Vagal Mediation of the Effects of Atrial Natriuretic Factor on Blood Pressure and Arterial Baroreflexes in the Rabbit

Massimo Volpe, Alberto Cuocolo, Filippo Vecchione, Alessandro F. Mele, Mario Condorelli, and Bruno Trimarco

We investigated the hemodynamic effect of synthetic atrial natriuretic factor Auriculin A (ANF) and its influence on arterial baroreflex control of heart rate, systemic blood pressure, and perfusion pressure in the hind limb (perfused at constant flow) in rabbits anesthetized with α-chloralose and urethane. The neural mechanisms underlying these effects were also studied. In the intact animal, a 45-minute constant infusion of ANF (2 μg/kg prime, 0.2 μg/kg/min) significantly reduced mean blood pressure and increased mean perfusion pressure, while heart rate did not change. Comparable data were obtained with lower (0.5 μg/kg + 0.05 μg/kg/min; 1 μg/kg + 0.1 μg/kg/min) or higher (4 μg/kg + 0.4 μg/kg/min; 8 μg/kg + 0.8 μg/kg/min) doses of ANF. In addition, ANF enhanced bradycardic reflex responses to phenylephrine i.v. bolus administration, while it did not change baroreflex-mediated responses to nitroglycerin i.v. bolus administration and to 30-second bilateral carotid occlusion. The specificity of the influence of ANF on arterial baroreflex responses was confirmed by the observation that no significant change in reflex responses to phenylephrine or carotid occlusion was detectable during a comparable decrease in blood pressure induced by a constant infusion of nitroglycerin. Bilateral vagotomy prevented both the fall in blood pressure and the increase in perfusion pressure induced by ANF, while cholinergic blockade (atropine, 0.5 mg/kg i.v.) or adrenergic blockade (propranolol, 0.3 mg/kg i.v. + phentolamine, 0.3 mg/kg i.v.) did not modify the hemodynamic response to ANF observed in the intact animal. The ANF-induced enhancement of the reflex bradycardic response to phenylephrine-induced rise in blood pressure was prevented by both vagotomy and atropine. In conclusion, our data suggest that in this experimental model an increase in parasympathetic tone is involved in the blood pressure lowering effect of synthetic ANF as well as in the potentiation of the reflex bradycardic response to phenylephrine-induced arterial baroreceptor loading caused by the peptide. (Circulation Research 1987;60:747–755)

In their initial studies on atrial natriuretic factor (ANF), de Bold and coworkers observed that, in addition to the characteristic natriuretic effect, the injection of atrial extracts in rats induced a slight but consistent reduction in blood pressure. This effect was later confirmed with synthetic ANF peptides in both conscious and anesthetized normotensive and hypertensive animals and in man.

The blood pressure lowering effect of ANF was originally attributed to its vasodilator properties, but recent studies seem to indicate that more complex hemodynamic mechanisms are involved in the response to ANF administration. In particular, it has been reported that bolus or sustained infusion of ANF can lower cardiac output. The intrinsic mechanisms that lead to a reduction in cardiac output in response to ANF have not yet been defined. In this regard, Ackermann et al. showed that the hypotensive effect induced by the administration of crude atrial extracts in rats is mediated by a failure of cardiac output to increase in compensation for peripheral vasodilation and is attenuated by vagotomy, thus suggesting that vagal stimulation partially mediates the blood pressure reduction caused by atrial extract. The observation that the expected reflex tachycardia does not occur during the ANF-induced hypotension further supports the possibility of a vagomimetic effect of the peptide or of an interference with arterial baroreflexes. In fact, a direct interaction of atrial peptides with baroreflex control of circulation has been suggested by Imazumi et al. who showed that in the rat the administration of atrial peptides resets arterial baroreflex control of lumbar sympathetic nerve activity. However, no conclusive evidence for participation of the autonomic nervous system in the hemodynamic effect of synthetic ANF has been provided.

