

Arterial Baroreflex Regulation of Blood Pressure in Patients With Congestive Heart Failure

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Objectives. This study was designed to determine whether arterial baroreflex control of blood pressure is altered in patients with congestive heart failure.

Background. Arterial baroreceptor reflexes normally contribute to cardiovascular homeostasis by preserving blood pressure during changes in volume and posture.

Methods. Arterial baroreceptor reflex function was studied in 18 patients with congestive heart failure and 18 age-matched healthy subjects. The arterial baroreceptor-blood pressure reflex was assessed by measuring the blood pressure response to perturbations in carotid sinus pressure. Carotid baroreceptors were stimulated by applying negative pressure to a custom neck chamber (-10, -20 and -30 mm Hg) and were unloaded by applying neck positive pressure (+10, +20 and +30 mm Hg).

Results. Peak carotid baroreceptor-blood pressure reflex sensitivity was lower in patients with heart failure than in normal subjects (0.19 ± 0.02 vs. 0.30 ± 0.03 mm Hg/mm Hg, $p < 0.05$).

During neck positive pressure, blood pressure increased less in the heart failure group than in the normal group. During neck suction, however, the decrease in blood pressure was similar in the two groups.

Conclusions. Patients with heart failure are less able than normal subjects to increase blood pressure during arterial baroreceptor unloading, but they can reduce blood pressure appropriately during baroreceptor stimulation. These observations suggest that the resting blood pressure position on the arterial baroreceptor stimulus-response curve, the operational point, is closer to the baroreceptor threshold in patients with heart failure than in normal subjects. As a result, reduced inhibitory signals from arterial baroreceptors most likely contribute to a heightened state of sympathetic activity and vasoconstriction in patients with congestive heart failure.

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The irony of congestive heart failure, a state characterized by sodium retention and volume overload, is that it is associated with excessive sympathetic and decreased parasympathetic nervous system activity (1-5). Normally, cardiopulmonary baroreceptors, located in the heart and pulmonary vasculature, and arterial baroreceptors, located in the aortic arch and carotid sinuses, respond to stretch by initiating reflexes that promote parasympathetic and restrain sympathetic efferent activity. Therefore, heightened sympathetic activity is an appropriate response to hypovolemia or hypotension when the stretch imparted to cardiopulmonary and arterial baroreceptors is reduced. The similarity of the neurohumoral milieu between hypovolemic or hypotensive conditions and heart failure has led several groups of investigators to suggest that the ability of baroreceptors to modulate sympathetic efferent activity is impaired in patients

with congestive heart failure, thereby contributing to the vasoconstrictive state that is characteristic of this disorder (6-8). Indeed, studies in animals and humans have found that cardiopulmonary baroreflex function is abnormal in heart failure (9,10). In patients with heart failure, there are attenuated sympathetic and vasoconstrictive responses to orthostatic maneuvers that selectively reduce cardiac filling pressures (7,11,12).

Less is understood about arterial baroreflex regulation of the circulation in patients with heart failure. Impaired arterial baroreceptor reflex function may exacerbate vasoconstriction by failing to modulate sympathetic efferent activity. Alternatively, increased sympathetic nervous system activity and vasoconstriction may be appropriate arterial baroreflex responses to the decreased stroke volume and pulse pressure that occurs in heart failure. Impaired arterial baroreflex regulation of the circulation cannot be deduced from studies in either animals or humans with heart failure that have demonstrated reduced heart rate responses to perturbations of arterial baroreceptors (13-18). Accordingly, the purpose of this investigation was to determine whether arterial baroreflex regulation of the circulation is abnormal in humans with congestive heart failure. To examine the issue we measured the blood pressure responses to perturbations of carotid sinus pressure induced through a neck chamber in normal volunteers and patients with congestive heart failure.

