Conclusions—These observations are consistent with the concept that ANP exerts a sympathoinhibitory action in heart failure (HF). These observations suggest a potential sympathoinhibitory stimulus in HF arising from ordinarily quiescent afferent nerve endings situated in "low-pressure" chambers and vessels. Indeed, in patients with severe HF, Kaye et al.17 were able to inhibit norepinephrine (NE) spill-over across the heart by infusing sodium nitroprusside (SNP), which lowered pulmonary artery and cardiac filling pressures. Thus by reducing cardiac, pulmonary, and peripheral venous pressures and thereby deactivating these several excitatory stimuli, ANP might have greater sympathoinhibitory effects in patients with HF than in normal subjects.

Key Words: atrial natriuretic factor ■ blood pressure ■ heart failure ■ nervous system, autonomic ■ nitroglycerin
Alternatively, the sympathoneural effects of ANP may be blunted. There is controversy as to whether the hemodynamic, natriuretic, and diuretic effects of endogenous or exogenous ANP are attenuated in HF. Previous investigators have used plasma NE concentrations as an indirect index of the effects of ANP on sympathetic activity in HF, with conflicting results. Because ANP infusion increases total body NE clearance, these observations cannot address the issue of whether ANP has sympathoinhibitory actions in human HF. In contrast, the microneurographic technique permits the direct recording of efferent sympathetic discharge to skeletal muscle. MSNA is increased in young subjects with dilated cardiomyopathy. The effect of ANP on MSNA in such patients has not been reported.

To test the hypothesis that ANP inhibits postganglionic MSNA in HF, we adapted the protocol used in our previous experiments in healthy subjects. We had 2 aims: (1) to determine the effect of exogenous ANP on hemodynamics and on efferent MSNA under resting conditions and (2) to determine whether ANP alters the cardiopulmonary or arterial baroreceptor reflex control of MSNA in these patients. We applied nonhypotensive and hypotensive LBNP for this purpose. As in our previous experiments, NTG was infused as a hemodynamic control to ensure that effects on MSNA were specific to ANP rather than a nonspecific response to reductions in cardiac filling pressures or to increases in stroke volume (SV).

### Methods

#### Subject Selection

Fifteen nonsmoking men with idiopathic dilated cardiomyopathy, 27 to 59 years of age (39±2 years, mean±SE), in sinus rhythm and stable condition, were recruited from our Heart Failure Service. They were characterized by normal coronary arteries, left ventricular end-diastolic dimensions ≥60 mm, and a mean ejection fraction, as assessed by radionuclide angiography, of 18%±3%. Patients were classified as New York Heart Association class I (n=1), II (n=6), III (n=7), or IV (n=1) and were prescribed 1 or more of angiotensin-converting enzyme (ACE) inhibitors or receptor antagonists (n=14), diuretics (n=13), and β-blockade with metoprolol (n=7). Subjects abstained from diuretics for 12 hours before their study. This protocol was approved by our University Human Subjects Review Committee. Informed written consent was obtained from all participants.

#### Procedures

Studies were conducted in the morning. Subjects emptied their bladder, then lay supine in a chamber built for recording MSNA from the right peroneal nerve during LBNP. BP was measured from the left arm by an automatic cuff recorder. A respiratory belt was secured around the abdomen. Central venous pressure (CVP) and arterial pressure were determined over 3 minutes. The infusions were NTG as a hemodynamic control to ensure that effects on MSNA were specific to ANP rather than a nonspecific response to reductions in cardiac filling pressures or to increases in stroke volume (SV).

MSNA was expressed as frequency (bursts/min), incidence (bursts/100 cardiac cycles), and integrated nerve activity (the product of burst frequency and mean burst amplitude, which is a quantitative representation of the strength of each burst). Because the application and release of LBNP might shift the microelectrode and influence mean burst amplitude, or because in some subjects experiments might be performed in 2 sessions, we identified the maximum

#### Results

Effect of Infusions on Baseline Values

There was no significant difference in any baseline value for hemodynamics or MSNA before these 2 infusions (Table).

### Hemodynamics

NTG lowered diastolic BP (DBP) (−9.1±1.5 mm Hg; P<0.0001) and CVP (−1.4±0.4 mm Hg; P=0.003) but did not affect systolic BP (SBP) (−3.7±2.1 mm Hg) or HR. ANP infusion, which increased its plasma concentration from 190±37 pg/mL to 1635±262 pg/mL (n=14, P<0.001), lowered DBP and CVP (−5.8±1.8 P=0.004, and −2.5±0.6 mm Hg P=0.0006) without affecting HR and lowered SBP (−4.7±2.1 mm Hg; P<0.03) (Table and Figure 1). There were no significant differences between the effects of NTG and ANP on SBP, DBP, CVP, HR, SV (51±7 vs 52±7 mL), or cardiac output (3.73±0.55 vs 3.92±0.53 L/min).

