and isosorbide dinitrate exerted a greater benefit on symptoms and exercise capacity than the converting enzyme inhibitor enalapril, but enalapril reduced mortality to a greater degree. This suggests that mechanisms other than (or in addition to) vasodilating effects are important in reducing mortality.

Neurohumoral excitation is a hallmark of congestive heart failure, manifested by elevations in sympathetic nerve activity (2), plasma norepinephrine (3) and plasma renin activity (4,5). The degree of neurohumoral excitation, as measured by circulating norepinephrine, is directly proportional to mortality (6). Angiotensin-converting enzyme inhibitors have sympathoinhibitory effects in patients with heart failure characterized by reductions in circulating norepinephrine levels (7) (or blunting of the expected rise in norepinephrine over time [8]), which may be important in their beneficial effects in heart failure (8).

The mechanism of the sympathoinhibitory effects of angiotensin-converting enzyme inhibitors has not been elucidated. Cody et al. (9) found that captopril administration resulted in an improved response of systemic vascular resistance and norepinephrine release during tilt testing in patients with heart failure. This suggests that captopril exerts salutary effects on cardiopulmonary baroreflex control of sympathetic

From the Department of Medicine (Cardiology), University Hospitals of Cleveland, Case Western Reserve University and Department of Veterans Affairs Medical Center, Cleveland, Ohio. This work was supported by funds from the Medical Research Service of the Department of Veterans Affairs, Washington, D.C.; by Grant HL 30506 from the National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland; and by a Medical School Grant from Merck Human Health Division, West Point, Pennsylvania. Dr. Dibner-Dunlap is the recipient of a Clinical Investigator Award from the Department of Veterans Affairs. Dr. Kinugawa is the recipient of a Research Fellowship Award from the American Heart Association, Northeast Ohio Affiliate, Inc.

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Address for correspondence: Dr. Mark E. Dibner-Dunlap, Medical Research Service 151 W, Veterans Affairs Medical Center, 10701 East Boulevard, Cleveland, Ohio 44106.



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**Table 1.** Baseline Characteristics of the Heart Failure Group

| Pt No. | Age (yr) | Diagnosis | Ejection Fraction (%) | NYHA | Medications |
|---|---|---|---|---|---|
| 1 | 56 | Idiopathic | 16 | III | Captopril, hydralazine, lanoxin, isosorbide, furosemide, metolazone, aspirin, potassium chloride |
| 2 | 54 | Idiopathic | 12 | II | Captopril, lanoxin, warfarin |
| 3 | 40 | Idiopathic | 16 | III | Captopril, hydralazine, lanoxin, furosemide, hydrochlorothiazide, potassium chloride, warfarin, indomethacin |
| 4 | 49 | Myocarditis | 8 | III | Lisinopril, lanoxin, furosemide, warfarin, metolazone, potassium chloride |
| 5 | 65 | Alcoholic | 19 | III | Lisinopril, lanoxin, furosemide, aspirin, isosorbide, theophylline |
| 6 | 32 | Idiopathic | 24 | III | Captopril, lanoxin, furosemide, warfarin |
| 7 | 62 | Idiopathic | 13 | III | Captopril, hydralazine, furosemide, lanoxin, warfarin |
| 8 | 42 | Idiopathic | 18 | II | Lisinopril, lanoxin, furosemide, warfarin, potassium chloride |
| 9 | 54 | Idiopathic | 39 | II | Lisinopril, lanoxin, furosemide, warfarin, buspirone, sertraline, ranitidine |
| 10 | 39 | Idiopathic | 28 | III | Lisinopril, lanoxin, isosorbide, hydrochlorthiazide, warfarin |

NYHA = New York Heart Association functional class.

outflow. Because arterial and cardiopulmonary baroreflexes normally exert tonic restraint over sympathetic outflow, and this restraint is diminished in heart failure (10–12), we tested the hypothesis that the angiotensin-converting enzyme inhibitor enalaprilat acutely augments both arterial and cardiopulmonary baroreflex control of directly measured sympathetic nerve activity in patients with heart failure.

