Sympathoadrenal Inhibition by Atrial Natriuretic Peptide Is Not Attenuated During Development of Congestive Heart Failure in Dogs

Jürgen Holtz, MD, Thomas Münzel, MD, Olaf Sommer, and Eberhard Bassenge, MD

The feedback control of neuroendocrine activity by cardiopulmonary blood volume is disturbed in congestive heart failure. By analyzing plasma catecholamine kinetics, we tested in 11 chronically instrumented conscious dogs whether attenuations in the sympathoadrenal inhibition induced by atrial natriuretic peptide (ANP) contributed to this disturbance. Low-output failure was brought about by continuous ventricular pacing at 265 beats/min for 2 weeks. This resulted in a decline in aortic flow by 37±5% (SEM), an increase in peripheral vascular resistance by 48±4%, a 13±3-fold elevation in plasma ANP, a 9±3-fold elevation in plasma renin activity, and an augmentation of the norepinephrine-release rate into plasma by 132±17%. During ANP infusion, the epinephrine-release rate declined by 26±5% per 10-fold elevation in plasma ANP before pacing and by 31±7% (not significantly different) after 2 weeks of pacing. Before pacing, ANP attenuated plasma renin activity and caused hypotension without a rise in norepinephrine-release rate. After 2 weeks of pacing, ANP lowered norepinephrine release (by 16±6%) without affecting blood pressure or plasma renin activity, and vascular nonresponsiveness to ANP was verified under autonomic blockade. These data indicate that, during the development of heart failure, an inhibitory action of ANP on norepinephrine release is unmasked by an ANP-specific vascular desensitization, whereas the inhibition of epinephrine release is observed throughout. It is concluded that ANP-induced sympathoadrenal inhibition is not attenuated and, therefore, does not contribute to the disturbed regulation observed early in the development of failure. (Circulation 1989;80:1862–1869)

Changes in cardiopulmonary blood volume stimulate compensatory changes in vasoconstrictor tone and in plasma renin activity, sympathetic activity, and vasopressin release. When stretch receptors in the thoracic parts of the vascular low-pressure system are activated, mainly inhibitory neural afferent signals are generated. In addition, atrial natriuretic peptide (ANP), released from the cardiac myoendocrine cells by atrial stretch, is also a potent inhibitor of the neuroendocrine activity that promotes vasoconstriction and volume retention. In congestive heart failure, however, this activity is augmented, even though the cardiopulmonary compartment is severely overfilled and the plasma levels of ANP are chronically elevated.

The reasons for this defective cardiopulmonary afferent control are not completely understood. The neurohumoral and circulatory reflex responses to rapid changes in thoracic blood volume are abnormal and attenuated in congestive heart failure, but changes of the cardiac hormonal feedback loop by ANP are incompletely characterized in this syndrome. Most studies agree that plasma ANP levels in heart failure still do respond to changes in cardiac filling pressures, whereas changes in target organ responsiveness have been studied only for vascular and renal actions of the hormone. Therefore, we studied the effect of exogenous ANP on sympathetic activity in dogs during the development of low-output failure. The kinetics of plasma catecholamines in these animals during infusions of

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ANP indicate that the inhibition of sympathoadrenal activity by ANP is maintained during progressive low-output failure.

Methods

Animals

Fifteen mongrel dogs of either sex, weighing 25–34 kg, were used in this study after thorough inspection by a veterinarian and a quarantine of 3 weeks. They were chronically instrumented under anesthesia and allowed to recover from surgery for at least 10 days. They were fed standard chow with 2–4 meq/kg Na+/day and had free access to tap water. The care of the animals and the execution of the experimental protocol were supervised by an independent veterinarian in accordance with German laws and the animal welfare regulations of the University of Freiburg (corresponding to the guidelines for animal welfare of the American Physiological Society).

