Effects of Atrial Natriuretic Peptide on Left Ventricular Function in Hypertension

Marc J. Semigran, Constantine N. Aroney, Howard C. Herrmann, G. William Dec, Charles A. Boucher, Michael A. Fifer

Abstract  Atrial natriuretic peptide (ANP) has natriuretic and vasodilator actions that lower arterial pressure and may be beneficial to hypertensive patients. To assess the effects of ANP on left ventricular function in patients with hypertension, we compared it with the pure vasodilator nitroprusside. Simultaneous left ventricular micromanometer pressure and radionuclide volume were obtained at baseline, during nitroprusside infusion, during a second baseline period, and during ANP infusion in 10 patients with hypertension. Mean arterial pressure fell during ANP and nitroprusside. Heart rate and plasma norepinephrine levels increased by similar amounts during the two agents, whereas cardiac index and stroke volume index were unchanged during both. Peak positive left ventricular dP/dt at a developed pressure of 40 mm Hg, a less load-dependent index of contractility, was unchanged during both. The relation between end-systolic pressure and volume during ANP infusion was not shifted leftward or rightward from that during nitroprusside infusion, indicating no inotropic effect. Both ANP and nitroprusside shortened the time constant of isovolumic relaxation calculated by the logarithmic method but did not change the time constant calculated by the derivative method. Peak filling rate was unchanged from baseline during both agents. ANP did not shift the end-diastolic pressure-volume point away from the relation constructed from baseline and nitroprusside points. We conclude that ANP has no direct effect on myocardial contractile or diastolic function in patients with hypertension. (Hypertension. 1994;24:271-279.)

Key Words  • atrial natriuretic peptide • ventricular function • hypertension, systemic

Patients with systemic hypertension have several physiological abnormalities, including a delayed ability to excrete a sodium load and an increase in systemic vascular resistance (SVR). Atrial natriuretic peptide (ANP) is a 28-amino acid polypeptide that has natriuretic, diuretic, and vasodilator actions and suppresses renin and aldosterone release in healthy humans. Since these actions should lower blood pressure and directly antagonize some of the abnormalities observed in patients with hypertension, ANP may have a role in the treatment of this disorder.

Previous studies of ANP administration in animal models of hypertension have shown that the hypotensive effect of ANP is associated with a reduction in cardiac output. Administration of ANP to humans with hypertension produced a fall in mean arterial pressure (MAP) accompanied by a decline in stroke volume index (SVI) and no change in SVR. The decrease in SVI could be accounted for by a decrease in venous return associated with a decrease in intravascular volume produced by ANP, by an impairment of myocardial contractile performance, or by a combination of these factors.

In studies of the intact circulation, it is difficult to isolate the inotropic effect of an agent such as ANP that alters preload, afterload, or both because most measures of systolic function are influenced by loading conditions. The end-systolic pressure-volume relation is a relatively load-independent measure of left ventricular (LV) contractile function. The inotropic effect of an agent can be assessed by comparison of the relation between end-systolic pressure and volume during infusion of the agent with that during infusion of a vasodilator such as nitroprusside. Similarly, indexes of diastolic function are affected by loading conditions as well as by intrinsic properties of the myocardium. The direct action of an agent on myocardial diastolic properties may also be inferred from a comparison of its effect with that of nitroprusside.

Therefore, to determine whether ANP has direct effects on myocardial contractile and diastolic function in patients with chronic hypertension, we compared the actions of ANP and nitroprusside in 10 hypertensive patients during right and left heart catheterization.

Methods

Patients

The study population consisted of 8 men and 2 women, aged 50±3 (mean±SEM) years, with chronic systemic arterial hypertension (Table 1). Table 1 shows the cause and duration of hypertension as well as blood pressure on admission to the hospital. Patients 4, 6, 7, 8, and 10 had undergone cardiac transplantation 26±3 months before study and were histologically free of rejection at the time of study. Chronic renal failure was present in several patients (Table 1), but no patient had electrocardiographic or echocardiographic evidence of LV hypertrophy. The duration of hypertension was 1.8±0.5 years in the transplant recipients (excluding a pretransplant history of essential hypertension in patient 6) and 8.0±1.7 years in the other patients.

