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Effects of Atrial Natriuretic Peptide on Myocardial Contractile and Diastolic Function in Patients With Heart Failure

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Atrial natriuretic peptide alters left ventricular performance in patients with heart failure. To assess the direct effects of this hormone on myocardial function, its actions were compared with those of the pure vasodilator nitroprusside in 10 patients with heart failure. Simultaneous left ventricular micromanometer pressure and radionuclide volume were obtained during a baseline period, during nitroprusside infusion, during a second baseline period and during atrial natriuretic peptide infusion. The baseline end-systolic pressure-volume relation was generated in nine patients from pressure-volume loops obtained during the two baseline periods and during afterload reduction with nitroprusside.

Mean arterial pressure decreased with atrial natriuretic peptide (89 ± 3 to 80 ± 2 mm Hg, $p < 0.05$) and by a greater amount with nitroprusside (90 ± 4 to 73 ± 3 mm Hg, $p < 0.05$). Left ventricular end-diastolic pressure also decreased with atrial natriuretic peptide (24 ± 2 to 16 ± 3 mm Hg, $p < 0.05$) and by a greater amount with nitroprusside (24 ± 2 to 13 ± 3 mm Hg, $p < 0.05$). Cardiac index increased during infusion of each agent from 2.0 ± 0.2 to 2.4 ± 0.2 liters/min per m² ($p < 0.01$). Heart rate increased slightly with nitroprusside but did not change with atrial natriuretic peptide. Peak positive first derivative of left ventricular pressure (dP/dt), ejection fraction and stroke work index were unchanged by either agent. The relation between end-systolic pressure and volume during atrial natriuretic peptide infusion was shifted slightly leftward from the baseline value in four patients, slightly rightward in four and not at all in one patient, indicating no consistent inotropic effect. Both agents shortened the time constant of isovolumetric relaxation, calculated by the logarithmic method, but only nitroprusside shortened the time constant calculated by the derivative method. Peak filling rate was unchanged from baseline with either agent. Atrial natriuretic peptide did not shift the end-diastolic pressure-volume point away from the relation constructed from baseline and nitroprusside points.

It is concluded that atrial natriuretic peptide has no direct effect on myocardial contractile or diastolic function in patients with heart failure.

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Atrial natriuretic peptide is a 28-amino acid peptide released by atrial myocytes in response to stretch (1,2). It induces diuresis, natriuresis, vasodilation and inhibition of aldosterone secretion in normal humans (3–5). In response to atrial natriuretic peptide, stroke volume decreases (6–13) or does not change (3,14) in animals or humans with normal left ventricular systolic function. In contrast, atrial natriuretic peptide increases stroke volume in patients with heart failure, with a simultaneous decrease in pulmonary capillary wedge pressure (3,14–18).

Although it has been demonstrated that the vasodilator action of atrial natriuretic peptide accounts in part for its hemodynamic effects, there has been continued speculation regarding possible direct effects of the peptide on myocardial contractile and diastolic function. It has been suggested (15) that the increase in cardiac index seen in response to atrial natriuretic peptide infusion in patients with heart failure is due to a positive inotropic effect. In contrast, the *decrease* in stroke volume shown in some studies of subjects with normal ejection fraction has led other investigators (7,11) to postulate that atrial natriuretic peptide exerts a *negative* inotropic effect. A negative inotropic effect would explain the decrease in stroke volume index without a change in preload observed during atrial natriuretic peptide infusion in patients with hypertension (7). Studies in cat papillary muscles (19) and isolated perfused hearts (20) have suggested such a negative inotropic effect of atrial natriuretic peptide, whereas a study in the chronically instrumented conscious dog found no inotropic effect (21). It has also been observed (19) that atrial natriuretic peptide causes early relaxation of cat papillary muscle. Thus, the hemodynamic effects of this peptide could be due in part to direct influences on myocardial contractile or diastolic function, or both

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In studies of the intact circulation, it is difficult to isolate the inotropic effect of an agent that alters preload or 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 contractile function (22,23). The baseline end-systolic pressure-volume relation can be generated in patients with heart failure by infusion of nitroprusside (24); the inotropic actions of a drug can be judged from a drug-induced shift away from the baseline relation (25,26). Indexes of diastolic function are also influenced by changes in loading conditions as well as by direct myocardial effects (27). The direct actions of an agent on myocardial diastolic properties may be inferred from a comparison of its effects with those of a "pure" vasodilator such as nitroprusside (28,29).

