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Effects of Intravenous Brain Natriuretic Peptide on Regional Sympathetic Activity in Patients With Chronic Heart Failure as Compared With Healthy Control Subjects

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OBJECTIVES We sought to assess the effects of brain natriuretic peptide (BNP) on systemic and regional sympathetic nervous activity (SNA) in both patients with congestive heart failure (CHF) and healthy control subjects.

BACKGROUND Although the response of SNA to atrial natriuretic peptide (ANP) has been well documented, the response of SNA to BNP is largely unknown.

METHODS We assessed cardiac and whole-body SNA using the norepinephrine (NE) tracer dilution method before and after infusion of two doses of BNP (3 and 15 ng/kg body weight per min) in 11 patients with stable CHF (ejection fraction 24 ± 2%) and 12 age-matched healthy control subjects. In addition, renal SNA and hemodynamic variables were assessed at baseline and after the higher BNP dose.

RESULTS Low dose BNP did not change blood pressure or whole-body NE spillover, but reduced cardiac NE spillover in both groups by 32 ± 13 pmol/min ($p < 0.05$). In both groups, high dose BNP reduced pulmonary capillary pressure by 5 ± 1 mm Hg ($p < 0.001$) and mean arterial pressure by 6 ± 3 mm Hg ($p < 0.05$), without a concomitant increase in whole-body NE spillover; however, cardiac NE spillover returned to baseline levels. Renal NE spillover remained virtually unchanged in healthy control subjects (501 ± 120 to 564 ± 115 pmol/min), but was reduced in patients with CHF (976 ± 133 to 656 ± 127 pmol/min, $p < 0.01$).

CONCLUSIONS Our results demonstrate a sympathoinhibitory effect of BNP. Cardiac sympathetic inhibition was observed at BNP concentrations within the physiologic range, whereas high dose BNP, when arterial and filling pressures fell and reflex sympathetic stimulation was expected, systemic and cardiac SNA equated to baseline values. There was inhibition of renal SNA in patients with CHF, but not in healthy control subjects. Whether this effect is specific to BNP or related to reduced filling pressure remains to be determined. (J Am Coll Cardiol 2001;37: 1221–7) © 2001 by the American College of Cardiology

With the progression of congestive heart failure (CHF), various neurohumoral systems, including the renin-angiotensin-aldosterone system (RAAS), sympathetic nervous system (SNS) and natriuretic peptides (NP), are activated (1). Although the RAAS and SNS contribute to the progression of CHF, NP are thought to be beneficial by counteracting vasoconstriction and water and salt retention (2). Atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) have a spectrum of biologic actions potentially favorable in CHF, including diuretic, natriuretic and hypotensive properties, as well as inhibition of the RAAS and of endothelin secretion (3–5). It has been suggested that BNP is a more slowly responding but more powerful hormone than ANP in terms of improving cardiovascular function in CHF. Thus, infusion of BNP has been proposed as a novel therapy for CHF (6,7).

Although some studies observed that ANP might increase sympathetic activity (8,9), the majority reported a suppressive effect of ANP on the SNS (10–13). The effects of BNP on sympathetic activity, however, are largely unknown, as they have not been investigated directly in humans, and indirect evidence derived from plasma norepinephrine (NE) was not conclusive (14,15). In CHF, cardiac stimulation and renal sympathetic stimulation are very important, as they precede generalized sympathetic activation (16), and cardiac sympathetic activation contributes to a poor prognosis (17). The effect of NP on regional sympathetic activity is largely unknown, and in this study, we investigated the effect of exogenous BNP on the cardiac, renal and whole-body sympathetic activity in patients with CHF as compared with normal control subjects.