Antihypertensive therapy consisted of diuretics in 3 patients (patients 2, 6, and 7) and calcium channel antagonists in 5
Hemodynamic Measurements

Diuretics and calcium channel antagonists were discontinued 12 to 24 hours before study. Diphenhydramine premedication was given. Right ventricular catheterization was performed from the internal jugular approach with a triple-lumen balloon-tipped thermodilution catheter. Left ventricular catheterization was performed via the femoral approach with a micromanometer-tipped catheter (Millar Instruments) in 9 patients and a fluid-filled catheter in 1 patient.

The following hemodynamic variables were recorded: heart rate (HR), right atrial pressure (RAP), pulmonary arterial pressure (PAP), pulmonary capillary wedge pressure (PCWP), LV pressure, systemic arterial pressure, and, in 9 patients, LV dP/dt (by electronic differentiation). LV dP/dt was not recorded in the patient with the fluid-filled catheter. Cardiac output (CO) was determined by the thermodilution technique. Calculations of stroke volume (SVI), and stroke work index (SWI) were made using the following formulas: CI (L • min • m⁻²)=CO/body surface area; SVI (mL • m⁻²)=CI/HR; SWI (g • m • M⁻²)=(0.0186)(MAP−LV end-diasstolic pressure)/SVI; SVR (dyne • s • cm⁻⁵)=80(MAP−RAP)/CO; and PVR (dyne • s • cm⁻⁵)=80(mean PAP−PCWP)/CO.

The logarithmic time constant of LV isovolumic relaxation (Tᵣᵣ) was calculated from micromterometer LV pressure by the method of Weiss et al. The period of isovolumic relaxation was taken to be from aortic diastolic notch pressure to the pressure corresponding to the peak of the v wave of the simultaneous pulmonary capillary wedge tracing. Tᵣᵣ was defined as the negative reciprocal of the slope of the linear fit of ln(LV pressure) versus time. The derivative time constant, Tᵣᵣ, was calculated by the method of Raff and Glantz during the same time interval as Tᵣᵣ from the negative reciprocal of the slope of a linear fit of LV dP/dt versus pressure.

Hemodynamic data were obtained during a baseline period, during nitroprusside infusion, during a second baseline period, and during ANP infusion. Nitroprusside was infused initially at 25 μg • min⁻¹ and titrated upward to achieve a 15 to 20 mm Hg decrease in MAP. Measurements on nitroprusside were made 5 minutes after the desired hemodynamic effect was achieved, and second baseline measurements were made 10 minutes after nitroprusside was discontinued, when hemodynamic parameters matched those in the first baseline period. Anaritide (Wyeth-Ayerst Laboratories) is a synthetic 25-amino acid peptide (human ANP 102-126) that lacks three amino acids from the amino terminus of human ANP and has similar biological activity. The ANP infusion was titrated to achieve either a similar decrement in MAP to that achieved during the nitroprusside infusion or a maximal rate of 0.6 μg • kg⁻¹ • min⁻¹. Measurements were made at least 10 minutes after the final infusion rate of ANP was begun.

Radionuclide Scanning

LV volume was calculated from gated blood pool images in 9 patients as previously described. Images were not recorded in 1 patient (patient 5) because of a technical error. After in vivo labeling of patients' red blood cells with stannous pyrophosphate and 30 mCi of technetium-99m, supine gated blood pool images were acquired in the anterior and left anterior oblique views. The timing of the first frame of the scan corresponded to the peak of the R wave of the electrocardiogram, which was recorded simultaneously on the pressure tracings. The acquisitions were then normalized to the frame with the maximal number of counts. A time-activity curve was constructed using a semiautomated edge detection method with a variable region of interest. Background counts were calculated from an area of the frame adjacent to the left ventricle and were subtracted from each frame. Counts were smoothed using a three-point weighted moving average (coefficients: 0.25, 0.50, 0.25). Ejection fraction was calculated as stroke counts/end-diastolic counts.