The dogs were instrumented under pentobarbital anesthesia and sterile conditions. During thoracotomy, an electromagnetic flowmeter was implanted around the ascending aorta and a pair of piezoelectric crystals was attached to the epicardial surface of the left ventricle, positioned to measure the external diameter of the minor ventricular axis. A polyethylene catheter was implanted into the pulmonary artery, and a pair of electrodes was sewn to the left ventricular apex. In addition, a common carotid artery was translocated into a cutaneous loop at the ventral surface of the neck for transcutaneous puncture. All cables and catheters were tunneled subcutaneously to the back. The dogs received antibiotics for 1 week postoperatively and catheters were flushed daily. During the recovery period, the dogs were familiarized with the laboratory and the personnel.

Protocols and Measurements

The protocols studied in the 11 dogs of the experimental group and in the four dogs of the control group are listed in Table 1. For protocol A, the dogs were anesthetized with sodium pentobarbital (25 mg/kg i.v. and 2.5 mg/kg/hr i.v.) and breathed spontaneously through an endotracheal tube. Arterial blood gases were kept within 36–44 mm Hg PCO₂, 74–89 mm Hg PO₂, and 7.37–7.45 pH by adjusting the infusion rate of the anesthetic or by infusion of 8.4% sodium bicarbonate. The carotid artery in the loop was punctured for recording arterial blood pressure, a catheter was placed in the right atrium through a punctured jugular vein for recording central venous pressure, the aortic flow probe was connected to a Gould-Statham SP 2202 flowmeter, and two peripheral intravenous lines were inserted for drug infusions. Reflexes were minimized by ganglionic blockade (10 mg/kg plus 10 mg/kg/hr hexamethonium, 0.5 mg/kg methylatropine) and by β-adrenergic blockade (2 mg/kg nadolol). Volume was infused (2.5 ml/kg/hr saline and 2.5 ml/kg/hr dextran), and the vasculature was preconstricted with norepinephrine (0.15 μg/kg/min). Under steady-state conditions, ANP (0.1 and 0.3 μg/kg/min human α-ANP, i.e., ANF₉₉₋₁₂₆) and iloprost (0.03 and 0.1 μg/kg/min) were each infused over 5 minutes with a 15-minute interval between. Afterwards, the norepinephrine infusion was stopped. The aortic flowmeter was calibrated against cardiac output by dye dilution (subtracting 4% for coronary flow), and this calibration was used in each dog for all subsequent recordings of aortic flow. All infusions were stopped, catheters and cannulas were withdrawn, and the dogs were allowed to recover from the anesthesia and the autonomic blockade.

In protocols B and C, in the conscious dogs at rest, the carotid artery was punctured for recording of arterial pressure and for withdrawal of blood samples, two veins were punctured for infusions, and aortic flow and left ventricular external diameter (on-line analysis of the transit time between the implanted piezoelectric crystals) were recorded. The catecholamine-release rate (sometimes referred to as “spillover rate”) was determined according to

<table>
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<tr>
<th>Table 1. Sequence and Time Schedule of Protocols</th>
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<tr>
<td><strong>Experimental group</strong></td>
</tr>
<tr>
<td>Protocol A; n=11 (anesthesia, autonomic blockade)</td>
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<tr>
<td>Vascular responsiveness to ANP and iloprost</td>
</tr>
<tr>
<td>Interval: 2 weeks</td>
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<tr>
<td>Protocol B; n=11 (conscious dogs, sinus rhythm)</td>
</tr>
<tr>
<td>ANP effects on catecholamine kinetics</td>
</tr>
<tr>
<td>Interval: 3–8 days</td>
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<tr>
<td>Protocol C; n=11 (conscious dogs)</td>
</tr>
<tr>
<td>Cathelicoldam kinetics during start of chronic tachypacing</td>
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<tr>
<td>Tachypacing for 5–7 days</td>
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<tr>
<td>Protocol B; n=11 (conscious dogs, tachypacing)</td>
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<tr>
<td>Tachypacing for 5–7 days</td>
</tr>
<tr>
<td>Protocol B; n=8†</td>
</tr>
<tr>
<td>Stop of tachypacing</td>
</tr>
<tr>
<td>One day later:</td>
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<tr>
<td>Protocol A; n=7‡</td>
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*Manipulations, infusions, and blood withdrawal as in the true protocol, but analyses were not performed; unlabeled norepinephrine was infused rather than labeled tracer, and tachypacing was not applied.
†One dog died unexpectedly after 10 days of pacing; two dogs were excluded because of damage of the implanted flowmeter.
‡In one dog, arterial blood gases during anesthesia and autonomic blockade could not be stabilized at the desired level after tachypacing for 2 weeks.
the method of Esler et al., with $^3$H-norepinephrine as tracer. After 1 hour of tracer infusion and equilibration, ANP (0.1 μg/kg/min) was infused for 15 minutes in protocol B. Arterial blood samples were withdrawn at minutes 45, 50, 55, and 60 during the equilibration period and at minutes 6, 9, and 12 during the infusion. Hemodynamic parameters were obtained for 1 minute before each sampling time. In protocol C, tachycardia (265 beats/min) was induced by the portable pacemakers after the 60-minute equilibration period, and samples were obtained 5, 15, 30, and 60 minutes after the pacing began. In each of these protocols, 2.8–3.1 ml/kg arterial blood were withdrawn for analyses. Concentrations of labeled and unlabeled catecholamines, plasma renin activity and plasma ANP immunoreactivity were determined by established methods as described previously.