## Methods

We studied 10 male patients with heart failure in New York Heart Association functional classes II and III and 8 age-matched control subjects. All patients had been admitted to the hospital previously for congestive heart failure but were studied at least 3 months after their most recent exacerbation. The characteristics of the patients with heart failure are shown in Table 1. All patients were taking angiotensin-converting enzyme inhibitors, digoxin and diuretic drugs (specific medications are shown in Table 1 for each patient). All medications were withdrawn for ~5 half-lives before the study, including digoxin. The last dose of diuretic drugs was administered the day before the study. All study subjects were asked to refrain from drinking caffeinated beverages on the day of the study. The study protocol was approved by the Institutional Review Board of Case Western Reserve University, and all subjects gave written informed consent before participation in the study.

**Measurements.** Subjects were brought to the laboratory after a light morning meal. Electrocardiographic leads were attached, and subjects were instructed to lie supine in a lower body negative-pressure chamber that was constructed with a hinged panel to allow access to the right leg. Muscle sympathetic nerve activity was recorded using a microelectrode in the right peroneal nerve, as has been described previously by our group (13) and others (14). Briefly, transcutaneous mapping was performed over the peroneal nerve as it emerges from the fibular head. After surface mapping, a tungsten microelectrode was inserted into the peroneal nerve. The signal was amplified (Nerve Traffic Analyzer, model 662C-3, University of Iowa Bioengineering), filtered, rectified and discriminated. Sympathetic efferent activity was confirmed by the presence of pulse-synchronous activity during diastole, its relation to respiratory activity, its unresponsiveness to arousal stimuli as well as an increase in nerve activity in response to nitroprusside-induced hypotension. A catheter was placed in the intrathoracic cavity through the brachiocephalic vein for measurement of central venous pressure and administration of drugs. Beat to beat arterial pressure was measured by photoplethysmography with a Finapress device (Ohmeda).

**Protocol.** After instrumentation, subjects rested in the supine position for 10 min. Arterial baroreflex stimulation was performed by sequential challenges with sodium nitroprusside and phenylephrine intravenously, administered at the nadir of the nitroprusside-induced hypotension. Doses of each drug were adjusted to provide a 10- to 20-mm Hg change in arterial pressure below and above baseline. Thus, a 20- to 40-mm Hg range of arterial pressure was used to calculate arterial baroreflex control of heart rate and muscle sympathetic nerve activity (15).

Cardiopulmonary baroreflex provocation was performed by applying lower body negative pressure to −15 mm Hg. Data were collected during the second minute of the stimulus. After a rest period to allow restoration of baseline conditions, head-down tilt at 10° was initiated. Data were collected during the second minute of head-down tilt.

We then administered enalaprilat, 0.02 mg/kg body weight intravenously, over 5 min, a dose that is slightly higher than the recommended treatment dose of 1.25 mg for a 70-kg patient. After a 10-min rest period, the preenalaprilat protocol was repeated, including arterial baroreflex testing and cardiopulmonary baroreflex provocation with lower body negative pressure and head-down tilt.

**Analysis.** Data were collected and stored on tape (TEAC RD-111T) and analyzed post hoc. The stored data were played back and digitized at 500 Hz/channel using an analog-to-digital converter (DATAQ Instruments). Electrocardiographic, arterial blood pressure and integrated muscle sympathetic nerve activity were peak detected (CODAS software) and visually inspected to ensure appropriate detection. To correct for baseline differences in heart rate between heart failure and

**Table 2.** Baseline Variables in Heart Failure and Control Groups

| | Heart Failure Group (mean ± SE) | Control Group (mean ± SE) | p Value |
|---|---|---|---|
| Heart rate (beats/min) | 77 ± 4 | 67 ± 3 | 0.08 |
| Systolic BP (mm Hg) | 134 ± 5 | 135 ± 5 | 0.93 |
| Diastolic BP (mm Hg) | 79 ± 3 | 65 ± 3 | 0.004 |
| Mean arterial pressure (mm Hg) | 97 ± 2 | 88 ± 2 | 0.01 |
| Central venous pressure (mm Hg) | 8.3 ± 1.1 | 2.7 ± 0.3 | 0.001 |
| Muscle sympathetic nerve activity (bursts/100 beats) | 62.8 ± 6.4 | 37.3 ± 4.7 | 0.007 |

BP = blood pressure.

control groups, nerve activity was computed as bursts/100 heart beats (2,14,16).