Baseline LV end-diastolic volume was calculated from the anterior and left anterior oblique views using a previously validated geometric biplane area-length method. Volumes at other points in the cardiac cycle and during subsequent scans were calculated from the left anterior oblique scan as the ratio of counts in a given frame to those in the baseline end-diastolic frame multiplied by the baseline end-diastolic volume. The number of counts in scans subsequent to the baseline scan were corrected for differences in acquisition time and frame.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age, y</th>
<th>Sex</th>
<th>Clinical Diagnosis</th>
<th>Coronary Arteriography (% Stenosis)</th>
<th>Cause of HTN</th>
<th>Duration of HTN, y</th>
<th>Arterial Pressure on Admission, mm Hg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Systolic</td>
</tr>
<tr>
<td>1</td>
<td>43</td>
<td>M</td>
<td>Chest pain</td>
<td>40% RCA</td>
<td>1°</td>
<td>4</td>
<td>165</td>
</tr>
<tr>
<td>2</td>
<td>65</td>
<td>F</td>
<td>Chest pain</td>
<td>30% diag, 35% RCA</td>
<td>1°</td>
<td>16</td>
<td>180</td>
</tr>
<tr>
<td>3</td>
<td>63</td>
<td>M</td>
<td>Chest pain</td>
<td>30% RCA</td>
<td>1°</td>
<td>9</td>
<td>153</td>
</tr>
<tr>
<td>4</td>
<td>34</td>
<td>M</td>
<td>Transplant</td>
<td>Normal</td>
<td>Csa, Pred</td>
<td>0.5</td>
<td>150</td>
</tr>
<tr>
<td>5</td>
<td>61</td>
<td>F</td>
<td>Chest pain</td>
<td>Normal</td>
<td>1°</td>
<td>7</td>
<td>164</td>
</tr>
<tr>
<td>6</td>
<td>48</td>
<td>M</td>
<td>Transplant</td>
<td>Normal</td>
<td>1°, Csa, Pred</td>
<td>1</td>
<td>165</td>
</tr>
<tr>
<td>7</td>
<td>46</td>
<td>M</td>
<td>Transplant</td>
<td>Normal</td>
<td>Csa, Pred, CRF</td>
<td>2.5</td>
<td>180</td>
</tr>
<tr>
<td>8</td>
<td>45</td>
<td>M</td>
<td>Transplant</td>
<td>Normal</td>
<td>1°, Csa, Pred</td>
<td>2</td>
<td>130</td>
</tr>
<tr>
<td>9</td>
<td>45</td>
<td>M</td>
<td>Chest pain</td>
<td>Normal</td>
<td>1°</td>
<td>8</td>
<td>168</td>
</tr>
<tr>
<td>10</td>
<td>54</td>
<td>M</td>
<td>Transplant</td>
<td>Normal</td>
<td>Csa, Pred, CRF</td>
<td>3</td>
<td>135</td>
</tr>
<tr>
<td>Mean</td>
<td>50</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>5.3</td>
<td>159</td>
</tr>
<tr>
<td>SEM</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.5</td>
<td>5</td>
</tr>
</tbody>
</table>

HTN indicates hypertension; RCA, right coronary artery; diag, diagonal branch of left anterior descending coronary artery; Csa, cyclosporin A; Pred, prednisone; and CRF, chronic renal failure.
duration as well as for physical and biological decay of the isotope.