The purpose of the present study was to investigate whether neural mechanisms are involved in the mediation of the hemodynamic response to sustained infusion of synthetic ANF and to determine the influence of ANF on arterial baroreflexes in the anesthetized rabbit.

Materials and Methods

General Procedures

New Zealand white male rabbits, weighing 3–3.5 kg, were anesthetized with α-chloralose (50 mg/kg)
and urethane (500 mg/kg) i.v. Supplemental doses of α-chloralose were given as needed during the study. The animals were placed on a warming blanket to maintain their body temperature at 37° C, and temperature probes were inserted in their rectums throughout the experiment. After tracheal intubation, the animals were artificially ventilated with a mixture of O2 and room air. The arterial blood gases and pH were monitored periodically and, when necessary, were corrected by adjusting respiratory frequency. The Pco2 was maintained at 25–35 mm Hg and pH at 7.34–7.43.

A midline cervical incision was performed to expose the vagosympathetic trunks and carotid arteries bilaterally. The common carotid arteries were separated from the vagosympathetic trunks so as not to damage the nerve. A loose ligature was placed around the carotid arteries and the 2 ends of the ligature were passed through a plastic sleeve so that the arteries could be reversibly occluded.

Arterial blood pressure was monitored continuously through a catheter placed in the thoracic aorta via the femoral artery. Another catheter was positioned in the inferior vena cava and used for drug injection. A Harvard multichannel polygraph and Statham P23Db transducers were used to measure blood pressure. Heart rate was recorded with a Harvard cardiotachometer triggered by the arterial pressure pulse. The effects of drugs and the reflex control of vascular resistance were assessed in the isolated hind limb perfused at constant flow. In brief, the abdomen was opened in the midline, and the iliac artery was ligated. Sodium heparin (500 U/kg i.v.) was given to the animal and supplemental doses of heparin were given hourly. The femoral artery then was cannulated and perfused using a Harvard peristaltic pump with blood of the same animal obtained through a catheter introduced via the iliac artery and positioned in the abdominal aorta below the renal arteries. In this condition, changes in vascular tone of the perfused district are reflected by proportional changes in perfusion pressure. Blood flow rate was adjusted to give perfusion pressure values slightly higher than systemic blood pressure to compensate for the resistance of the tubing system. The blood flow rate was left unchanged throughout the experiment. Collateral circulation to the perfused hind limb was minimized by ligating vessels in the lower abdomen, and a perfusion pressure of less than 15 mm Hg with the extracorporeal circuit occluded was taken to indicate insignificant collateral circulation. Perfusion pressure was measured through a T-connection of the outflow side of the perfusion circuit as close as possible to the perfused hind limb.

**Experimental Protocol**

The protocols were begun 30–60 minutes after completion of surgery. After baseline measurements of blood pressure (BP), heart rate (HR), and hind limb perfusion pressure (PP) were obtained, hemodynamic reflex responses to 30-second bilateral carotid occlusion to phenylephrine (PE) (2 μg/kg i.v.) and nitroglycerin (NG) (4 μg/kg i.v.) bolus administration were recorded. The stimuli were performed in random sequence in the different experiments and separated by at least 5 minutes. After a new baseline was recorded, ANF was administered as a 2 μg/kg bolus followed by a constant infusion of 0.2 μg/kg/min (n = 15) for 45 minutes. BP, HR, and PP were monitored continuously during the ANF infusion and the responses to 30-second carotid occlusion, PE, and NG bolus injections were evaluated again between 30 and 45 minutes from the beginning of infusion. A 30-minute recovery period was also monitored.

In these animals the same protocol was repeated after bilateral vagotomy (n = 9) or after cholinergic receptor blockade induced by the administration of atropine (0.5 mg/kg i.v.) (n = 6).

In another group of animals the effects of 4 different dosages of ANF (0.5 μg/kg bolus + 0.05 μg/kg/min, n = 5; 1 μg/kg + 0.1 μg/kg/min, n = 5; 4 μg/kg + 0.4 μg/kg/min, n = 5; 8 μg/kg + 0.8 μg/kg/min, n = 5) on BP, HR, and PP and on the reflex responses to 30-second carotid occlusion, i.v. PE and NG bolus injections were evaluated. No more than 2 individual doses were administered in each animal.