Arterial baroreflex control of heart rate was calculated from the slope of the linear regression relating peak systolic pressure to the following RR interval (17). Because muscle sympathetic nerve activity is correlated most closely to diastolic blood pressure of the previous cardiac cycle (18), arterial baroreflex control of sympathetic nerve activity was determined from the regression relating diastolic pressure to muscle sympathetic nerve activity. Values for muscle sympathetic nerve activity (burst amplitude times burst incidence) were determined for consecutive bins of diastolic pressure (bin width 3 to 5 mm Hg) obtained during the pressure increase from the nadir of hypotension. Cardiopulmonary baroreflex control of sympathetic nerve activity was determined by calculating change in nerve activity from the 1-min baseline period preceding each intervention (either lower body negative pressure or head-down tilt) to the second minute during the intervention. To account for different starting values between groups, percent change in nerve activity was compared (14). Absolute changes also are presented.

The SAS System for Windows 3.10, release 6.08, was used for all data analysis. Two-way analysis of variance was used to test the effects of group (control vs. heart failure) and treatment (before vs. after enalaprilat). Individual variables were compared within groups by paired two-tailed *t* tests (before vs. after enalaprilat) and between groups by unpaired *t* tests (two-tailed). Data were tested for normality (Shapiro-Wilk statistic) and analyzed by nonparametric tests when found to be nonnormal. A p value $<0.05$ was considered statistically significant. Results are expressed as mean value ± SE.

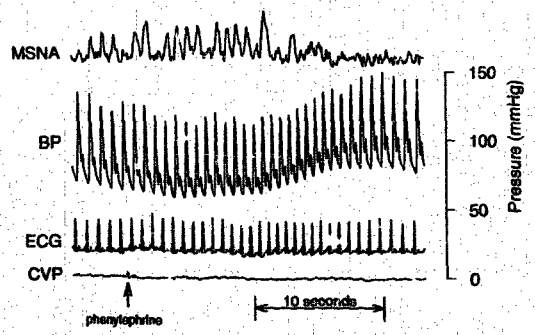
## Results

**Baseline responses.** Baseline variables of the heart failure and control groups are shown in Table 2. As expected, heart rate was increased in patients with heart failure compared with that in control subjects. Mean arterial pressure was also slightly higher in the heart failure group than in control subjects because of a higher diastolic blood pressure. Rest sympathetic nerve activity was significantly elevated in patients with heart failure, as has been reported previously (2).

Figure 1 shows responses of arterial pressure, electrocardiogram, muscle sympathetic nerve activity and central venous pressure to sequential boluses of nitroprusside and phenylephrine in one subject. Clearly evident is the increase in sympathetic nerve activity and concomitant RR interval shortening associated with the fall in arterial pressure, followed by the sympathoinhibitory response and RR interval prolongation accompanying the rise in pressure. Central venous pressure remained relatively constant during the changes in pressure. In control subjects, nitroprusside, 50 to 200 μg, followed by phenylephrine, 75 to 250 μg intravenously, was administered to produce sweeps of systolic pressure of 28 ± 4 mm Hg. In heart failure, these doses were 50 to 300 μg of nitroprusside and 125 to 350 μg of phenylephrine to produce pressure changes of 30 ± 3 mm Hg. After enalaprilat, the same doses were used, resulting in pressure changes of 31 ± 4 mm Hg in control subjects and 32 ± 2 mm Hg in patients with heart failure (both $p > 0.5$, before vs. after enalaprilat).