Calculations and Drugs

Values are given as mean±SEM. Significance of differences between values within a protocol was tested by a repeated-measures analysis of variance (ANOVA). The ANOVA of the plasma renin-activity data was performed following logarithmic transformation, but absolute values are given in the results. If ANOVA indicated significant differences ($p<0.05$), groups of values in the equilibration period (control) were compared with values during infusion or during pacing, with linear contrasts calculated according to Scheffe for a two-tailed hypothesis and a significance level of $p$ less than 0.05 ($p$ values close to this level are mentioned if $0.1>p>0.05$). Catecholamine clearance and release rate were calculated as described. Peripheral vascular resistance was calculated by dividing mean arterial pressure by aortic flow. The following drugs were used: $l$-[7-$^3$H(N)]norepinephrine (20 Ci/mmol) (NEN, Dreieich, FRG), human $\alpha$-ANP (Ampuwa, Bissendorf, FRG), iloprost (Schering, Berlin, FRG), $l$-norepinephrine HCl (Hochst, Frankfurt, FRG), hexamethonium bromide, methylatropine (Merck, Darmstadt, FRG), nadolol (Von Heyden, Regensburg, FRG), sodium bicarbonate 8.4% (Delta Pharma, Pfullingen, FRG), and dextran 60 (Siwia, Glandorf, FRG).

Results

Hemodynamic and Endocrine Effects of Ventricular Pacing

Similar control values of the conscious resting dogs were obtained on two different occasions, before the first ANP infusion (protocol B, Table 2) and before the start of ventricular pacing (protocol C, Figures 1 and 2). During the first hour of ventricular pacing, mean arterial pressure did not change significantly, although aortic flow declined slowly by 18±3% of the prepacing value and peripheral vascular resistance increased correspondingly by 25±7%. Left ventricular end-diastolic external diameter declined by 6.5±0.6% within 5 minutes after the onset of pacing and remained at this level for 1 hour (Figure 1). With ongoing pacing for 2 weeks,
aortic flow declined by 37±5%, mean arterial pressure decreased by 17±3%, and peripheral vascular resistance increased by 43±7% (Table 2), compared with the corresponding prepacing values. Left ventricular end-diastolic diameter increased by 6.0±0.9%, compared with the minimal value after 1 hour of pacing.

The endocrine effects of the first hour of ventricular pacing are shown in Figure 2. Within 5 minutes of the onset of pacing, arterial plasma ANP rose fivefold and remained above this level for the rest of the hour. Plasma renin activity declined by 27±4% (average of measurements at 15, 30, and 60 minutes of pacing), the epinephrine-spillover rate fell by 26±9%, and the catecholamine-clearance rate decreased by 15±2%. As pacing continued, the plasma ANP increased to a plateau after 1 week (13±3-fold the prepacing level) (Table 2). The chronic changes of the other endocrine parameters, however, tended to differ from the acute responses during the first hour of pacing. Plasma renin activity fell initially (Figure 2) but was elevated 8.9±3.4-fold after 2 weeks. The norepinephrine-release rate, unchanged in the first hour, was augmented by 132±17% after 2 weeks.