### Sympathetic Activity

Both NTG and ANP caused significant reductions in mean values for both DBP and CVP without eliciting anticipated

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reflex increases in MSNA.\(^3,24\)–\(^28\) There was no difference in the effect of NTG and ANP on MSNA (Table).

There were significant but similar inverse relations between MSNA burst frequency at baseline and the response to these infusions (Figure 2). When the subgroup of 8 subjects with class III and IV heart failure (and the greatest degree of sympathetic activation) was considered separately, neither NTG (+0.2±2.1 bursts/min; +21.5±45.7 Units) nor ANP (−3.5±1.9 bursts/min; −14.0±47.5 Units) affected MSNA significantly.

**Effect of Infusions on Responses to LBNP**

**Hemodynamics**

LBNP at −6 mm Hg caused significant reductions in CVP (P<0.05) without inducing systemic hypotension, whereas LBNP at −12 mm Hg caused significant reductions in CVP, SBP, and DBP (Table). The effects of nonhypotensive (−6 mm Hg) and hypotensive (−12 mm Hg) LBNP on SBP and DBP, CVP, and HR were similar during infusion of ANP and NTG. During the ANP infusion, 1 subject developed presyncope at the onset of LBNP. Subsequent paired comparisons were based on the remaining 14 subjects.

**Sympathetic Activity**

Although the hemodynamic stimuli to reflex sympathetic activation during LBNP were similar during both infusions, MSNA was significantly lower during ANP across all conditions (ie, both before and during application of LBNP) whether expressed as burst frequency (P<0.02) or burst incidence (P<0.02) (Figure 3). In response to nonhypotensive LBNP (−6 mm Hg), burst frequency (+3.2±2.2 bursts/min; P<0.05) and burst incidence (+4.1±2.5 bursts/100 cardiac cycles; P<0.05) increased reflexively during NTG infusion but not during the ANP infusion (+0.6±1.2 bursts/min and +0.4±1.2 bursts/100 cardiac cycles, respectively). Normalized integrated sympathetic nerve activity increased by 133±68 Units (P<0.001) during NTG infusion but not

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**Effects of Infusions and Lower Body Negative Pressure on Hemodynamics and Muscle Sympathetic Nerve Activity**

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<thead>
<tr>
<th></th>
<th>NTG</th>
<th>ANP</th>
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<tr>
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<tr>
<td>DBP, mm Hg</td>
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<td>MSNA</td>
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<td>474±59</td>
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</table>

\(n=15\), mean±SE.

One patient who developed presyncope during combined stimuli of LBNP −6 mm Hg and ANP was excluded from this analysis.

\(∗P<0.05; †P<0.01; ‡P<0.001\) for LBNP−0 versus baseline; §P<0.05 for LBNP −6 or −12 versus LBNP 0.

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**Figure 1.** Changes in resting DBP, CVP, HR, and MSNA burst incidence (bursts/100 heart beats; h.b.) in response to NTG and ANP. Values represent mean±SE in 15 subjects except for CVP (n=14). Both NTG and ANP caused significant reductions in DBP and CVP (\(∗P<0.05\)) from preinfusion values.

**Figure 2.** Inverse relations between baseline MSNA burst frequency (bursts/min) and changes in MSNA burst frequency in response to NTG (\(r=−0.64; P=0.01\)) and ANP (\(r=−0.79; P=0.005\)).
during ANP (+24±23 Units, P=NS). In response to hypotensive LBNP, normalized integrated sympathetic nerve activity increased significantly during both infusions (+247±120 Units for NTG, P<0.001; +177±69 Units for ANP, P<0.005) (Table, and Figure 4).

**Discussion**

Most investigators have focused on the hemodynamic, renal, and endocrine actions of ANP in HF, whereas we have directed our attention at interactions between this peptide and the autonomic nervous system. Our previous experiments in young men with normal ventricular function demonstrated a relative inhibitory effect of ANP on MSNA at rest and during nonhypotensive LBNP. Our present objective was to determine whether ANP exerts a similar action in young patients with HF and increased central sympathetic outflow caused by dilated cardiomyopathy, and if so, to determine whether ANP alters reflex sympathoneural responses to reductions in atrial or systemic arterial pressure. NTG was infused as a control to ensure that any effect on MSNA was due to a specific neural action of ANP rather than a nonspecific reflex response to any hemodynamic changes caused by these infusions.

In subjects with normal ventricular function, reductions in either DBP or CVP increase MSNA reflexively by decreasing the firing rate of afferent nerves arising from arterial and cardiopulmonary mechanoreceptors, respectively. Reductions in diastolic and atrial pressures caused by SNP infusion increase total body NE spillover by the same extent in subjects with normal ventricular function and HF. In the present series, ANP infusion lowered both DBP and CVP, yet MSNA did not increase in response to these hemodynamic changes, an observation consistent with a sympathoinhibitory action of this peptide. However, NTG also lowered DBP and CVP without increasing MSNA reflexively. By contrast, in healthy subjects, there was a distinct and significant difference in the MSNA response to ANP when compared with SNP. The absence of a reflex increase in MSNA during the first part of this study is therefore consistent with a sympathoinhibitory effect of both vasodilators in heart failure rather than a specific neural action of ANP.