Before enalaprilat, arterial baroreflex control of sympathetic nerve activity was similar in the heart failure group (6.1 ± 0.7 bursts/mm Hg) and in control subjects (6.5 ± 0.6 bursts/mm Hg, $p = 0.72$) (Fig. 2). This result contrasts with

**Figure 1.** Record from one subject during sequential nitroprusside and phenylephrine administration. Note the increase in muscle sympathetic nerve activity (MSNA) during nitroprusside-induced hypotension followed by the decrease in sympathetic nerve activity during phenylephrine-induced increase in arterial blood pressure (BP). Central venous pressure (CVP) remains constant throughout the recording. Arterial baroreflex gain was computed during the rise in blood pressure from the nitroprusside-induced nadir. Nitroprusside was given just before the strip shown below. ECG = electrocardiogram.



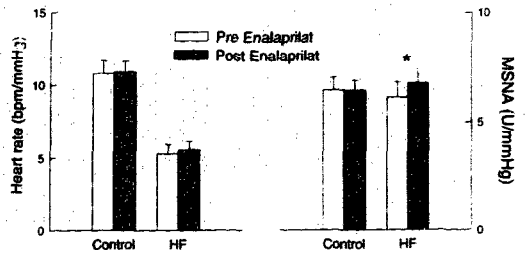



**Figure 2.** Effect of enalaprilat on arterial baroreflexes. **Left,** Arterial baroreflex control of heart rate. **Right,** Arterial baroreflex control of muscle sympathetic nerve activity (MSNA). After enalaprilat, there was a significant increase in baroreflex control of muscle sympathetic nerve activity in the heart failure group (HF) only. There was no change in baroreflex control of heart rate in either group after enalaprilat. bpm = beats/min; U = Burst amplitude × Bursts/100 heartbeats. *$p < 0.05$, before versus after enalaprilat. Results are mean value ± SE.

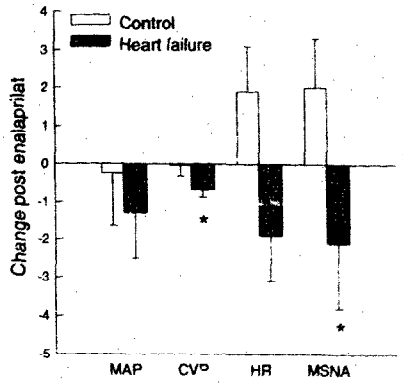



**Figure 3.** Changes in baseline variables after enalaprilat, 0.02 mg/kg intravenously. Sympathetic nerve activity decreased in the heart failure group despite a reduction in central venous pressure (CVP [mm Hg]) that was not present in control subjects. HR = heart rate (beats/min); MAP = mean arterial pressure (mm Hg); MSNA = muscle sympathetic nerve activity (bursts/100 heartbeats). *$p < 0.05$ before versus after enalaprilat, heart failure group. Results are mean value ± SE.

arterial baroreflex control of heart rate, which was attenuated significantly in the heart failure group (heart failure group 5.3 ± 0.6 beats/min per mm Hg vs. control group 10.8 ± 0.9 beats/min per mm Hg, $p < 0.0001$).

Lower body negative pressure reduced central venous pressure by 3.5 ± 0.5 mm Hg in control subjects and by 3.4 ± 0.8 mm Hg in patients with heart failure. These changes were accompanied by a 36 ± 6% (12.3 ± 1.3 absolute U) increase in muscle sympathetic nerve activity in control subjects but only 18 ± 6% (9.5 ± 2.0 absolute U) in patients with heart failure ($p < 0.05$). Head-down tilt increased central venous pressure by 1.3 ± 0.2 mm Hg in control subjects and by 0.7 ± 0.4 mm Hg in patients with heart failure. These were accompanied by insignificant changes in muscle sympathetic nerve activity in both groups.