To assess the specificity of the response to ANF, hemodynamic and reflex responses to carotid occlusion and i.v. bolus PE were evaluated in another group of 5 animals before and during a 45-minute infusion of NG at a dose of 3–5 μg/kg/min. This dosage had previously been shown to produce a fall in BP comparable to that induced by ANF.

The effects of sympathetic receptor blockade (propranolol 0.3 mg/kg i.v. + phentolamine 0.3 mg/kg i.v.) on hemodynamic responses to ANF were evaluated in the animals receiving the lowest dose of ANF (0.5 μg/kg + 0.05 μg/kg/min) since sympathetic blockade per se induced a remarkable fall in BP.

The effectiveness of cholinergic or sympathetic blockade was confirmed by the absence of any detectable hemodynamic response to i.v. bolus administration of acetylcholine (5 μg) or phenylephrine (8 μg), respectively.

The possibility that time-dependent changes in hemodynamic and reflex responses could occur during the study was ruled out in 4 pilot experiments showing that the adopted protocol provided stability of BP, HR, and PP during a 3-hour observation period. In these same experiments, the reflex responses to PE, NG, and carotid occlusion were quite comparable at the beginning and at the end of the observation period (data not shown).

**Materials**

The synthetic ANF used for this study was the 24-amino acid residue atrial natriuretic peptide Auriculin A (MW 2543), based on the sequence isolated by Atlas et al20 in rat atria and obtained from Peninsula Labs., Europe Ltd (St. Helens Merseyside, England). This peptide is substantially equipotent in terms of natriuretic and vasorelaxant properties to the other related atrial natriuretic peptides.21,22 The peptide was dissolved in saline immediately prior to use, and the
natriuretic activity was previously tested in intact animals.

Analysis of the Data

The average of seven measurements of BP, HR, and PP obtained during each experimental phase (baseline, 5, 15, and 30 minutes of the infusion and 30 minutes recovery) was used for the analysis of the hemodynamic responses to ANF or NG infusion. Significance of the responses to ANF within each group was evaluated by two-way analysis of variance (ANOVA) and a posteriori comparisons of the means were performed by Dunnett's t test. Simultaneous multiple comparisons between groups were made, following ANOVA, by the Duncan test.

To analyze the reflex responses to PE and NG i.v. bolus injections, each R-R interval and the corresponding preceding value of systolic BP, beginning with the rise or the decrease in BP, were measured at a paper speed of 50 mm/sec. The individual slopes of the regression lines obtained by plotting each R-R interval value vs. the preceding systolic BP value were calculated. The correlation coefficient achieved significance in all cases. The comparison between the slopes obtained before and during ANF infusion was performed by paired t test. A more detailed analysis of the reflex chronotropic responses evoked by changing systemic blood pressure with PE or NG was also performed by comparing the changes in heart period (HP) produced by 4 graded arterial pressure increases (ranging +10– +25 mm Hg) above the baseline (preinjection) and by 4 arterial pressure decreases (ranging −10 to −25 mm Hg) below the baseline. The values of HP change obtained at each level of BP in control conditions were compared with the corresponding values obtained during ANF infusion by paired t test.

To evaluate the baroreflex responsiveness before and during NG infusion, the response of carotid baroreceptors to 30-second carotid occlusion and the reflex response to bolus i.v. PE (2 µg/kg) were studied. To analyze this latter response, the slopes of the reflex responses obtained before and during NG infusion were compared to paired t test. Results are means ± SEM.