METHODS

Study group. The study group comprised 11 patients (age 58 ± 4 years) with stable CHF. Patients had a left

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Abbreviations and Acronyms

ANP = atrial natriuretic peptide
BNP = brain, or b-type, natriuretic peptide
CHF = congestive heart failure
NE = norepinephrine
NP = natriuretic peptides
RAAS = renin-angiotensin-aldosterone system
SNS = sympathetic nervous system

ventricular ejection fraction <40% (mean 24 ± 2%), as assessed by radionuclide ventriculography, secondary to coronary artery disease in nine patients and dilated cardiomyopathy in two patients. All patients were taking angiotensin-converting enzyme inhibitors; diuretics (n = 8); digoxin (n = 7); nitrates (n = 4); amiodarone (n = 4); and beta-blockers (n = 5).

Twelve healthy control subjects of comparable age (mean 52 ± 2 years) were recruited from the Health Care Centre of the Baker Medical Research Institute, where they attended screening for heart risk factors. All were free of a history of cardiovascular disease; they had no cardiovascular risk factors; and none were receiving long-term drug therapy. Clinical examination, laboratory testing (e.g., electrolytes, liver and kidney function, blood lipids, blood cell count) and the electrocardiogram were normal in all patients. Healthy control subjects underwent the same procedures, apart from radionuclide measurement of ejection fraction, as did patients with CHF. The protocol was approved by the Ethics Review Committee of the Alfred Hospital, and patients and healthy control subjects gave written, informed consent to participate in the study.

Study schedule. The subjects were studied in the morning; they did not have tea or coffee overnight. A 3F cannula was inserted into a radial artery for blood pressure monitoring and blood sampling. Thereafter, an 8F sheath was inserted into the right internal jugular vein in patients with CHF, and into the medial antecubital vein of either arm in healthy control subjects. Catheters were advanced and exchanged through the same sheath. Pulmonary artery pressure measurements (mean and wedge) were recorded by using a Swan-Ganz catheter. Cardiac output was measured by thermodilution. Hemodynamic measurements were impossible in three healthy control subjects for technical reasons. After the hemodynamic evaluation, a Cournand catheter was placed under fluoroscopic guidance in one of the renal veins for blood sampling. Renal plasma flow was measured using *p*-aminohippurate clearance. Arterial versus renal vein concentrations of *p*-aminohippurate were determined using steady-state infusion into a peripheral vein. Thereafter, a thermodilution catheter (Webster CCS 7/8U 90A, Cordis Corp., Miami, Florida) was placed under fluoroscopic guidance in the coronary sinus and was used to sample coronary sinus blood and to measure coronary sinus blood flow. Coronary sinus plasma flow was calculated using the subject's hematocrit.

After completion of the baseline measurements, a loading dose of BNP (100 ng/kg body weight over 5 min; human BNP, Bachem, Switzerland) was given intravenously, followed by a infusion of 3 ng/kg per min for 25 min. Thereafter, blood sampling and blood flow measurement in the coronary sinus were repeated. Then, a second loading dose of BNP (400 ng/kg given over 5 min) was followed by an infusion of 15 ng/kg per min for 25 min. Blood flow measurement and blood sampling in the coronary sinus were repeated. Subsequently, the Cournand catheter was reinserted into the same renal vein for blood sampling, which was not possible in one patient with CHF and one healthy subject. Finally, the Swan-Ganz catheter was reinserted for hemodynamic measurements. Thus, whole-body and cardiac NE spillover were assessed at baseline and after each dose of infused BNP, whereas renal SNS and hemodynamic data were measured at baseline and after the high dose of BNP only.

Estimation of sympathetic activity. Measurements of the spillover of NE to plasma from the heart, kidneys and body as a whole were used to estimate regional and systemic sympathetic activity (18). All patients received an intravenous infusion of tritiated *levo*-NE (New England Nuclear, Boston, Massachusetts; 0.5 to 1.5 μCi/min). Arterial and venous blood samples were drawn simultaneously at least 30 min after the start of radiotracer infusion. Plasma was separated by centrifugation at 4°C and stored at −80°C until analysis.