Data Analysis

LV pressure measurements from four or five representative beats were traced and digitized at a sampling interval of 2 milliseconds on a Summagraphics MM1812 Bitpad interfaced to a VAX 780 computer. The pressure was then averaged at intervals corresponding to the frame interval of the radionuclide scan. Pressure-volume loops were constructed from these pressures plotted with the corresponding volumes. End-systolic pressure and volume were defined as the pressure and volume at the time of maximal instantaneous ratio of pressure to volume. A change in LV distensibility during nitroprusside or ANP infusion was defined prospectively as an LV pressure change of 3 mm Hg or more from baseline during the period of overlap of the passive portions of the diastolic pressure-volume relations. The end-diastolic pressure-volume relation was constructed from LV end-diastolic pressure and LV end-diastolic volume during the two baseline periods and the nitroprusside infusion. An exponential function was fit to these points, with the two baseline periods each given half the weight of the nitroprusside period.

Plasma samples were drawn during the baseline periods and at the end of the nitroprusside and ANP infusions, and norepinephrine level was assayed using liquid chromatography.

Statistics

Results are expressed as mean±SEM. Comparisons between the cardiac transplant recipients and the other patients were made by unpaired t tests with a significance level of .05. Comparisons among the four treatment periods were made by two-way ANOVA and subsequent comparisons of group means by the Newman-Keuls test with a significance level of .05.

Results

Baseline Measurements (Table 2)

Systolic arterial pressure during the first baseline period was elevated at 147±6 mm Hg and diastolic pressure was 88±6 mm Hg. MAP was elevated at 115±6 mm Hg. CI was low at 2.4±0.1 L • min • m^-2 and SVR high at 2090±228 dyne-s • cm^-5. There were no significant differences between the two baseline periods in any of the measured or derived variables.

Hemodynamic Responses to Nitroprusside and ANP (Table 2)

During nitroprusside infusion (63±13 μg • min^-1), systolic, diastolic, and mean arterial pressures decreased. RAP, PAP, and PCWP also decreased. HR increased slightly, and CI was unchanged. SVR and PVR decreased. LV end-diastolic pressure and volume fell, as did LV end-systolic volume.

ANP infusion (0.40±0.12 μg • kg^-1 • min^-1) also resulted in decreases in systolic, diastolic, and mean systemic arterial pressures, as well as RAP, PAP, and PCWP. HR increased, and CI was unchanged. SVR fell, but PVR was unchanged. LV end-diastolic pressure fell, whereas end-diastolic volume did not change significantly. As during nitroprusside infusion, LV end-systolic volume decreased.

MAP fell by a greater amount during nitroprusside than during ANP. SVR fell by similar amounts during infusion of the two drugs, but PVR fell only during nitroprusside. Increases in HR were similar during nitroprusside and ANP.

HR (89±4 versus 69±5 min^-1, P<.05), RAP (8±1 versus 5±1 mm Hg, P<.05), and diastolic arterial pressure (99±6 versus 84±5 mm Hg, P<.05) were greater at baseline in the transplant recipients than in the other hypertensive patients, although MAP was similar. Transplant recipients required more nitroprusside (94±15 versus 33±5 μg • min^-1, P<.05) and more ANP (0.54±0.04 versus 0.25±0.09 μg • kg^-1 • min^-1, P<.05) to achieve similar reductions in arterial pressure than did the nontransplant patients. HR increased during nitroprusside and ANP in the transplant recipients, whereas it was unchanged in the other patients. In the transplant recipients, RAP and diastolic arterial pressure fell during nitroprusside but not during ANP, whereas these pressures were unchanged in the nontransplant patients. Otherwise, there were no differences in the hemodynamic responses to nitroprusside and ANP between the transplant recipients and the other patients.

Effects on Contractile Function

In association with decreases in preload and afterload, peak positive LV dP/dt decreased by similar amounts during infusion of nitroprusside and ANP (Table 2). A less load-dependent measure of contractility, LV dp/dt at a developed pressure of 40 mm Hg, was unchanged during both nitroprusside and ANP, consistent with a lack of effect of either agent on myocardial contractility. LV ejection fraction increased by a statistically significant amount during both nitroprusside and ANP. On the other hand, SWI fell during nitroprusside but was unchanged during ANP.