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Methods

Subjects. The participants in this study included 18 normal volunteers and 18 patients with congestive heart failure. The normal group comprised 16 men and 2 women, whose ages ranged from 29 to 62 years and averaged 41 ± 2 years (mean \pm SEM). Normalcy was determined by history, physical examination and laboratory analyses to exclude hematologic, renal or hepatic dysfunction. The patients with congestive heart failure comprised 17 men and 1 woman, whose ages ranged from 25 to 72 years and averaged 47 ± 3 years ($p = \text{NS}$ vs. normal subjects). The cardiac rhythm was sinus in 13 patients, atrial fibrillation in 3, and electronically paced in 2. The etiology of heart failure was primary cardiomyopathy in 14 patients and coronary artery disease in 4. Left ventricular ejection fraction, assessed by radionuclide ventriculography, contrast ventriculography or echocardiography, ranged from 10% to 28% (average $21 \pm 2\%$). One patient was in New York Heart Association functional class I, 7 were in class II and 10 were in class III. All patients had been treated with digitalis, and nine had been treated with angiotensin-converting enzyme inhibitors. This research protocol was approved by the Committee for the Protection of Human Research of the Brigham and Women's Hospital, and each volunteer provided written informed consent.

Experimental protocol. All subjects were studied in the postabsorptive state without premedication in a 23°C temperature-controlled room. Alcohol, caffeine and cigarettes were all prohibited within 12 h of study. Digitalis glycosides and diuretic and vasodilator medications were withheld at least 24 h before the study. Catheters were inserted into the brachial artery of each subject for determination of blood pressure and intravenously for infusion of drugs. The vascular research laboratory was quiet, and lights were dimmed. All subjects rested at least 30 min after catheter placement to establish a stable baseline before data collection.

The arterial baroreceptor–blood pressure reflex was assessed by measuring the blood pressure response to perturbations in carotid sinus pressure. A custom-built chamber, formed of sheet lead and ribboned with sponge rubber (University of Iowa Medical Instrument Department) was placed comfortably around each subject's neck. The carotid baroreceptors were stimulated by applying negative pressure to the neck chamber. Neck suction was applied at levels of 0, -10 , -20 and -30 mm Hg, each for approximately 8 to 10 s during end-expiratory apnea. Blood pressure was measured under basal conditions and at each level of negative pressure. This sequence was repeated at least five times in each subject, and the blood pressure responses at each level were averaged to generate a dose-response curve relating chamber pressure to arterial pressure. Thereafter, neck positive pressure was applied in a comparable manner at levels of 0, $+10$, $+20$ and $+30$ mm Hg, each for approximately 8 to 10 s during end-expiratory apnea. This sequence

was repeated five times, and hemodynamic measurements obtained at each level were averaged.

The arterial baroreceptor–heart rate reflex was assessed in 16 normal subjects and 9 patients with heart failure by measuring the heart rate response to changes in systemic blood pressure induced by administration of sodium nitroprusside and phenylephrine hydrochloride. It was not assessed in patients with atrial fibrillation or electronic pacemakers. To decrease blood pressure and thereby unload arterial baroreceptors, sodium nitroprusside was infused intravenously in incremental doses of $25 \mu\text{g}/\text{min}$. The dose was increased every 2 min until systolic blood pressure decreased 20 mm Hg. Blood pressure and heart rate were measured at each dose. The drug infusion was discontinued, and baseline conditions were reestablished. Thereafter, to increase blood pressure and stimulate arterial baroreceptors, phenylephrine was infused intravenously in incremental doses of $50 \mu\text{g}/\text{min}$. The dose was increased every 2 min until a 20-mm Hg increase in systolic blood pressure occurred. Blood pressure and heart rate were measured during each dose increment.

Blood pressure was measured by means of an intraarterial cannula that was attached to a Statham P23 pressure transducer aligned to an amplifier on a Gould physiologic recorder. Heart rate was determined from a simultaneously obtained electrocardiographic signal and calculated from the RR interval. Venous blood was withdrawn during the baseline period, centrifuged at 2°C and stored at -20°C . Plasma norepinephrine concentration was determined subsequently by radioimmunoassay (19).

Statistical analysis. The arterial baroreceptor–blood pressure reflex was analyzed by relating neck chamber pressure to the change in systolic blood pressure. The arterial baroreceptor–heart rate reflex was analyzed by relating the change in systolic blood pressure during phenylephrine and nitroprusside infusions to the change in RR interval. Linear regression curves were fitted to each set of data to determine baroreflex sensitivity. For the arterial baroreceptor–blood pressure reflex, baroreflex sensitivity was defined as the slope relating the change in neck chamber pressure to the change in systolic blood pressure (mm Hg/mm Hg) and calculated for the set point. In addition, separate slopes were derived from the neck positive and negative pressure interventions. For the arterial baroreceptor–heart rate reflex, baroreflex sensitivity was derived similarly and defined as the slope relating the change in heart rate (RR interval) to the change in systolic blood pressure (ms/mm Hg).