The total (SP_{NEtot}) and regional (SP_{NEreg}) NE spillover (SP) rates to the plasma were measured by using methods developed by Esler et al. (18):

$$SP_{NEtot} = \frac{[^3H]NE_{in}}{SA_{NE}}$$

where $[^3H]NE_{in}$ is the $[^3H]$NE infusion rate, and SA_{NE} is the specific activity of plasma NE.

$$SP_{NE_{reg}} = ([NE_V - NE_A] + [NE_A \times ER]) \times Q_P$$

where NE_V and NE_A are the venous (either cardiac or renal) and arterial plasma NE concentrations, respectively; ER is the fractional extraction of tracer NE across the heart and kidneys; and Q_P is the regional plasma flow.

Assays. Catecholamines in plasma (1 ml) and samples of the infusion preparation (10 μl) were adsorbed onto alumina and quantified by liquid chromatography with electrochemical detection, as previously described (19). Timed collections of the eluent as it leaves the electrochemical cell enable separation of $[^3H]$-NE for assay by liquid scintillation spectrometry.

Plasma levels of BNP. Arterial blood was collected into chilled tubes containing EDTA and aprotinin (500 KIU/ml blood) for assessment of plasma BNP. Plasma was separated immediately using a refrigerated centrifuge and stored at −80°C until measurement. Brain natriuretic peptide was determined directly, without previous extraction in duplicate by a solid-phase immunometric radioimmunoassay

Table 1. Baseline Characteristics of Patients With Congestive Heart Failure and Healthy Control Subjects

	Patients With CHF (n = 11)	Control Subjects (n = 12)	p Value
Heart rate (beats/min)	76 ± 6	68 ± 3	0.1
MAP (mm Hg)	88 ± 4	97 ± 3	0.06
RAP (mm Hg)	6.9 ± 0.7	4.8 ± 0.5	0.05
PAP (mm Hg)	26.9 ± 2.7	12.7 ± 0.6	0.001
PCWP (mm Hg)	18.3 ± 2.2	7.3 ± 0.6	0.001
CI (liters/m^2 per min)	2.49 ± 0.15	3.13 ± 0.17	0.01
SVR (dyne*cm^{-5}*s)	1,363 ± 129	1,322 ± 133	> 0.1
PVR (dyne*cm^{-5}*s)	145 ± 17	73 ± 8	0.001
Arterial NE (nmol/liter)	2.17 ± 0.34	1.54 ± 0.19	0.1
Body NE SP (nmol/min)	7.43 ± 1.32	4.04 ± 0.42	0.05
Cardiac NE SP (nmol/min)	0.250 ± 0.051	0.170 ± 0.025	0.1
Coronary sinus NE (nmol/liter)	3.17 ± 0.60	1.85 ± 0.30	0.05
Renal NE SP (nmol/min)	0.967 ± 0.127	0.502 ± 0.100	0.005
Renal vein NE (nmol/liter)	3.92 ± 0.56	1.75 ± 0.25	0.005
BNP (pmol/liter)	66.7 ± 15.3	7.8 ± 1.7	0.001

Data are presented as the mean value ± SEM.

BNP = brain, or b-type, natriuretic peptide; CHF = congestive heart failure; CI = cardiac index; MAP = mean arterial pressure; NE = norepinephrine; PAP = pulmonary artery pressure; PCWP = pulmonary capillary wedge pressure; PVR = pulmonary vascular resistance; RAP = right atrial pressure; SP = spillover; SVR = systemic vascular resistance.

using ^{125}labeled BNP antibody (Shionogi Chemical Co., Osaka, Japan).

Statistical analysis. Data are expressed as the mean value ± SEM. Baseline characteristics were compared between the two groups using the independent samples *t* test. Two-way analysis of variance for repeated measures was used to test the responses to the BNP infusions. Spearman rank correlation was used to assess the relationship between baseline values and changes after BNP infusion of NE spillover. A p value ≤0.05 was considered to show a statistically significant difference. Analyses were performed using the statistical package SPSS for Windows 9.0.