Hemodynamic and Endocrine Effects of ANP Infusions

Figure 3 shows the ANP–induced changes, relative to the preinfusion values (Table 2), averaged over the measurements from minutes 6, 9, and 12 of the infusions. Under control conditions (sinus rhythm), ANP significantly lowered the epinephrine-release rate, the plasma renin activity, and mean arterial pressure. Heart rate was 89±4 beats/min before the infusion and 86±4 beats/min (0.1>p>0.05) during the infusion; the other measured parameters were not modified. During chronic ventricular pacing, ANP infusions caused declines in epinephrine-release rate similar to those before pacing (Figure 3). Although the effects of ANP on plasma renin activity and mean arterial pressure
disappeared in the last week of pacing, the norepinephrine-release rate declined significantly during the ANP infusion in the last week (Figure 3). The changes in the plasma levels of the catecholamines during ANP infusions under all conditions paralleled the changes in the corresponding release rates because catecholamine clearance was not modified by ANP under any condition (Figure 3). ANP effects on aortic flow, on peripheral vascular resistance, and on left ventricular diameter were not observed during pacing.

The relations of epinephrine-release rate and of plasma-epinephrine concentration to ANP plasma levels (Figure 4) were not changed during pacing. The epinephrine-release rate decreased 26±5% per 10-fold elevation in plasma ANP under control conditions and 31±7% in both the first and the second week of pacing.

**ANP Responsiveness Under Autonomic Blockade**

The experiments under anesthesia and autonomic blockade (Protocols A) demonstrated that the direct vasodilator action of ANP infusions up to 0.3 μg/kg/min disappeared after 2 weeks of pacing (Figure 5). This was not the consequence of a nonspecific attenuation of vascular responsiveness after pacing because the vasodilation in response to the prostacyclin analogue iloprost (0.03 and 0.1 μg/kg/min) was not attenuated. The preconstriction by infused norepinephrine caused similar augmentations in peripheral vascular resistance before and after pacing (Figure 5). The consequences of this arteriolar vasoconstriction, however, differed markedly between the two conditions. Before pacing, aortic flow remained essentially constant under the norepinephrine-induced hypertension; after pacing, aortic flow declined by 27±4% during this vasoconstriction and the iloprost-induced arteriolar vasodilation partially normalized this lowered aortic flow (Figure 5).

**ANP Effects in Dogs of the Control Group**

In this group, the hemodynamic effects of ANP and of iloprost under autonomic blockade (Protocol A, data not shown) were similar to those in the first protocol A of the experimental group (Figure 5). The ANP effects on catecholamine kinetics in the conscious dogs (Protocol B) were studied twice in these dogs with a 3-week interval and with sham-protocols within this interval (Table 1). The ANP-induced reduction of the epinephrine-release rate per 10-fold augmentation of plasma ANP was 33±5% and 35±7% in the first and last protocol B, respectively. Plasma renin activity fell during ANP infusion by 38±8% and by 46±10%, whereas mean arterial pressure declined by 6±1% and 5±1%, respectively, in the first and last protocol B. Baseline values of any parameter did not differ (Table 3), demonstrating the stability of the endocrine parameters and of the response to ANP over the duration of the entire protocol.