Fig 1 shows the results of LV pressure-volume analysis. In 6 of the 9 patients in whom LV pressure-volume loops were constructed (patients 1, 2, 3, 7, 8, and 10), the end-systolic portions of the loops during ANP infusion were shifted upward and rightward toward the baseline loops relative to the loops during nitroprusside, indicative of less afterload reduction, but no effect on ventricular contractile function was apparent. In 2 patients (patients 4 and 9), a slight leftward shift of the end-systolic portion of the ANP loop relative to the nitroprusside loop suggested a positive inotropic effect, whereas in 1 patient (patient 6), a slight rightward shift suggested a negative inotropic effect. Thus, there was no consistent leftward or rightward shift of the end-systolic pressure-volume point during ANP, indicating no inotropic effect.

There was no difference at baseline in either peak positive LV dp/dt or LV dP/dt at a developed pressure of 40 mm Hg between the transplant recipients and other hypertensive patients. The changes observed in these parameters during infusion of ANP or nitroprusside were similar in the two patient groups.

Effects on Diastolic Function

Peak negative dP/dt was unchanged during nitroprusside and ANP infusions (Table 2). Tp decreased similarly during nitroprusside and ANP, whereas Tp was unchanged during infusion of both agents. Neither agent affected peak filling rate.

Lack of overlap of the LV diastolic pressure-volume relation (Fig 2) between baseline and nitroprusside infusion precluded comparison in 1 patient (patient 6). Of the remaining 8 patients, the relation was shifted downward during nitroprusside in 3 patients (patients 7, 8, and 10),
was shifted upward in 1 (patient 3), and remained unchanged in 4 (patients 1, 2, 4, and 9). During ANP infusion, there was overlap of the diastolic pressure-volume relation with the immediately previous baseline relation in all 9 patients in which it was determined. The relation was shifted downward during ANP in 3 patients (patients 7, 8, and 10), was shifted upward in 1 (patient 2), and remained unchanged in 5 (patients 1, 3, 4, 6, and 9). Fig 3 demonstrates that the group mean end-diastolic pressure and volume during ANP was slightly higher than during nitroprusside. The group mean end-diastolic pressure-volume point during ANP infusion was not shifted relative to the exponential end-diastolic pressure-volume relation derived from the data obtained during the baseline and nitroprusside periods.

Both T_L and T_D were higher in the transplant recipients (50±3 and 105±12 milliseconds, respectively) than in the other patients (39±3 and 77±9 milliseconds, P<.05 for both). During nitroprusside infusion in the transplant recipients, T_L and T_D fell to 43±2 and 81±6 milliseconds, respectively (P<.05 for both). There was a similar fall in T_L in the transplant group during ANP infusion to 45±3 milliseconds (P<.05), whereas T_D did not change. No change was seen in T_L or T_D during nitroprusside or ANP infusion in the nontransplant hypertensive patients. All of the patients in whom downward shifts in the diastolic pressure-volume relation were observed (patients 7, 8, and 10) were transplant recipients.

Neuroendocrine Effects

Plasma norepinephrine increased by similar amounts during nitroprusside and ANP infusions. Plasma norepinephrine levels were higher at baseline in the transplant recipients than in the other patients (2.21±0.29 versus 1.50±0.24 mmol • L⁻¹, P<.05) but increased similarly during nitroprusside and ANP in the two groups.

Side Effects

Four patients complained of flushing during nitroprusside infusion. ANP infusion caused no side effects.
Figs. 1. Plots show left ventricular pressure-volume loops in 9 patients during the first (○) and second (●) baseline periods and during nitroprusside (●) and atrial natriuretic peptide (ANP) (●) infusions. In 6 patients (patients 1, 2, 3, 7, 8, and 10), the end-systolic portions of the loops during ANP were shifted upward and rightward toward the baseline loops relative to the loops during nitroprusside, indicative of less afterload reduction, but there was no effect on ventricular contractile function. In 2 patients (patients 4 and 9), a slight leftward shift of the end-systolic portion of the ANP loop suggested a positive inotropic effect, whereas in 1 patient (patient 6), a slight rightward shift indicated a negative inotropic effect.