**Effects of enalaprilat.** Enalaprilat treatment resulted in small effects on hemodynamic variables. Systolic blood pressure was reduced in both groups (by 6.5 ± 2.0 mm Hg in control subjects, by 5.8 ± 1.7 mm Hg in patients with heart failure, both $p < 0.02$). Diastolic pressure did not change significantly in either group (+2.9 ± 1.4 mm Hg in control subjects, +1.0 ± 1.2 mm Hg in patients with heart failure, both $p > 0.05$). Figure 3 shows additional changes in baseline variables in the heart failure and control groups after enalaprilat. Mean arterial pressure and central venous pressure were unchanged in control subjects after enalaprilat treatment, and there were small increases in heart rate and muscle sympathetic nerve activity. None of the changes in control subjects were statistically significant. In the heart failure group, responses of heart rate and muscle sympathetic nerve activity to enalaprilat were directionally opposite to those of control subjects, consisting of reductions in both measurements. This reached statistical significance for muscle sympathetic nerve activity ($p = 0.04$, before vs. after enalaprilat) and occurred despite a significant reduction in central venous pressure in heart failure and a trend toward reduced mean arterial pressure.

Figure 2 shows the effects of enalaprilat on arterial baroreflexes. In control subjects, arterial baroreflex control of both heart rate and sympathetic nerve activity was unchanged after enalaprilat. In patients with heart failure, arterial baroreflex control of heart rate also was unchanged after enalaprilat. However, arterial baroreflex control of sympathetic nerve activity was augmented significantly after enalaprilat in patients with heart failure.

The effect of enalaprilat on cardiopulmonary baroreflex control of sympathetic nerve activity was different in the two groups, and responses are depicted in Figure 4. In control subjects, the increase in muscle sympathetic nerve activity with lower body negative pressure was unchanged by enalaprilat (−1 ± 4%). In contrast, patients with heart failure exhibited significantly augmented cardiopulmonary baroreflex gain of muscle sympathetic nerve activity as measured by an increase of 8.3 ± 3.6% ($p < 0.05$, before vs. after enalaprilat). Head-down tilt had essentially no effect on muscle sympathetic nerve activity, and responses of muscle sympathetic nerve activity to head-down tilt were unchanged in both groups after enalaprilat. Thus, angiotensin-converting enzyme inhibitors increased the gain in response to unloading of cardiopulmonary baroreflexes in patients with heart failure.

## Discussion

Treatment with angiotensin-converting enzyme inhibitors has been shown to blunt the sympathoexcitation that is a hallmark of congestive heart failure. The mechanism responsible for this sympathoinhibitory effect has not been elucidated. Because direct vasodilators that normally activate rather than inhibit sympathetic outflow are not as effective as angiotensin-converting enzyme inhibitors in reducing mortality from heart

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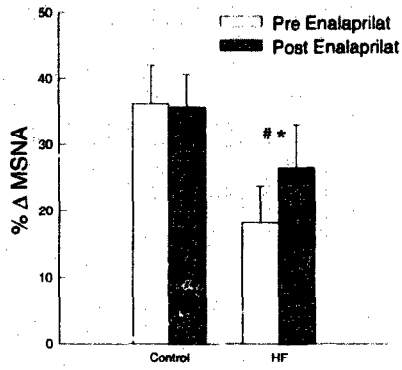


**Figure 4.** Effect of enalaprilat on cardiopulmonary baroreflexes. Baseline cardiopulmonary baroreflex control of muscle sympathetic nerve activity (MSNA) was reduced in patients with heart failure (HF) compared with that in control subjects. After enalaprilat, cardiopulmonary baroreflex control of muscle sympathetic nerve activity was augmented in patients with heart failure only. #$p < 0.05$, patients with heart failure versus control subjects. *$p < 0.05$, before versus after enalaprilat. Results are mean value ± SE.

failure (1), this effect appears to be important in improving outcome in these patients. To our knowledge, our study demonstrates for the first time that short-term treatment with enalaprilat augments baroreflex control of sympathetic outflow in patients.

**Control of sympathetic outflow.** Both arterial and cardiopulmonary baroreflexes normally exert tonic restraint over sympathetic outflow. Experiments in both humans and animals have revealed marked impairment of baroreflexes in heart failure, including reduced arterial baroreflex control of heart rate (19), decreased sensitivity of arterial baroreceptor afferents (12,20), and decreased cardiopulmonary baroreflex control of forearm vascular resistance (21,22).