Results are presented as mean value \pm SEM. Linear regression analyses were performed with use of the REG procedure of the SAS statistical package (SAS Institute). The unpaired *t* test was used to compare baroreflex sensitivity at the set point and the minimal and maximal blood pressure and heart rate responses to baroreflex perturbations between normal subjects and patients with congestive heart failure. Statistical significance was accepted at the 95% confidence limit ($p < 0.05$).

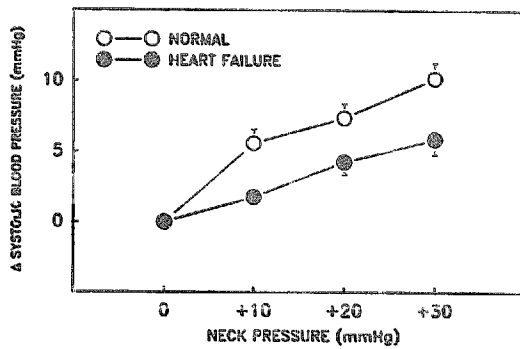


Figure 1. Effect of neck positive pressure (carotid sinus unloading) on systolic blood pressure in normal subjects and patients with heart failure. The slopes of the blood pressure response to neck positive pressure are significantly different between the two groups ($p < 0.05$). Values are presented as mean value \pm SEM.

Results

Baseline systolic and diastolic blood pressure was $126 \pm 3/65 \pm 1$ mm Hg in normal subjects and $124 \pm 3/66 \pm 2$ mm Hg in patients with congestive heart failure (each $p = \text{NS}$). Heart rate was faster in the patients with heart failure (64 ± 2 vs. 78 ± 3 beats/min, $p < 0.01$). Plasma norepinephrine concentrations were 181 ± 17 pg/ml in normal subjects and 455 ± 61 pg/ml in patients with heart failure ($p < 0.01$).

Arterial baroreceptor–blood pressure reflex. Perturbation of carotid sinus pressure by way of a neck chamber was used to assess the arterial baroreceptor–blood pressure reflex. Neck positive pressure decreased transmural pressure and unloaded carotid sinus baroreceptors. As a result, systolic and diastolic blood pressure increased in both normal subjects and patients with heart failure (Fig. 1). The increases in both systolic and diastolic blood pressure during neck positive pressure were significantly less in the heart failure group than in the normal group. Neck negative pressure stimulated carotid sinus baroreceptors and reduced blood pressure (Fig. 2). The decrease in systolic and diastolic blood pressure during neck suction was similar in both control and heart failure groups. Peak sensitivity determined

Figure 2. Effect of neck negative pressure (carotid sinus stimulation) on systolic blood pressure in normal subjects and patients with heart failure. The slopes of the blood pressure response to neck suction are not significantly different between the two groups.

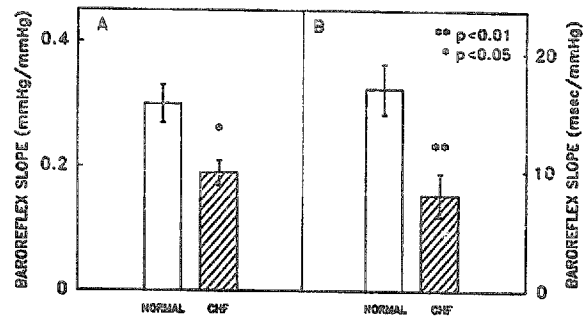
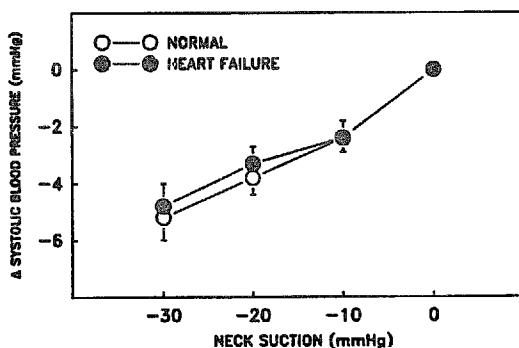
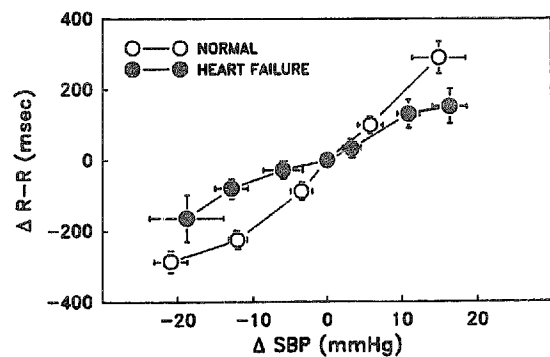