RESULTS

The baseline characteristics of the patients and control subjects are summarized in Table 1. Patients with CHF had elevated filling pressures and a reduced cardiac index, as compared with healthy control subjects. The SNS was activated in patients with CHF, although the differences in cardiac NE spillover failed to reach statistical significance. The baseline BNP concentration was significantly elevated in patients with CHF.

Infusion of BNP resulted in a significant ($p < 0.001$) increase in the arterial BNP concentration in both healthy subjects (8 ± 2 to 31 ± 5 to 188 ± 44 pmol/liter) and patients with CHF (67 ± 15 to 138 ± 15 to 520 ± 80 pmol/liter). A lesser increase in clearance and maintained production of BNP (data not shown) caused a larger increase in arterial BNP levels in patients with CHF ($p < 0.001$).

Hemodynamic response to BNP. There was no change in blood pressure with the lower BNP dose in both patients with CHF and control subjects (systolic: −1.7 ± 1.2 and 0.0 ± 2.5 mm Hg; mean: −1.1 ± 1.0 and 1.2 ± 1.5 mm Hg; diastolic: −0.7 ± 1.4 and 1.7 ± 1.3 mm Hg, respectively; all $p > 0.1$). Heart rate also did not change in patients with CHF or control subjects (−1.0 ± 1.2 beats/min and −2.1 ± 1.4 beats/min, respectively; both $p > 0.1$). Figure 1 depicts the hemodynamic responses to high dose BNP. There was a significant reduction in cardiac filling pressures in both groups. However, pulmonary artery and capillary wedge pressures fell more in patients with CHF ($p < 0.05$). A fall in diastolic pressure was evident in the CHF group only, but the fall in systolic pressure did not

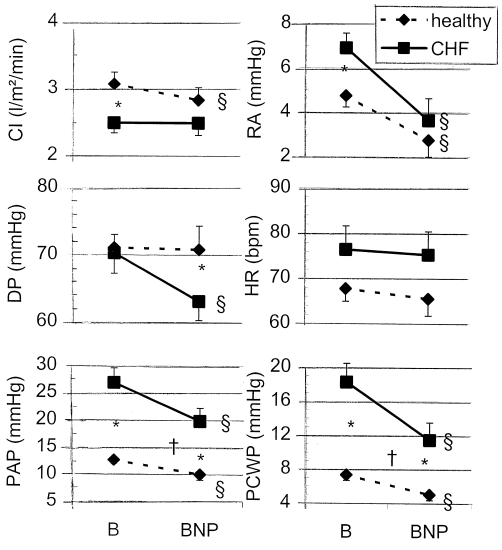

Figure 1. Hemodynamic data in patients with CHF as compared with healthy subjects before **(B)** and after **(BNP)** infusion of BNP (15 ng/kg per min). *$p < 0.05$ between groups; §$p < 0.05$ after BNP infusion versus baseline; †$p < 0.05$ response to BNP between different groups. BNP = brain, or b-type, natriuretic peptide; CHF = congestive heart failure; CI = cardiac index; DP = diastolic pressure; HR = heart rate; PAP = pulmonary artery pressure; PCWP = pulmonary capillary wedge pressure; RA = right atrial (pressure).

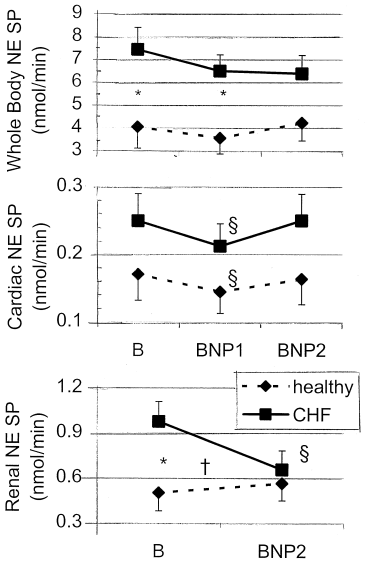

Figure 2. Whole-body **(top panel)**, cardiac **(middle panel)** and renal **(bottom panel)** NE SP in patients with CHF as compared with healthy subjects before **(B)** and after the lower **(BNP1)** and higher **(BNP2)** BNP dose. *$p < 0.05$ between groups; §$p < 0.05$ after BNP infusion versus baseline; †$p < 0.05$ response to BNP between different groups. BNP = brain, or b-type, natriuretic peptide; CHF = congestive heart failure; NE = norepinephrine; SP = spillover.