Previous studies from our laboratory and elsewhere have demonstrated that cardiopulmonary baroreflex control of forearm vascular resistance is attenuated in patients with heart failure (21,22). To our knowledge, the current study is the first in patients with heart failure to record muscle sympathetic nerve activity directly in response to lower body negative pressure and confirms that cardiopulmonary baroreflex control of sympathetic outflow is attenuated in heart failure, rather than effects mediated by other mechanisms, such as changes in end-organ responsiveness or norepinephrine kinetics.

Distension of the atria and ventricles normally activates vagal afferent fibers and leads to a reduction in sympathetic outflow. Despite (or because of) chronic increases in cardiac filling pressure, these normal sympathoinhibitory responses are blunted in heart failure (10,22,23). Decreased function of these reflexes would be expected to lead to chronic increases in sympathetic outflow, as were found in our study as well as in previous studies in patients with heart failure (2).

Ferguson et al. (24) studied arterial baroreflex function in patients with heart failure using infusions of phenylephrine and nitroprusside to stimulate baroreflexes. They interpreted their results to suggest that arterial baroreflex control of sympathetic activity was blunted in patients with heart failure. However, as pointed out previously (25), their study could not differentiate between activation of arterial and cardiopulmonary baroreflexes. The technique used in the current study resulted in changes in arterial pressure in the absence of significant changes in central venous pressure, thus isolating the two sets of reflexes. Our data from the current study show that the major defect is in cardiopulmonary baroreflex and not in arterial baroreflex control of sympathetic activity. These data are in agreement with previous animal studies from both our laboratory (10) and others (26).

The effects of angiotensin-converting enzyme inhibitors on circulating norepinephrine levels in patients with heart failure have been found to vary, with some studies showing no change (27–29), some showing a decrease (30–33) and some showing the lack of an expected increase over time with angiotensin-converting enzyme inhibitor treatment (8). Because angiotensin-converting enzyme inhibitors decrease arterial and cardiac filling pressures, this deactivation of baroreflexes would normally be expected to result in increases in heart rate and sympathetic outflow. The lack of an increase in norepinephrine after angiotensin-converting enzyme inhibitors—a result consistent in all these studies—is consistent with a sympathoinhibitory effect of angiotensin-converting enzyme inhibitors in heart failure.

Angiotensin II facilitates norepinephrine release from sympathetic nerve endings (34). Blocking these effects could account in part for some of the sympathoinhibitory action of angiotensin-converting enzyme inhibitors. However, this does not explain our findings, as we measured nerve activity directly. Cody et al. (9) found that captopril significantly enhanced changes in systemic vascular resistance and plasma norepinephrine (but not heart rate) in response to tilt. Our data are consistent with those observations and extend these previous findings by showing that angiotensin-converting enzyme inhibitors decrease sympathetic nerve activity measured directly in patients with heart failure, despite effects on hemodynamic variables that tend to counter this effect. Because this is accompanied by augmented baroreflex control of sympathetic outflow, it is possible that improvement in baroreflexes could be the mechanism by which angiotensin-converting enzyme inhibitor treatment leads to sympathoinhibitory effects.

**Mechanism of action of angiotensin-converting enzyme inhibitors on baroreflexes.** We studied the effect of enalaprilat on baroreflex control of sympathetic nerve activity as well as heart rate. Arterial baroreflex control of heart rate was reduced in patients with heart failure but was unchanged after enalaprilat. This suggests that the site of action was probably not sensitization of baroreceptor afferents because this would have been expected to result in enhanced baroreflex control of both sympathetic nerve activity and heart rate. This is consistent with animal studies that show that angiotensin II tends to increase carotid sinus baroreceptor sensitivity (35). Therefore, blocking production of angiotensin II would be expected to

decrease, not increase, sensitivity of afferent pathways, so improvements in baroreflexes cannot be explained by this mechanism.

In experiments in cats, Schmid et al. (35) found that graded doses of angiotensin II caused a smaller change in lumbar sympathetic nerve activity per change in aortic nerve activity than either phenylephrine or vasopressin, indicative of central depression of the baroreceptor–sympathetic reflex. Further, Hayashi et al. (36) found that central administration of angiotensin II inhibited sympathoinhibitory responses to aortic depressor nerve stimulation in rats. These findings indicate that angiotensin II acts centrally to attenuate baroreflex control of sympathetic activity. Data from our study are consistent with a central site of action on baroreflexes.