**Discussion**

This study in an experimental model of congestive heart failure, produced by sustained ventricular tachypacing, demonstrates that adrenomedullary inhibition by ANP is maintained and that sympathoinhibition by ANP is manifested during the development of failure.
TABLE 3. Hemodynamic and Endocrine Effects of Repeated ANP Infusions (0.1 μg/kg/min) in Conscious Dogs at Rest (Control Group)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>First protocol B</th>
<th>Last protocol B*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (1/min)</td>
<td>Control</td>
<td>ANP infusion</td>
</tr>
<tr>
<td></td>
<td>85±6</td>
<td>80±7</td>
</tr>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>100±2</td>
<td>94±1†</td>
</tr>
<tr>
<td>Aortic flow (ml/kg/min)</td>
<td>114±8</td>
<td>109±7</td>
</tr>
<tr>
<td>Peripheral vascular resistance (mm Hg/kg·min/ml)</td>
<td>0.89±0.06</td>
<td>0.88±0.07</td>
</tr>
<tr>
<td>Left ventricular end-diastolic external diameter (mm)</td>
<td>65.7±1.8</td>
<td>65.6±1.8</td>
</tr>
<tr>
<td>Norepinephrine-release rate (ng/kg/min)</td>
<td>15.6±3.2</td>
<td>15.1±2.3</td>
</tr>
<tr>
<td>Epinephrine-release rate (ng/kg/min)</td>
<td>10.6±3.2</td>
<td>4.9±1.0†</td>
</tr>
<tr>
<td>Catecholamine clearance (ml/kg/min)</td>
<td>74±3</td>
<td>72±5</td>
</tr>
<tr>
<td>Plasma renin activity (ng/ml/hr)</td>
<td>0.78±0.28</td>
<td>0.56±0.29†</td>
</tr>
<tr>
<td>Plasma atrial natriuretic peptide (pg/ml)</td>
<td>26±2</td>
<td>897±83†</td>
</tr>
<tr>
<td>Number of dogs</td>
<td>4</td>
<td>4</td>
</tr>
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</table>

*After an interval of 3 weeks, including sham-protocols B and C (see Table 1). †p<0.01, ‡0.1>p>0.05; significance of difference from preceding control value.

Limitations of the Pacing-Induced Failure Model

Two features of our model should be considered here. First, the mechanism of the progressive decline in cardiac output is unknown. The initial hemodynamic changes in this model might be due to shortened diastole, incomplete ventricular relaxation, asynchrony of ventricular activation, and loss of coordination between atrial and ventricular systole. With chronic pacing, however, a slowly progressing low-output failure is evident from the decline in aortic flow and from the increase in left ventricular external diameter (Table 2), confirming previous observations. A substantial impairment of ventricular contractile performance in the dogs after 2 weeks of ventricular tachypacing is demonstrated by the sharp decline in aortic flow in response to norepinephrine-induced vasoconstriction under ganglionic and β-adrenergic blockade (Figure 5). The pathophysiologic mechanism of this myocardial deterioration has not yet been identified. However, the neurohormonal changes in this model (Table 2) are similar to those typically found in patients with low-output failure. Thus, hormonal interactions observed in this particular model may have relevance for low-output failure in general.

Second, the natural history of heart failure development and the basal neuroendocrine activity in these dogs might have been modified by the applied protocols, especially by the repeated removal of blood. The basal norepinephrine-release rate before chronic tachypacing (Figure 2, Table 2) was substantially higher than in dogs of a previous study. This difference might have resulted from different degrees of training for quiet rest, and from the fact that the dogs in the previous series had not undergone thoracotomy, chronic instrumentation, and autonomic blockade in anesthesia. All these interventions and the various protocols did not modify, however, the actions of ANP infusions on catecholamine release and blood pressure in the conscious dogs of the control group (Table 3), thereby excluding nonspecific effects of time and of protocols as cause for the altered ANP actions in the experimental group (Figure 3).