Figure 3. A, Peak carotid baroreceptor–blood pressure reflex sensitivity, determined at the set point, in normal subjects and patients with congestive heart failure (CHF). B, Peak arterial baroreceptor–heart rate sensitivity, also determined at the set point, in normal subjects and patients with congestive heart failure.

at the set point (zero pressure) was lower in the patients with heart failure than in normal subjects (0.19 ± 0.02 vs. 0.30 ± 0.03 mm Hg/mm Hg, $p < 0.05$) (Fig. 3A). Exclusion of the patients with atrial fibrillation and electronic pacemakers from statistical analysis did not alter these findings.

Arterial baroreceptor–heart rate reflex. The arterial baroreceptor–heart rate reflex was assessed by relating the change in RR interval to the change in systolic blood pressure that occurred during the infusions of phenylephrine and sodium nitroprusside. The dose of phenylephrine required to increase systolic blood pressure 20 mm Hg in the patients with congestive heart failure tended to be higher than that required in normal subjects, but the difference did not achieve statistical significance (172 ± 26 vs. 123 ± 13 $\mu\text{g}/\text{min}$, $p = \text{NS}$). Conversely, the dose of nitroprusside required to lower blood pressure 20 mm Hg tended to be less in patients with congestive heart failure than in normal subjects (105 ± 41 vs. 122 ± 19 $\mu\text{g}/\text{min}$, $p = \text{NS}$). Heart rate responses to both increases and decreases in blood pressure were attenuated in the patients with heart failure (Fig. 4). At the set point, peak baroreflex sensitivity was 8 ± 2 ms/mm

Figure 4. Effect of decreased systolic blood pressure (SBP), induced by sodium nitroprusside, and increased systolic blood pressure, induced by phenylephrine, on the RR interval in normal subjects and patients with congestive heart failure. The heart rate responses to both decreases and increases in blood pressure were significantly different between the two groups.



Hg in patients with heart failure and 17 ± 2 ms/mm Hg in control subjects ($p < 0.01$) (Fig. 3B).

Discussion

The important new finding in this study is that arterial baroreceptor-reflex regulation of blood pressure is altered in patients with congestive heart failure. Peak baroreflex sensitivity determined during perturbations of carotid sinus pressure is lower in patients with heart failure than in normal subjects.

The novel aspect of this study is that we studied arterial baroreflex regulation of both blood pressure and heart rate. The pressor and chronotropic responses to arterial baroreceptor unloading were abnormal in the patients with heart failure. During arterial baroreceptor stimulation, however, there were discordant responses between heart rate and blood pressure in the patients with heart failure. The change in heart rate was attenuated, whereas the vasodepressor response was preserved. These findings in humans are similar to those reported by Wilson et al. (20) in dogs with heart failure caused by rapid ventricular pacing. There was an impaired heart rate response to changes in blood pressure induced by infusions of phenylephrine and nitroglycerin in the dogs with heart failure. However, arterial baroreflex control of hind limb vascular resistance was preserved.

Heart rate versus vasodepressor responses to baroreceptor stimulation. Several groups of investigators have measured nerve activity from carotid sinus and aortic baroreceptors during changes in perfusion pressure and reported that arterial baroreceptor threshold is increased and sensitivity is decreased in animal models of heart failure (21-24). Such measurements are not feasible in humans, and we cannot be certain that findings in animals are readily extrapolated to our patients. However, if one were to assume that arterial baroreceptor function is abnormal in humans, as it is in animal models of heart failure, it is reasonable to postulate that central mechanisms modulate afferent traffic differently to sympathetic efferent neurons that primarily regulate vascular tone and parasympathetic efferent neurons that affect heart rate.