Results

Figure 1 shows the time course of mean blood pressure (MBP), mean hind limb perfusion pressure (MPP), and heart rate (HR) responses to a 30-minute constant infusion of ANF (2 µg/kg prime followed by 0.2 µg/kg/min) (n = 15). ANOVA showed that ANF infusion significantly modified MBP (F = 28.5, p < 0.01) and MPP (F = 12.7, p < 0.01) but not HR. A

![Figure 1](http://circres.ahajournals.org)
significant fall in MBP ($p<0.01$) and an increase in MPP ($p<0.05$) were observed after 5 minutes and were sustained throughout the infusion of ANF. Both parameters returned to baseline after 30 minutes of recovery.

Dose–response experiments with 5 graded doses of ANF (from 0.5 µg/kg prime + 0.05 µg/kg/min to 8 µg/kg prime + 0.8 µg/kg/min) (see “Materials and Methods”) showed that the lowest dose of ANF was already able to significantly reduce MBP. In Table 1, the steady-state changes in MBP, MPP, and HR induced by the different doses of ANF are compared. With the lower 3 doses of ANF, a progressive, albeit not significant, increase in the BP lowering effect of ANF was observed, and a maximal depressor response was achieved with the intermediate dose of ANF (2 µg/kg + 0.2 µg/kg/min). No significant difference in the MPP and HR responses to the graded doses of ANF could be observed.

The effects of bilateral vagotomy, cholinergic blockade (i.v. atropine), and sympathetic blockade (i.v. propranolol + phentolamine) on the time-course of systemic and hind limb PP responses to ANF are shown in Figure 2. The decrease in MBP induced by ANF infusion in control conditions ($n = 9$) ($F = 21.5$, $p<0.01$) was completely prevented by vagotomy ($F = 0.9$, NS). In contrast, after treatment of the animal either with atropine ($n = 6$) or with propranolol plus phentolamine ($n = 5$), the systemic depressor responses induced by ANF were similar to those observed in the corresponding control group. In particular, the ANOVA constantly showed significant changes in MBP during the time-course of the experiment in these groups ($F = 10.1$, $p<0.01$ before and $F = 7.1$, $p<0.05$ after atropine; $F = 5.6$, $p<0.05$ before and $F = 5.5$, $p<0.05$ after sympathetic blockade), and the fall in MBP was statistically significant at each time point (Figure 2). BP always tended to recover after the infusion was stopped.

Direct comparisons of the MBP steady-state responses obtained in control conditions and after the different treatments are shown in Figure 3. Also with this analysis, the depressor response to ANF was significantly reduced only by vagotomy, while cholinergic or sympathetic blockade did not modify the responses to ANF observed in control conditions.

With regard to MPP, the significant increase observed during ANF infusion in control conditions was prevented by vagotomy and not by atropine administration ($F = 9.5$, $p<0.01$ before and $F = 1.8$, NS after vagotomy; $F = 10.2$, $p<0.01$ before and $F = 5.8$, $p<0.05$ after atropine) (Figure 2). No significant change in MPP was caused by ANF in the animals infused with the lowest dose of the peptide (0.5 µg/kg + 0.05 µg/kg/min) either before or after sympathetic blockade (Figure 2). However, it must be pointed out that in this group of animals the lowest dose of ANF was chosen for the infusion in order to minimize the possibility of an excessive fall in BP, as it could be provoked by the administration of propranolol plus phentolamine associated with a larger amount of ANF. The infusion of a lower dose of ANF could thus ac-

![Figure 2](http://circres.ahajournals.org/)

**FIGURE 2.** Time course of effects of ANF infusion on blood pressure and on hind limb perfusion pressure in control conditions and after bilateral vagotomy, atropine, and combined administration of propranolol and phentolamine. Abbreviations and analysis as in Figure 1.
count for the lack of an increase in MPP, as observed in the other groups of animals. A tendency for MPP to decrease was observed during ANF infusion after sympathectomy. Actually, the direct comparison of the changes in MPP observed at the steady-state of ANF infusion before and after sympathetic blockade showed a statistically significant difference (Figure 3).