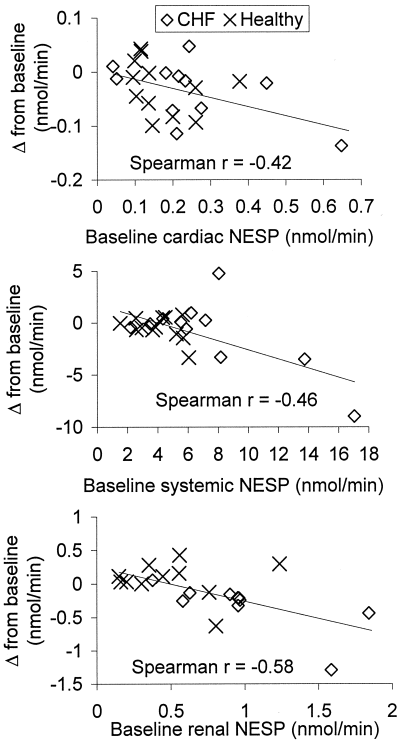

Figure 3. Scatter plots of changes in cardiac (**top panel**; lower BNP dose), whole-body (**middle panel**; lower BNP dose) and renal (**bottom panel**; higher BNP dose) NESP in relation to baseline levels in both groups. The "r" values are rank correlations. BNP = brain, or b-type, natriuretic peptide; CHF = congestive heart failure; NESP= norepinephrine spillover.

differ between the two groups (CHF vs. control: -10.3 ± 3.3 vs. -8.1 ± 6.5 mm Hg). There was a significant reduction in the cardiac index in healthy control subjects, whereas it did not change in patients with CHF. There were only minor changes in systemic vascular resistance (CHF vs. control: $-9 \pm 8\%$ vs. $5 \pm 8\%$; both $p > 0.1$), and no change in pulmonary vascular resistance. Although renal plasma flow fell in both groups (CHF vs. control: from 682 ± 80 to 514 ± 61 ml/min vs. from 787 ± 73 to 627 ± 51 ml/min; both $p < 0.01$), coronary sinus blood flow did not change significantly.

Effects of BNP on SNS. Figure 2 depicts the responses of whole-body, cardiac and renal NE spillover to BNP infusions. Whole-body NE spillover tended to decrease in response to the lower BNP dose in both groups; in healthy subjects, it returned to baseline values with the higher dose, whereas in patients with CHF, it remained low. Cardiac NE spillover was similarly and significantly reduced in both groups by the lower BNP dose ($p < 0.05$), but returned to baseline values with the higher dose. Renal NE spillover rose slightly with the higher BNP dose in healthy control subjects ($p > 0.1$), but decreased significantly in patients with CHF ($p < 0.01$). Similarly, the renal venous NE concentration tended to rise in healthy control subjects (from 1.75 ± 0.25 to 1.92 ± 0.30 nmol/liter, $p > 0.1$), but fell significantly in patients with CHF (3.92 ± 0.56 to 3.08 ± 0.65 nmol/liter, $p < 0.05$).

There was a negative correlation between baseline NE spillover and its reduction after BNP infusion in both groups combined (whole body: $r = -0.46$, $p < 0.05$; cardiac: $r = -0.42$, $p < 0.05$; renal: $r = -0.58$, $p < 0.01$) (Fig. 3). The sympathetic response was not correlated with changes in filling and arterial pressures, nor with the medication in patients with CHF.