Discussion
The myocardial effects, either direct or indirect, of an antihypertensive agent may be important in determining its role in therapy. Drugs that lower arterial pressure without increasing the inotropic state of the heart, such as angiotensin-converting enzyme inhibitors, β-blockers, and calcium channel antagonists, induce the regression of LV hypertrophy. Ventricular hypertrophy is less effectively reversed by hydralazine and diuretics, agents whose hypotensive effect is accompanied by an increase in adrenergic activity, which can have positive inotropic effects. ANP has been found to be effective in lowering systemic arterial pressure in healthy subjects, patients with heart failure, and patients with hypertension. Thus, ANP itself, or endopeptidase inhibitors designed to increase plasma levels of endogenous ANP, are potentially useful antihypertensive agents. This study was designed to evaluate the myocardial effects of ANP in patients with hypertension.

Effects of ANP on Systemic Hemodynamics
The fall in MAP observed during ANP infusion in this study was accompanied by increases in HR and plasma norepinephrine level. This is in agreement with previous observations in hypertensive patients and in healthy subjects but not in patients with heart failure. Although previous studies in hypertensive patients did not demonstrate a fall in ventricular preload or SVR during ANP...
infusion, we observed that RAP, PCWP, and SVR decreased in our patients during ANP administration. ANP did not alter CI or SVI in the present study, in contrast to the decrease reported in some previous studies of hypertensive patients. These differences may have been due to the higher baseline elevation of SVR in our patients and its greater decrease with the higher dose of ANP used in this study.

Bradycardia and hypotension during ANP infusion have been noted in previous studies of patients with hypertension. We did not observe any adverse effects of ANP in our patients. In the previous studies, patients consumed a diet severely restricted in sodium, and the duration of ANP infusion was greater than 60 minutes; these factors may account for the disparate results.

Effects of ANP on Contractile Function

Several experimental models have been used to assess the inotropic effect of ANP. Neyses and Vetter observed that ANP reduced the maximal contractile extent of rat cardiac myocytes in a dose-dependent manner. A study of isolated rat cardiac trabeculae by Stone et al found that ANP caused a depression of the force-length relation. Wangler et al reported a negative inotropic effect of ANP on isolated, perfused guinea pig hearts, which they attributed to coronary vasoconstriction. In anesthetized dogs, Ertl et al found that ANP had a negative inotropic effect that was independent of its coronary vasoconstrictor effect. In contrast to these studies, Natsume et al found that ANP had no effect on myocardial contractility in anesthetized rats, as it induced a fall in SVI and LV
end-diastolic pressure, but when the intravascular volume was reexpanded, the relation between end-diastolic pressure and SVI was unchanged. Studies of the myocardial effects of ANP in humans have also yielded conflicting results. In patients with normal LV systolic function, Volpe et al found that ANP caused a fall in stroke volume with a decrease in afterload but no change in preload, raising the possibility of a negative inotropic effect. Herrmann et al found that intracoronary infusion of ANP did not affect peak positive LV dP/dt at doses that did not alter loading conditions. In patients with impaired LV systolic function, ANP increased stroke volume, with a simultaneous decrease in PCWP. We have previously shown by end-systolic pressure-volume analysis that the beneficial effect of ANP on ventricular performance in patients with heart failure is not accompanied by a change in LV contractility.11 In the current study, to assess the inotropic effect of ANP in patients with hypertension, we compared the changes in LV end-diastolic pressure and volume during ANP infusion to changes during nitroprusside, a vasodilator with no known direct myocardial effect. Previous studies of patients with heart failure have used nitroprusside infusion to alter afterload and allow the construction of the baseline end-systolic pressure-volume relation.11 Since acute vasodilator administration does not cause activation of the sympathetic nervous system in patients with severe heart failure, nitroprusside may be administered without any reflex effect on the contractile state of the ventricle.15 In the present study of patients with hypertension, reflex activation of the sympathetic nervous system during nitroprusside infusion, as indicated by increases in HR and plasma norepinephrine level, may have altered the contractile state of the myocardium. Fortunately, the extent of sympathetic stimulation during ANP infusion was similar to that during nitroprusside, as indicated by similar increases in HR and plasma norepinephrine level. This allowed us to compare the position of the end-systolic portion of the pressure-volume loops during ANP to that of the loops during nitroprusside. The lack of a consistent leftward or rightward shift of the end-systolic portion of the pressure-volume loop during ANP away from that during nitroprusside indicates the lack of a significant inotropic effect of ANP.