Two nonspecific inhibitory mechanisms could account for the similar MSNA responses to ANP and NTG. There is a strong positive relation in patients with HF between sympathetic activity and both pulmonary artery and capillary wedge pressure.
pressures. Consequently, reductions in cardiac filling pressures caused by either infusion might diminish these stimuli to central sympathetic outflow. Second, reductions in right atrial pressure will release pericardial constraint on left ventricular filling and as a consequence increase left ventricular SV and stimulate inotropically sensitive left ventricular mechanoreceptors. SV was similar during these 2 infusions.

By studying only treated patients, we may have underestimated any sympathoinhibitory effect of ANP in severe HF. However, ANP infusion did not lower MSNA significantly in the subgroup with class III and IV HF or in the class IV patient intolerant of ACE inhibition. It is more likely that any sympathoinhibitory effect of ANP, exerted by modulation of the cardiopulmonary baroreflex, was offset by the reflex response of arterial baroreceptors to the fall in DBP, which is the proximate stimulus to MSNA. Our group has compared total body and transcardiac NE spillover responses to ANP (1 μg/kg bolus then 100 ng/kg per minute) and NTG in HF. Both infusions caused similar reductions in cardiac filling pressures, but only ANP lowered DBP and at the same time increased total body NE spillover. There was a significant inverse relation between changes in BP and changes in NE spillover across the heart. These observations are consistent with the concept that the neural response to these vasodilators in HF is a function of the relative interaction between the sympatoexcitatory response to arterial baroreceptor unloading and a sympathoinhibitory response to reductions in cardiac filling pressures. A nonhypotensive stimulus may be required to demonstrate any inhibitory effect of ANP on cardiac and systemic sympathetic outflow in HF.

We therefore applied nonhypotensive LBNP. In our previous study in normal subjects, this intervention increased NISNA (by 80%) during NTG but had no effect on NISNA when ANP was infused. In the present series, the effects of nonhypotensive (–6 mm Hg) and hypotensive (–12 mm Hg) LBNP on SBP, DBP, CVP, and HR were similar during the 2 infusions. Despite these comparable hemodynamic stimuli to sympathetic activation, the reflex response, MSNA was significantly lower during ANP than during NTG both before and during the application of LBNP. The principal difference again emerged during nonhypotensive LBNP: NISNA increased by 28% during the NTG infusion (P<0.001) but by only 5% during the ANP infusion (P=NS). When hypotensive LBNP was applied there were significant increases in NISNA during both infusions. By comparison, in another study in patients with HF treated with ACE inhibitors, nonhypotensive LBNP alone increased MSNA by 26%. These findings are consistent with the concept that ANP exerts a specific sympathoinhibitory action in HF in response to a selective reduction in cardiac filling pressure. This would reduce the stimulus to firing of stretch-sensitive atrial and ventricular baroreceptor afferent nerves. Indeed, initial experiments in rats suggested that the hypotensive response to atrial peptides was augmented by withdrawal of sympathetic outflow, effected reflexively through sensitization of cardiac receptors with vagal afferents. Sensitization of cardiac mechanoreceptors could account for the present observations, whereas if 1 or more other potential sympathoinhibitory mechanisms, such as a reduction in sympathetic ganglionic neurotransmission, sensitization of aortic arch baroreceptors, or a brain stem action were active, a difference in MSNA between ANP and NTG should have emerged under resting conditions.

Observations during the NTG infusion merit comment. In normal volunteers, we documented a 32% increase in MSNA in response to intravenous NTG. Recently, Noll et al reported that oral isosorbide dinitrate increased MSNA in healthy subjects, whereas oral captopril did not, and suggested that nitrate-induced sympathoexcitation may have adverse implications for treated patients with HF. However, their observations were likely due to the different effect of these 2 interventions on cardiac filling pressures, which were not reported. There was an inverse relation between MSNA at rest and the response to NTG in these patients with HF (Figure 2), with no net sympathoexcitatory action (Figure 1).

The present observations are consistent with 2 concepts. In patients with HF, in the setting of ACE inhibition, (1) both ANP and NTG lower CVP and DBP without eliciting reflex increases in MSNA. This nonspecific sympathoinhibitory effect may be a response to reductions in cardiac filling pressures; and (2) ANP exerts, in addition, a specific sympathoinhibitory action. This is most evident when atrial pressure is lowered by nonhypotensive LBNP, a maneuver that simulates upright posture. These findings suggest a potential sympathomodulatory role for endogenous ANP in mild to moderate HF and a potential therapeutic role for exogenous ANP or for neutral endopeptidase inhibition. However, when compared with responses in healthy subjects, this effect is modest, suggesting that patients with HF may be relatively resistant to the sympathoinhibitory actions of ANP. Loss of this restraint could contribute to sympathetic nervous system activation in HF.

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References


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