DISCUSSION

Our study shows that BNP may inhibit the SNS, an effect mostly apparent if the sympathetic activity at rest was elevated. In addition, to the best of our knowledge, we are the first to measure the response of renal sympathetic activity in humans during infusion of NP and to demonstrate suppression of renal sympathetic activity by BNP in patients with CHF. Moreover, BNP infusion at doses leading to increases in circulating BNP in the physiologic range resulted in a reduction in cardiac sympathetic activity in both healthy control subjects and patients with CHF.

Effects of BNP on SNS. After the higher BNP dose, the reduction in arterial and cardiac filling pressures, which would be expected to unload cardiopulmonary and arterial baroreceptors, did not result in the expected reflex increase in whole-body NE spillover, suggesting a relative sympathoinhibitory action of BNP. We did not directly compare BNP with a vasodilating agent, such as sodium nitroprusside or nitroglycerin, but these agents have consistently been shown to significantly increase systemic sympathetic activity in both healthy control subjects and patients with CHF (9,10,20–23). In addition, studies investigating the effects of reduction in cardiac filling pressures by lower body,

negative pressure described stimulation of the systemic SNS in healthy subjects (8,10,24). Reductions in both central venous and diastolic blood pressure, similar to those observed in our study, by the combination of nitroglycerin and lower body, negative pressure resulted in a distinct increase in muscular SNS in patients with CHF (11). In contrast, with BNP, whole-body NE spillover tended to fall in our patients with CHF.

A significant reduction of renal sympathetic activity was observed in the patients with CHF. This is of potential therapeutic importance, because elevation of renal sympathetic activity plays an important role in the pathophysiology of CHF (16). Activation of the renal SNS stimulates the RAAS (25), one of the key pathophysiologic mechanisms in CHF, and directly promotes sodium and water retention (26). In contrast, renal sympathetic activity tended to increase in healthy control subjects in the present study. There are no data on the effect of baroreflex stimulation on renal sympathetic activity in humans, but in animal studies, the increase in renal sympathetic activity with direct-acting vasodilators was much greater than our observed increase in healthy control subjects (27). Nevertheless, our results cannot answer the question of whether BNP has direct renal sympathoinhibitory effects, or whether this is an effect resulting from the lowered filling pressures in patients with CHF.

Various mechanisms may account for the different response of renal sympathetic activity in patients with CHF and healthy control subjects. Reflex stimulation may be suppressed in patients with CHF because of reduced baroreflex sensitivity (20), in particular, that of cardiopulmonary baroreceptors (28), although intact arterial baroreflex control has been described in patients with CHF (29). The inhibitory action of BNP on renin release (30), and consequently angiotensin II formation, might also reduce sympathetic activity. Natriuretic peptides may modulate sympathetic nerve activity by antagonizing the action of angiotensin II (31). Likewise, cyclic guanosine monophosphate may exert a sympathoinhibitory action (32), particularly when angiotensin II is elevated (33).

The response of cardiac sympathetic activity to BNP infusion was dependent on the dose used and did not differ between the two groups. At low dose BNP, which did not affect arterial pressure in our study, cardiac sympathetic activity fell, supporting direct inhibition of cardiac sympathetic activity by BNP. This may be cardioprotective, because a high cardiac sympathetic drive is an important contributor to the progression of disease in CHF (34) and is a major determinant of prognosis (17).

However, cardiac sympathetic activity no longer remained suppressed when using a moderately high dose of BNP (i.e., 15 ng/kg per min); rather, it returned to baseline levels. This may be caused by baroreflex activation, but may also represent a relative inhibition of cardiac SNS, because baroreflex unloading results in an increase in cardiac NE spillover, at least in subjects with normal left ventricular function (21,24). However, it remains to be investigated whether BNP has an inhibitory effect on cardiac sympathetic activity in CHF that exceeds the effect of lowering left-sided filling pressures (22,24).