Further support for a lack of effect of ANP on myocardial contractility comes from the measurements of LV dp/dt during isovolumic contraction. Peak positive dp/dt fell by similar amounts during nitroprusside and ANP. The decrease in peak positive dp/dt reflects the load dependence of this index, which may fail when preload or afterload decreases. LV dp/dt at a common developed pressure is relatively independent of loading conditions. There was no change in LV peak positive dp/dt at a developed pressure of 40 mm Hg during either nitroprusside or ANP infusion. Effect of ANP on Diastolic Function

Although LV systolic function is usually normal in patients with hypertension, diastolic function is often impaired. Abnormalities may be present in ventricular relaxation and/or filling and can contribute to the development of exercise intolerance and heart failure. Cardiac transplant recipients, who develop hypertension as a result of cyclosporine immunosuppression, also have abnormalities of ventricular relaxation and filling. The effect of an antihypertensive agent such as ANP on diastolic function, either directly or indirectly by influencing the process of hypertrophy, may have hemodynamic and clinical significance.

ANP administration to animals and humans results in a fall in filling pressures, whether systolic function is normal or depressed. Meulemans et al have shown that ANP induces early relaxation of isolated cat papillary muscle. In studies of humans with normal ventricular function, Herrmann et al found no effect of ANP on isovolumic relaxation at doses that did not alter systemic hemodynamics. In patients with heart failure, we previously reported that changes in the logarithmic and derivative time constants of isovolumic relaxation during ANP administration paralleled those observed with nitroprusside, a vasodilator with no known direct myocardial effect. When the effects of a vasodilator on indexes of isovolumic relaxation are being studied, it is important to exclude indirect actions mediated by alterations in ventricular loading conditions.

To assess the effect of ANP on diastolic function in patients with hypertension, we compared measurements of LV relaxation, filling, and overall distensibility during ANP administration to those obtained during nitroprusside. LV peak negative dp/dt was unchanged during both nitroprusside and ANP. The change in LV peak negative dp/dt was similar during nitroprusside and ANP, whereas there was no change during both drugs. Thus, the effect of ANP on myocardial relaxation was similar to that of nitroprusside. The decrease in LV peak negative dp/dt was unaltered during both nitroprusside and ANP. The decrease in LV peak negative dp/dt was unchanged during both nitroprusside and ANP.

This allowed us to compare the position of the end-systolic portion of the pressure-volume loops during ANP to that of the loops during nitroprusside. The lack of a consistent leftward or rightward shift of the end-systolic portion of the pressure-volume loop during ANP away from that during nitroprusside indicates the lack of a significant inotropic effect of ANP.

Further support for a lack of effect of ANP on myocardial contractility comes from the measurements of LV dp/dt during isovolumic contraction. Peak positive dp/dt fell by similar amounts during nitroprusside and ANP. The decrease in peak positive dp/dt reflects the load dependence of this index, which may fail when preload or afterload decreases. LV dp/dt at a common developed pressure is relatively independent of loading conditions. There was no change in LV peak positive dp/dt at a developed pressure of 40 mm Hg during either nitroprusside or ANP infusion.
both medications was counterbalanced by the concomitant decrease in PCWP, which reflects the driving force for early diastolic filling.\textsuperscript{10}