Endocrine ANP Effects During the Development of Congestive Heart Failure

The decline in plasma renin activity and in epinephrine-spillover rate during ANP-induced hypotension in the dogs before ventricular pacing (Figure 3) is similar to previous observations in conscious healthy dogs. Inhibition of the sympathoadrenal system by ANP has been previously assumed from animal experiments that demonstrated little or no tachycardia during hypotension induced by pharmacologic doses of the hormone. Later, this inhibition was shown directly by measurements of catecholamine kinetics, by electrical recordings of postganglionic sympathetic activity, and by analyses of reflexes in humans. Actions of ANP on sensory cardiac nerve endings, on CNS structures outside the blood-brain barrier, and on catecholamine secreting cells in the adrenal medulla could have contributed. In the adrenal medulla, both membrane-binding sites for the hormone and synthesis of the prohormone have been documented.
Concomitant with the rise in plasma ANP levels during the onset of ventricular pacing, epinephrine spillover and plasma renin activity declined (Figure 2), similarly as during exogenous ANP infusions (Figure 3). Cardiopulmonary reflexes, triggered by the pacing-induced immediate rise in atrial pressures,14,31,32 probably contributed to these early changes. Obviously, this cardiopulmonary inhibition is not maintained with ongoing pacing (Table 2). The attenuation or disappearance of inhibitory cardiopulmonary reflexes in congestive heart failure is well established,7,33,34 although the data in our heart failure model (Figures 3 and 4) indicate that the sympathoadrenal inhibition by ANP is maintained. Alternative explanations for these observations in our model, however, should be considered, too. A short duration of the pacing-induced ANP elevation, too short for down-regulating the ANP responses of the sympathoadrenal system, should not play a role; the pacing period lasted long enough to abolish the systemic-hemodynamic ANP effect (Figures 3 and 5) and to depress renal vascular responsiveness to ANP.15 Furthermore, it appears unlikely that the large baseline changes of neuroendocrine parameters during chronic pacing (Table 2) would explain the increased ability of ANP to inhibit norepinephrine release or the reduced ability to inhibit renin activity. After 1 and 2 weeks of tachypacing, the basal norepinephrine-release rate in individual dogs varied 8.6–55.5 ng/kg/min and the basal renin activity varied 0.1–22.6 ng/ml/hr. Yet, none of the ANP–induced effects during this tachypacing period correlated significantly with basal renin activity or with the basal norepinephrine-release rate. Finally, the ANP–induced depression of epinephrine release under control conditions might be underestimated because of some sympathoadrenal activation, triggered by the 5% reduction in blood pressure during ANP infusion. Because epinephrine release in dogs is substantially less stimulated than norepinephrine release by moderate hypotension,4 the ANP effects on epinephrine release before and during pacing can be compared without bias by the differing ANP effects on pressure. On the other hand, the unchanged norepinephrine release under ANP–induced hypotension under control conditions indicates a relative sympathoinhibition,9 which appears “unmasked” by the lack of ANP effects on blood pressure in the chronically paced dogs (Figure 3).

Thus, our study demonstrates an attenuation of the vasodilator but a preservation of the sympathoadrenal inhibitory actions of ANP in this model of low-output congestive heart failure. This is a real shift within the broad spectrum of ANP actions.

Potential Clinical Implications

Such a change in ANP effects could have clinical relevance in several contexts, that is, in the regulation of sympathoadrenal activity during the development and progression of heart failure, in the application of sustained ANP infusions as therapy for cardiac unloading in the intensive care unit, and in the action of drugs designed to prolong the half-life of endogenous ANP by inhibiting ANP–degrading enzymes. A precondition for such potential clinical relevance of our findings is the existence of a comparable sympathoadrenal inhibition by ANP in humans.

ANP–induced attenuations of reflex vasoconstriction as well as of plasma renin activity have been documented in humans.25,26,35,36 Significant ANP–induced declines of plasma epinephrine have seldom been observed in humans37,38 probably because of the large scatter of plasma epinephrine levels and their large spontaneous fluctuations.36

Infusion of pharmacological doses of ANP in healthy humans generally induces elevation of plasma norepinephrine and other signs of sympathetich activation. Interestingly, however, in patients with heart failure, a significant decline in plasma norepinephrine concentration during infusion of high–ANP doses was shown recently.39 This is somewhat reminiscent of the unmasking of ANP–induced inhibition of norepinephrine spillover by prolonged pacing in our dogs (Figure 3). In the study of patients with heart failure,39 the high–ANP plasma levels achieved during the infusions still induced some vasodilation and cardiac unloading. The authors stress, however, that similar unloading by sodium nitroprusside in such patients does not lower plasma norepinephrine.39

These observations indicate that an ANP–induced sympathoadrenal inhibition in healthy humans and in patients with heart failure can occur. Compared with many other effects of ANP, the sympathoadrenal inhibition is rather poorly characterized so far but this does not necessarily reflect its biological relevance. The present study shows that the sympatho-inhibitory action of ANP persists, even when other ANP effects are attenuated. This means that the relative importance of the sympathoadrenal inhibitory effect of ANP actions may be increased during sustained augmentation of endogenous ANP levels as is seen in low-output congestive heart failure.

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References


**KEY WORDS** • nervous system, sympathetic • catecholamines • norepinephrine • epinephrine • atrial natriuretic peptide
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