Dorward and Rudd (37) infused an angiotensin II antagonist centrally in cats and were unable to demonstrate significant effects on heart rate or renal sympathetic nerve activity. From this they concluded that angiotensin II does not tonically modulate parasympathetic or sympathetic outflow. Our data showing a lack of effect of enalaprilat on baroreflexes in control subjects are consistent with the study by Dorward and Rudd and support the concept that angiotensin II does not tonically regulate baroreflexes in normal subjects. This contrasts with the situation in patients with heart failure, when angiotensin II does exert significant tonic inhibitory effect as evidenced by augmented baroreflexes after enalaprilat.

Our results in patients with heart failure have marked similarities to findings in rats from Kumagai et al. (38). They found no effect of captopril on baroreflexes in normotensive rats. In contrast, spontaneously hypertensive rats showed enhanced baroreflex control of renal sympathetic nerve activity after captopril but no effect on baroreflex control of heart rate. Therefore, tonic effects of angiotensin II on baroreflexes appear to become important only in the presence of activation of the renin–angiotensin system, for example, in heart failure or hypertension.

Osterziel et al. (39) studied the effects of a single oral dose of captopril, 25 mg, on RR interval changes induced by carotid sinus baroreceptor provocation with neck suction. They found that captopril increased arterial baroreflex control of RR interval in patients with heart failure. Vogt et al. (40) also found augmented RR interval responses to neck suction 24 h after a single oral dose of ramipril, 5 mg. Although the differences between these previous studies and ours cannot be ascertained for certain, one possible explanation could be that in both of those studies, patients were maintained on digoxin. We withdrew patients from all drugs for our study and found no effect of enalaprilat on heart rate responses. It is known that digoxin exerts important vagomimetic actions, even in patients with heart failure (41). Therefore, it is possible that angiotensin-converting enzyme inhibitors can potentiate the vagal effects of digoxin in heart failure but do not have direct effects on heart rate themselves.

Alternatively, both of the previous studies used heart rate responses to sustained neck suction to examine baroreflex effects, whereas we analyzed baroreflex control through dynamic pressure ramps induced by sequential nitroprusside/phenylephrine challenge. It is possible that these differences in techniques could account for observed differences in responses of baroreflex control of heart rate. Other medical therapy used for treatment of heart failure may also exert significant effects on baroreflexes. These have been reviewed previously (42).

**Study limitations.** In a study examining the short- and long-term effects of captopril, Cody et al. (9) found that the response of systemic vascular resistance to tilt was less pronounced during long-term therapy with captopril than after short-term administration. Because our study focused on acute effects of an angiotensin-converting enzyme inhibitor, we do not know whether these results would be maintained during long-term treatment. However, because the increase in norepinephrine was improved after both short- and long-term captopril treatment in the study by Cody et al. (9), we speculate that improvement in baroreflex control in sympathetic outflow might account for these changes and thus also be maintained during long-term treatment.

In addition to inhibiting conversion of angiotensin I to angiotensin II, angiotensin-converting enzyme inhibitors block the actions of kininase II, thus increasing local concentrations of bradykinin. Whereas central administration of angiotensin II (which is decreased by angiotensin-converting enzyme inhibitors) blunts baroreflexes, central administration of bradykinin (which is increased by angiotensin-converting enzyme inhibitors) augments baroreflexes (43). Therefore, either mechanism could account for the effects on baroreflexes that we demonstrated, and the relative contribution of each can be elucidated only with further study.

**Conclusions.** The present study demonstrates that cardiopulmonary baroreflex control of sympathetic nerve activity is blunted, but baseline arterial baroreflex control of sympathetic nerve activity is preserved in patients with heart failure. Short-term treatment with enalaprilat augments both arterial and cardiopulmonary reflex control of sympathetic activity in patients with heart failure. This improvement in baroreflexes leads to a reduction in sympathetic activity. We speculate that these effects of angiotensin-converting enzyme inhibitors are important for their beneficial effects in patients with heart failure.

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