Regional differentiation of efferent baroreflex regulation has been described (35), and our data suggest that this may depend on the activity of the SNS at rest. Thus, renal SNS, which was significantly stimulated in patients with CHF, as compared with healthy control subjects, was significantly inhibited by BNP. In contrast, the cardiac sympathetic activity response was comparable in both groups, possibly because cardiac SNS at rest was only mildly activated in patients with CHF. This is in line with the response to BNP being related to baseline sympathetic activity (Fig. 3).

Effects of BNP on hemodynamic data. It is beyond doubt that NP reduce cardiac preload, but the effects of NP on arterial vasomotion are less certain (6,30,36–38). Increased cyclic guanosine monophosphate production undoubtedly results in arterial vasodilation, but there are studies showing no decrease (38) or even an increase (30,36) in systemic vascular resistance by NP. The reason for this discrepancy, as well as the mechanism by which NP might mediate vasoconstriction, are completely unknown. Notably, the vasoconstricting response was not found to be mediated by the autonomic nervous system (30), and previous studies found a dissociation between the neural and vascular actions of NP (39). Interestingly, a reduction in systemic vascular resistance was mainly seen with relatively high doses of NP (6,7,37,40), whereas low doses were used when neutral or vasoconstricting effects were found (30,36,38). Moreover, the effects on vascular conductance may vary by region (30). In the vasculature of the kidneys, NP act on the afferent arterioles as a vasodilator, but on the efferent arterioles as vasoconstrictive agents, thereby increasing the glomerular filtration rate (41). Thus, it is conceivable that NP may cause either an increase or a decrease in renal blood flow, which is in accordance with the discrepant reports of the effects of NP on renal plasma flow (42,43).

Study limitations. There are some limitations of our study. We did not include a group of control subjects in whom a drug was administered to reduce cardiac filling pressures and arterial pressure, with no direct effects on the SNS. Therefore, we cannot exclude an indirect sympathoinhibitory effect of BNP, although this is unlikely to have occurred, at least in healthy subjects. In advanced CHF, a positive feedback relationship between pulmonary artery pressure/filling pressure and cardiac sympathetic activity has been found (22,24), such that a reduction in sympathetic activity could be an indirect effect of cardiac filling pressure lowered by BNP. However, in contrast to our study, elevation of systemic sympathetic activity was observed in previous studies where interventions reduced cardiac filling pressures, irrespective of underlying conditions (9,10,20–23). Also, cardiac NE spillover was not significantly elevated in our CHF group. On the one hand, this might explain the similar response of cardiac NE spillover in both groups,

with a distinct effect on renal sympathetic activity between the groups. On the other hand, we cannot exclude an influence of the medication on our results in patients with CHF. Although we did not find a statistical interaction with the medication, a larger study group would have been necessary to determine smaller influences.

Finally, to avoid further lengthening of an already long study by additional changes of the catheters, we did not measure central hemodynamic data and renal sympathetic activity at the lower rate of BNP infusion. Although reduced filling pressures with the lower BNP dose cannot be excluded, this would not explain the inhibitory effects on the cardiac sympathetic nervous system in healthy control subjects. Moreover, significant hemodynamic changes were not observed in patients with CHF with this dose of BNP (40). Nevertheless, we cannot exclude a favorable influence of a reduction of cardiac filling pressures on cardiac sympathetic activity in patients with CHF.

Conclusions. The present observations suggest a sympathoinhibitory effect of BNP. In healthy volunteers, there was cardiac sympathetic inhibition at BNP concentrations within the physiologic range, whereas at high dose BNP, when filling pressures fell and reflex sympathetic stimulation was expected, systemic and regional SNS activity equated to baseline values. In patients with CHF, as for healthy subjects, low dose BNP resulted in cardiac sympathetic inhibition, whereas at a higher dose, there was selective inhibition of the elevated renal SNS activity and no reflex stimulation of systemic and cardiac SNS in the face of a fall in arterial and cardiac filling pressures. Whether this effect in patients with CHF is due to a direct action of BNP, or whether it is indirectly related to a reduction in cardiac filling pressures, remains to be determined.

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