HR was not significantly modified by ANF infusion in any of the groups either before or after the different treatments. Vagotomy and atropine induced only a slight increase in control HR (255 ± 7 to 258 ± 7 b/min, NS, and 247 ± 6 to 250 ± 7 b/min, NS, respectively), while pretreatment with propranolol and phentolamine significantly reduced control HR (256 ± 9 to 179 ± 8 b/min, p<0.01).

The analysis of the effects of ANF infusion on baroreflex control of HR showed that the peptide administration resulted in substantial enhancement of HP increases when systemic BP was raised by PE. In fact, the slope of the HP/BP regression line obtained with PE was significantly increased during ANF infusion (baseline: 0.99 ± 0.17 msec/mm Hg; ANF: 1.4 ± 0.2 msec/mm Hg; p<0.05). In contrast, no significant difference was found between the HP reflex responses at any level of NG-induced hypotension before and during ANF infusion. These latter results are graphically represented in Figure 4, which shows the HP responses to changes in systolic BP induced by i.v. bolus administration of NG and PE in control conditions and during the steady-state phase of the infusion with ANF.

All the tested dosages of ANF were able to induce significant enhancement of the baroreflex mediated bradycardic responses to PE-induced increases in BP; the percent increases in the slope of the baroreflex responses to PE obtained with the different doses of the peptide were quite comparable (+20 ± 9, +23 ± 9, +27 ± 11, +24 ± 8, and +24 ± 8%, doubling progressively the dosage of ANF from 0.5 µg/kg + 0.05 µg/kg/min to 8 µg/kg + 0.8 µg/kg/min). No change in the reflex tachycardic response to NG was induced by the different doses of ANF (data not shown).

Vagotomy abolished the ANF-induced enhancement of the baroreflex bradycardic response. In fact, the slope of the HP/BP regression line, which was 1.02 ± 0.2 msec/mm Hg in the vagotomized animals, was not raised during ANF infusion (0.98 ± 0.2 msec/mm Hg, NS). In addition, no significant difference between the corresponding HP reflex responses to

---

**Figure 3.** Steady-state blood pressure and hind limb perfusion pressure responses (% changes = %Δ) to ANF obtained in control conditions and after vagotomy, atropine, or propranolol plus phentolamine. Abbreviations as in Figure 1. Analysis was performed by Duncan test. *p<0.05, **p<0.01.
changes in BP obtained before and during ANF infusion were detectable (Table 2). Also the pretreatment with atropine was able to prevent the statistically significant increase of the baroreflex bradycardic response caused by ANF (baseline slope: 1.22 ± 0.2 msec/mm Hg; ANF slope: 1.52 ± 0.7 msec/mm Hg; NS). However, with this latter treatment, for each level of BP change the chronotropic responses obtained during the ANF infusion were slightly greater than those obtained in control conditions (Table 2). No significant difference was found when the control reflex responses obtained before and after vagotomy or atropine were compared.

Table 3 shows the hemodynamic reflex responses to 30-second carotid occlusion. In control conditions, this maneuver evoked a significant increase in MBP and slight but consistent increases in HR and MPP. During ANF infusion, the reflex responses induced by carotid occlusion were comparable to those observed in control conditions. Neither vagotomy nor atropine significantly modified the reflex responses to carotid occlusion either in control conditions or during ANF infusion (Table 3).

To test the specificity of the response to ANF, the effects of a 30-minute infusion of NG, at a dose (3–5 μg/kg/min) that induced a fall in BP comparable to that provoked by ANF (~24%), were investigated. As shown in Table 4, NG infusion induced a fall in BP and reflex increases in HR and PP. All these parameters returned to baseline after 30 minutes of recovery. During NG infusion, however, the reflex responses to loading or unloading the arterial baroreceptors, as evaluated by hemodynamic responses to PE i.v. bolus injection or by 30-second carotid occlusion, respectively, were not statistically different from those observed in control conditions or in the recovery period.