Therefore, to determine whether atrial natriuretic peptide has direct effects on myocardial contractile and diastolic function, we sequentially administered nitroprusside and atrial natriuretic peptide to 10 patients with chronic heart failure.

Methods

Study patients. The study group comprised 10 patients: 7 men and 3 women, aged 58 ± 4 (mean ± SEM) years, with chronic New York Heart Association class II to IV heart failure due to either coronary artery disease (5 patients) or idiopathic dilated cardiomyopathy (5 patients). All patients were treated with digoxin, diuretic drugs and vasodilators; seven also received antiarrhythmic medication for ventricular arrhythmias. Radionuclide left ventricular ejection fraction was 0.14 ± 0.01 (range 0.10 to 0.20). All patients were in sinus rhythm. The study protocol was approved by the Subcommittee on Human Studies of the Massachusetts General Hospital on September 15, 1987; written, informed consent was obtained from all patients.

Hemodynamic measurements. Digoxin, diuretic drugs and vasodilators were discontinued 12 to 24 h before catheterization; antiarrhythmic therapy was continued. No premedication was given. Left heart catheterization was performed by the femoral approach with a micromanometer-tipped catheter (Millar Instruments) in nine patients and with a fluid-filled catheter in one patient (Patient 1). Right heart catheterization was performed from the internal jugular vein with a triple-lumen balloon-tipped thermodilution catheter.

The following hemodynamic variables were recorded: heart rate, right atrial pressure, pulmonary artery pressure, pulmonary capillary wedge pressure, left ventricular pressure, mean systemic arterial pressure, and, in eight patients, first derivative of left ventricular pressure (dP/dt) (by electronic differentiation). Left ventricular dP/dt was not recorded in Patient 1, who had a fluid-filled catheter, or in Patient 9, because of a technical error. Cardiac output was determined by the thermodilution technique in eight patients and by the Fick oxygen technique in two. Calculations were made by using the following formulas: Cardiac index (liters/min per m^2) = (Cardiac Output)/(Body Surface Area); Stroke Volume Index (ml/m^2) = (Cardiac Index)/(Heart Rate); Stroke Work Index (g-m/m^2) = (0.0136) (Mean Arterial Pressure − Left Ventricular End-Diastolic Pressure) (Stroke Volume Index); Systemic Vascular Resistance (dynes-s/cm^5) = 80 (Mean Systemic Arterial Pressure − Right Atrial Pressure)/(Cardiac Output); and Pulmonary Vascular Resistance (dynes-s/cm^5) = 80 (Mean Pulmonary Artery Pressure − Pulmonary Capillary Wedge Pressure)/(Cardiac Output).

The logarithmic time constant of left ventricular isovolumetric relaxation (T_L) was calculated from the micromanometer-obtained left ventricular pressure by the method of Weiss et al. (30). The period of isovolumetric relaxation was taken to be from the aortic dicrotic notch pressure to the pressure corresponding to the peak of the v wave of the simultaneous pulmonary capillary wedge tracing. The negative reciprocal of the slope of the linear fit of ln(left ventricular pressure) versus time defined T_L. The derivative time constant T_D was calculated by the method of Raff and Glantz (31) during the same time interval as T_L from the negative reciprocal of the slope of a linear fit of left ventricular dP/dt versus pressure. This method allows for a non-zero pressure asymptote, P_a.

Hemodynamic data were obtained during a baseline period, during constant infusion of nitroprusside, during a second baseline period and during atrial natriuretic peptide infusion. Nitroprusside was infused initially at a rate of 25 μg/min, which was titrated upward to achieve a 15- to 20-mm Hg decrease in mean arterial pressure. Measurements during nitroprusside infusion were made 5 min after the desired hemodynamic effect was achieved, and baseline measurements were repeated 10 min after nitroprusside was discontinued, when hemodynamic variables matched those in the first baseline period. Anaritide (Wyeth-Ayerst Laboratories) is a synthetic 25-amino acid peptide (human atrial natriuretic peptide 102–126) that lacks 3 amino acids from the amino terminus of human atrial natriuretic peptide, and has similar biologic activity (investigational brochure, Wyeth Laboratories, 1985). The atrial natriuretic peptide infusion was titrated either to achieve a decrement in mean arterial pressure similar to that obtained during the nitroprusside infusion or to achieve a maximal rate of 0.6 μg/kg per min. Measurements were made at least 10 min after the final infusion rate of atrial natriuretic peptide was begun.