We assessed overall LV distensibility by examining the diastolic pressure-volume relation. In 3 patients, all of whom were cardiac transplant recipients, both ANP and nitroprusside administration resulted in a downward shift in the diastolic pressure-volume relation, indicative of an improvement in ventricular distensibility. There were no significant changes in the diastolic pressure-volume relation during nitroprusside infusion in 4 patients or ANP infusion in 5 patients. One patient had an upward shift in the diastolic pressure-volume relation during ANP administration, and another had an upward shift during nitroprusside. The improvement in distensibility observed in some of the transplant recipients has several potential explanations. Abnormalities in right ventricular performance may develop in transplant recipients and may result from ischemic damage occurring during organ harvesting and implantation\textsuperscript{43} or from injury to the tricuspid valve apparatus during transplant right ventricular biopsy. Right ventricular dilation might in turn lead to extrinsic compression of the left ventricle, with an upward shift in the diastolic pressure-volume relation. This upward shift could be reversed by the preload-lowering effects of nitroprusside and ANP.\textsuperscript{46} Similarly, elevation in RAP could lead to an elevation in coronary venous pressure and a decrease in LV distensibility that is reversed by nitroprusside and ANP.\textsuperscript{47}

The lack of a direct effect of ANP on either myocardial contractility or diastolic function is supported by radioautographic studies showing a lack of specific binding of ANP to ventricular myocytes.\textsuperscript{48}

\textbf{Study Limitations}

Several potential limitations of this study should be considered. We studied two groups of patients who may have differing pathophysiological causes of their hypertension: essential hypertension and cyclosporine-induced hypertension. Furthermore, transplant recipients have high plasma levels of ANP,\textsuperscript{49} which might alter their response to exogenous ANP. We administered a higher dose of ANP, on average, to the transplant recipients than to the other patients in order to achieve the same change in MAP. Although the patient population was not homogeneous, there were no differences between the groups in the effects of ANP on any of the parameters we measured, except for LV distensibility (as discussed above). A second potential limitation is that the increase in HR observed during both ANP and nitroprusside administration may have altered indexes of ventricular contractile and diastolic function. Since the changes in HR were small and there was no difference between nitroprusside and ANP in the change in HR, it is unlikely that HR changes skewed our results. Although denervation of the heart in the transplant recipients might affect the hemodynamic response to vasodilators, the degree to which cardiac denervation was present in the transplant recipients is uncertain. Wilson et al\textsuperscript{19} have recently demonstrated that partial reinnervation of the heart is common late after transplantation. In fact, HR increased the transplant recipients in response to both vasodilators, indicating sensitivity to circulating or local adrenergic stimulation or withdrawal of parasympathetic tone. Lastly, the order of nitroprusside and ANP infusion was not randomized because of the longer duration of ANP action. However, all hemodynamic variables did return to baseline after the nitroprusside infusion.

\textbf{Summary and Conclusions}

ANP is an effective acute vasodilator in patients with systemic hypertension and is capable of producing a decrease in MAP and LV filling pressure without a change in cardiac output. These changes are not associated with an alteration of myocardial contractility. Changes in indexes of diastolic function during ANP administration are similar to those during nitroprusside and are most likely mediated by alteration of loading conditions rather than by a direct effect on myocardial diastolic properties. We conclude, therefore, that ANP has no hemodynamically important direct myocardial effects in this patient population.

\textbf{Acknowledgments}

This study was supported in part by a grant from Wyeth-Ayerst Laboratories, Philadelphia, Pa, and was performed during Dr Aroney's tenure as an Overseas Clinical Fellow of the National Heart Foundation of Australia, Canberra, ACT, and Dr Fifer's as a Clinician-Scientist of the American Heart Association, Dallas, Tex.

\textbf{References}


Effects of atrial natriuretic peptide on left ventricular function in hypertension.
M J Semigran, C N Aroney, H C Herrmann, G W Dec, C A Boucher and M A Fifer

_Hypertension_. 1994;24:271-279
doi: 10.1161/01.HYP.24.3.271

_Hypertension_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1994 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://hyper.ahajournals.org/content/24/3/271

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Hypertension_ 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 _Hypertension_ is online at:
http://hyper.ahajournals.org//subscriptions/