**Discussion**

In the present study, the hemodynamic effects and the interactions of ANF with the baroreflex control of cardiac interval and arterial blood pressure were examined before and after blockade of the different limbs of the autonomic nervous system. We found that in the anesthetized rabbit: 1) the BP lowering effect of synthetic ANF sustained infusion can be prevented by bilateral vagotomy and not by atropine or by sympathetic receptor blockade; 2) ANF infusion results in enhanced baroreflex-mediated bradycardia, and this effect is prevented by both vagotomy and atropine; and 3) baroreflex-mediated tachycardia in response to NG bolus administration or baroreflex vasoconstriction and tachycardia in response to bilateral reversible carotid occlusion are not modified by ANF. These data suggest that synthetic ANF sensitizes vagal afferents and that it exerts a selective influence on baroreflex responses to hypertensive stimuli. Vagus-mediated responses are enhanced, while sympathetic responses are not directly affected by ANF.

The hemodynamic responses to synthetic ANF infusion observed in our study are consistent with previous reports. In particular, the infusion of the intermediate dose of ANF (2 μg/kg prime, 0.2 μg/kg/min) induced a prompt and sustained fall in BP. Hind limb PP rose slightly during the course of the infusion, while no tachycardia was associated with the decrease in BP.

Although the dose-response experiments showed that the progressive increase in the dose of the peptide administered did not significantly change the BP response, more profound reductions in BP were achieved with the highest 3 doses. Hind limb PP was not significantly affected by the 2 lowest doses of ANF.
Volpe et al. ANF, Blood Pressure, and Arterial Baroreflexes

Table 2. Chronotropic Reflex Responses (ΔAHP) to Changes in Systemic Blood Pressure (ΔSBP) Induced by Phenylephrine and Nitroglycerine

<table>
<thead>
<tr>
<th>ΔSBP (mm Hg)</th>
<th>ΔAHP (msec)</th>
<th>p</th>
<th>ΔAHP (msec)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>ANF</td>
<td>Control</td>
<td>ANF</td>
</tr>
<tr>
<td>NG: -25</td>
<td>-9.8 ± 3</td>
<td>NS</td>
<td>-32 ± 6</td>
<td>NS</td>
</tr>
<tr>
<td>-20</td>
<td>-8.4 ± 2</td>
<td>NS</td>
<td>-24 ± 4</td>
<td>NS</td>
</tr>
<tr>
<td>-15</td>
<td>-5.6 ± 2</td>
<td>NS</td>
<td>-22 ± 5</td>
<td>NS</td>
</tr>
<tr>
<td>-10</td>
<td>-5.2 ± 2</td>
<td>NS</td>
<td>-16 ± 4</td>
<td>NS</td>
</tr>
<tr>
<td>PE: +10</td>
<td>+8.3 ± 3</td>
<td>NS</td>
<td>+16 ± 5</td>
<td>NS</td>
</tr>
<tr>
<td>+15</td>
<td>+11.7 ± 4</td>
<td>NS</td>
<td>+20 ± 4</td>
<td>NS</td>
</tr>
<tr>
<td>+20</td>
<td>+9.2 ± 3</td>
<td>NS</td>
<td>+24 ± 2</td>
<td>NS</td>
</tr>
</tbody>
</table>

Dosages: Phenylephrine (PE) 2 μg/kg, and nitroglycerin (NG) 4 μg/kg, both i.v. bolus administration in vagotomized (n = 9) and in atropine-pretreated animals (n = 6) before and during ANF infusion (2 μg/kg + 0.2 μg/kg/min). Data were compared by paired t test.