Two studies examined arterial baroreceptor function and sympathetic efferent activity during baroreceptor perturbations in dogs with heart failure induced by rapid ventricular pacing. Wang et al. (24) and Dibner-Dunlap et al. (21) each reported that arterial baroreceptor afferent activity was less in dogs with heart failure than in control dogs. However, each found that changes in renal sympathetic efferent activity were similar in control dogs and dogs with heart failure (21,24). Porter et al. (5) found that central parasympathetic control of heart rate is abnormal in patients with heart failure. Therefore, differential central mechanisms governing parasympathetic and sympathetic efferent activity may explain, in part, our observations that the heart rate, but not blood pressure, responses to carotid sinus stimulation are abnormal in patients with heart failure. Abnormalities of

end-organ responsiveness may also be relevant to these observations. Sinus node responsiveness to cholinergic and sympathetic stimuli is reduced in heart failure (16,25,26).

Effects of arterial baroreceptor unloading in heart failure. Of importance, the blood pressure response to carotid sinus unloading (i.e., deactivation) was significantly attenuated in the patients with heart failure. These observations suggest that the resting blood pressure position on the stimulus-response curve, also known as the operational point, is closer to the baroreceptor threshold in patients with heart failure than in normal subjects (15). Therefore, patients are less able to increase sympathetic efferent activity further during arterial baroreceptor unloading. As a consequence, blood pressure will increase less during neck pressure. These findings are consistent with those reported recently by Ferguson et al. (27), who measured muscle sympathetic nerve activity in normal subjects and patients with heart failure during changes in blood pressure induced by phenylephrine and nitroprusside infusions. They found that muscle sympathetic nerve activity increased less in patients with heart failure than in normal subjects during baroreceptor unloading, yet there were comparable sympathoinhibitory responses during baroreceptor stimulation.

Taken together, these findings indicate that reduced inhibitory signals from arterial baroreceptors most likely contribute to the heightened state of sympathetic activity and vasoconstriction in patients with congestive heart failure. Furthermore, one would infer from these observations that increased sympathetic nervous system activity and vasoconstriction are appropriate arterial baroreflex responses to the decreased stroke volume and pulse pressure that occur in many of these patients. However, we cannot discount the possibility that arterial baroreceptor function is abnormal and that central mechanisms facilitate sympathetic withdrawal when receptors are stimulated, as has been observed in animal models of heart failure (21,24).

Study limitations. We (28) recently demonstrated that carotid artery distensibility is decreased in patients with congestive heart failure. Thus, it is conceivable that the stretch imparted by comparable pressure stimuli was less in patients with heart failure than in normal subjects. It remains to be established whether abnormalities in compliance affect baroreflex sensitivity in patients with heart failure.

We also recognize that lingering effects of digoxin or of an angiotensin-converting enzyme inhibitor may have affected our findings. Digitalis glycosides increase arterial baroreceptor activity in dogs with heart failure (22,29). In humans, digitalis improves cardiopulmonary baroreflex function and decreases sympathetic efferent activity (7,30). Angiotensin-converting enzyme inhibitors restore the vasoconstrictive response to upright tilt, a maneuver that encompasses both cardiopulmonary and arterial baroreceptors, and they reduce plasma norepinephrine concentrations (31). In addition, uncontrolled trials suggest that angiotensin-converting enzyme inhibitors improve the arterial baroreceptor-heart rate reflex by augmenting parasympathetic activity (32,33).

Ethical constraints prevented us from withdrawing these medications for longer periods of time in these potentially fragile patients.

Clinical implications. Both plasma norepinephrine and abnormal baroreceptor function are markers of disease severity and prognosis in patients with heart failure (34-36). It is noteworthy that therapeutic interventions that are effective in patients with heart failure, such as digitalis glycosides and angiotensin-converting enzyme inhibitors, often improve baroreceptor function. It is intriguing to speculate that the observations that these drugs reduce plasma norepinephrine levels and improve survival in heart failure is related in part to their effects on arterial baroreceptor function.

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