The observation that bilateral vagotomy is able to prevent the fall in BP induced by ANF and the concurrent reflex vasoconstriction, while atropine and sympathetic receptor blockade are not, supports the hypothesis of Ackermann et al.17 that ANF lowers BP mainly through a reflex effect of direct stimulation of cardiopulmonary receptors with vagal afferents. These authors postulated such an effect to explain the cardiovascular response to atrial extracts. The observation in our experiments that HR is not modified by ANF and that there is no significant change in right atrial pressure during ANF infusion as was previously found4 seems to suggest that a negative inotropic effect caused by ANF-induced vagal stimulation might be responsible for the reduction in cardiac output. In this regard, vagal stimulation is known to depress ventricular contractility in several species.25-27 Furthermore, Barron and Bishop28 suggested that vagal afferents attenuate the positive inotropic effects of catecholamines via a cardiocardiac negative feedback reflex, which occurs through a vagal afferent inhibition on sympathetic efferent activity back to the left ventricle. The efferent mechanism of the postulated negative inotropic effect of ANF might be the withdrawal of sympathetic tone. However, in our study adrenergic receptor blockade did not modify the ANF-induced fall in BP. Although this finding might appear in contrast with the former hypothesis, it cannot be excluded that after sympathetic blockade other effects of the peptide might have

Table 3. Changes (Δ) in Mean Blood Pressure, Heart Rate, and Hind Limb Mean Perfusion Pressure

<table>
<thead>
<tr>
<th>ΔMBP (mm Hg)</th>
<th>Control</th>
<th>ANF</th>
<th>ΔMBP (mm Hg)</th>
<th>Control</th>
<th>ANF</th>
</tr>
</thead>
<tbody>
<tr>
<td>C</td>
<td>15.8 ± 3</td>
<td>16.2 ± 4</td>
<td>14.0 ± 3</td>
<td>6.3 ± 1.5</td>
<td></td>
</tr>
<tr>
<td>V</td>
<td>20.6 ± 4</td>
<td>29.6 ± 0</td>
<td>8.3 ± 2.2</td>
<td>8.5 ± 3.1</td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>15 ± 4</td>
<td>16.5 ± 6</td>
<td>4 ± 0.3</td>
<td>3.8 ± 1.5</td>
<td></td>
</tr>
</tbody>
</table>

Changes were induced by 30-second carotid occlusion before and during ANF infusion (2 μg/kg + 0.2 μg/kg/min). C, intact animal (n = 23); V, after vagotomy (n = 9); and A, after atropine (n = 6).
Therefore, it might be concluded that the reflex re-
lar resistance induced by transient carotid occlusion.
and on the reflex increase in HR and peripheral vascu-
tachycardia in response to NG-induced hypotension
and on the ANF-mediated potentiation of reflex brady-
icardia.

Our data demonstrate that the infusion of ANF poten-
tiates baroreflex-mediated bradycardia in response to
PE-induced rise in BP. Both vagotomy and atropine were
eable to prevent the facilitating effect of ANF on
reflex bradycardic response, thus suggesting that a
agal stimulation by ANF is involved in this phenom-
enon. In fact, after atropine, the ANF-induced en-
acement, with enhanced baroreflex mediated bradycardia
and no effect on reflex tachycardia, has been observed
also with captopril by Ebert.31 This author suggested that
captopril potentiates reflex-mediated bradycardia
via a reduction in central nervous system angiotensin II
levels, which augments vagal responses to carotid bar-
receptor stimuli. Since ANF has been reported to
agonize some of the vascular, 16 adrenal 43234 and
central nervous system35 effects of angiotensin II, it
also seems possible that the ANF-induced enhance-
ment in vagal tone might somehow be related to func-
tional antagonism of angiotensin II central effects.

The potentiation of chronotropic baroreflex re-
ponses to hypertensive stimuli by ANF may represent a
contributory antihypertensive effect of the peptide.
ANF-induced hypotension has been reported to be
more marked in anesthetized or in hypertensive ani-
mals as well as in sinoaortic deafferentated rats,7936
thus suggesting that baroreflexes play an unusually
more marked role in minimizing the ANF depressor effect in
the intact animal and, therefore, that the role of ANF in
the control of BP could be especially prominent when
arterial baroreflexes are impaired.

Although the role of ANF as a hormone involved in
the homeostatic control of BP and extracellular volume
has not yet been defined, the present data might sup-
port the hypothesis that these peptides play a physio-
logic role in the regulation of BP.

Table 4. Steady-State Effects of Nitroglycerin* Infusion

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>NG</th>
<th>Recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td>MBP (mm Hg)</td>
<td>96 ± 13</td>
<td>73 ± 10*</td>
<td>94 ± 12</td>
</tr>
<tr>
<td>HR (b/min)</td>
<td>263 ± 15</td>
<td>269 ± 14†</td>
<td>265 ± 14</td>
</tr>
<tr>
<td>MPP (mm Hg)</td>
<td>98 ± 9</td>
<td>104 ± 9†</td>
<td>99 ± 8</td>
</tr>
</tbody>
</table>

Responses evoked by:

<table>
<thead>
<tr>
<th>Phenylephrine HR/BP slope (msec/mm Hg)</th>
<th>2.3 ± 0.5</th>
<th>2.0 ± 0.8</th>
<th>2.1 ± 0.4</th>
</tr>
</thead>
<tbody>
<tr>
<td>30-second carotid occlusion AMBP</td>
<td>26 ± 6</td>
<td>17 ± 5</td>
<td>26 ± 6</td>
</tr>
</tbody>
</table>
| ANF infusion had no effect on baroreflex-mediated tachycardia in response to NG-induced hypotension and on the reflex increase in HR and peripheral vascular resistance induced by transient carotid occlusion. Therefore, it might be concluded that the reflex re-
ponses characterized by a prominent sympathetic participation are not affected by ANF. This is confirmed by the observation that the ANF-induced fall in BP is associated with a marked peripheral vasoconstriction, which is possibly reflex in nature, as discussed before.

The specificity of the effects of ANF on arterial baroreflex responses was confirmed in our study by 1) the reproducibility of the reflex responses in the time-control experiments; 2) the reproducibility of the effect on baroreflexes also with the lower dosage of ANF; and 3) the observation that the reflex responses evoked by PE and by carotid occlusion did not differ in control conditions and during a sustained reduction in systemic pressure, comparable in magnitude to that caused by ANF, induced through the infusion of NG, a known generic vasodilator.

An asymmetrical effect on arterial baroreflex function, with enhanced baroreflex mediated bradycardia and no effect on reflex tachycardia, has been observed also with captopril by Ebert.31 This author suggested that captopril potentiates reflex-mediated bradycardia via a reduction in central nervous system angiotensin II levels, which augments vagal responses to carotid bar-
receptor stimuli. Since ANF has been reported to
agonize some of the vascular, 16 adrenal 43234 and
central nervous system35 effects of angiotensin II, it
also seems possible that the ANF-induced enhance-
ment in vagal tone might somehow be related to func-
tional antagonism of angiotensin II central effects.

The potentiation of chronotropic baroreflex re-
ponses to hypertensive stimuli by ANF may represent a
contributory antihypertensive effect of the peptide.
ANF-induced hypotension has been reported to be
more marked in anesthetized or in hypertensive ani-
mals as well as in sinoaortic deafferentated rats,7936
thus suggesting that baroreflexes play an unusually
more marked role in minimizing the ANF depressor effect in
the intact animal and, therefore, that the role of ANF in
the control of BP could be especially prominent when
arterial baroreflexes are impaired.

Although the role of ANF as a hormone involved in
the homeostatic control of BP and extracellular volume
has not yet been defined, the present data might sup-
port the hypothesis that these peptides play a physio-
logic role in the regulation of BP.

References


**Key Words** • atrial natriuretic factor • arterial baroreceptors • blood pressure • vagal afferents • angiotensin II • adrenergic blockade.
Vagal mediation of the effects of atrial natriuretic factor on blood pressure and arterial baroreflexes in the rabbit.

M Volpe, A Cuocolo, F Vecchione, A F Mele, M Condorelli and B Trimarco

Circ Res. 1987;60:747-755
doi: 10.1161/01.RES.60.5.747

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1987 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/60/5/747

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation Research can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation Research is online at:
http://circres.ahajournals.org/subscriptions/