Radionuclide scanning. Left ventricular volume was calculated from gated blood pool images in nine patients as previously described (24–26,28). Images were not recorded in Patient 10 because of a technical error. After in vivo labeling of the patient's 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 by using a semiautomated edge detection method with a variable region of interest. Background count density was calculated from an area of the frame adjacent to the left ventricle, and subtracted from each frame. The time-activity curve was smoothed by using a 3-point weighted moving average (coefficients: 0.25, 0.50, 0.25). Ejection fraction was calculated as (End-Diastolic − End-Systolic Counts)/End-Diastolic Counts.

Baseline left ventricular end-diastolic volume was calculated from the anterior and left anterior oblique views using a previously validated geometric biplane area-length method (32). 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 duration as well as for physical and biologic decay of the isotope.

Pressure-volume analysis. Left ventricular pressure measurements from 4 or 5 representative beats were traced and digitized at a sampling interval of 2 ms 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.

The end-systolic pressure-volume relation was constructed from the two baseline measurements and the measurements taken during nitroprusside infusion by the iterative method of Kass et al. (33). A line was fit to the points in each cardiac cycle for which the ratio of pressure to volume (V) was maximized. To avoid giving disproportionate weight to the two baseline measurements, they were each given a weight half that of the measurement during nitroprusside infusion (26). The volume at the extrapolated zero pressure (V_d) was then subtracted from each volume in the cardiac cycle. A similarly weighted line was again fit from the points in the cardiac cycle for which (left ventricular pressure)/($V - V_d$) was maximized. The new V_d was again subtracted from all the points in the cardiac cycle, and the process repeated until there was no significant change in either the slope of the line or V_d. We have previously shown (24) that the end-systolic pressure-volume relation is linear in patients with heart failure in the range of end-systolic pressures and volumes obtained in the baseline state and during graded infusion of nitroprusside. This linearity allowed us to approximate the relation by using only two afterload conditions, an important consideration in view of the time constraints inherent in a left heart catheterization study.

A change in left ventricular distensibility during nitroprusside or atrial natriuretic peptide infusion was defined as a left ventricular pressure change ≥3 mm Hg from baseline during the period of overlap of the passive portions of the diastolic pressure-volume relations. Because right atrial pressure has been shown to approximate intrapericardial pressure (34), the diastolic transmural pressure-volume relation was created by plotting left ventricular intracavitary pressure minus right atrial pressure versus volume. The end-diastolic pressure-volume relation was constructed from left ventricular end-diastolic pressure and volume during the two baseline periods and during nitroprusside infusion. An exponential function was fit to these points, with the two baseline periods given half the weight of the nitroprusside period.

Statistics. Results are expressed as mean value ± SEM. Comparisons among the four treatment periods were made by two-way analysis of variance, and subsequent comparisons of group means by the Newman-Keuls test with a significance level of 0.05.

Results

Baseline measurements (Table 1). Baseline left ventricular end-diastolic pressure was elevated at 24 ± 2 mm Hg and cardiac index depressed at 2.0 ± 0.2 liters/min per m^2. The baseline left ventricular end-diastolic volume of 327 ± 29 ml indicates marked left ventricular dilation. There were no significant differences between the two baseline periods in any of the measured or derived variables.

Hemodynamic responses to nitroprusside and atrial natriuretic peptide (Table 1). During nitroprusside infusion (79 ± 13 μg/min), mean systemic arterial, right atrial, pulmonary artery and pulmonary capillary wedge pressures and systemic and pulmonary vascular resistances all decreased, while heart rate increased slightly. Left ventricular end-diastolic pressure decreased from 24 ± 2 to 13 ± 3 mm Hg ($p < 0.01$), while cardiac index increased from 2.0 ± 0.2 to 2.4 ± 0.2 liters/min per m^2 ($p < 0.01$). Left ventricular end-diastolic and end-systolic volumes decreased.

Infusion of atrial natriuretic peptide (0.4 ± 0.05 μg/kg per min) also resulted in decreases in mean systemic arterial, right atrial, pulmonary artery and pulmonary capillary wedge pressures. Systemic vascular resistance decreased but pulmonary vascular resistance was unchanged; heart rate was unchanged. Left ventricular end-diastolic pressure decreased from 24 ± 2 to 16 ± 3 mm Hg ($p < 0.01$), while cardiac index increased from 2.0 ± 0.2 to 2.4 ± 0.2 liters/min per m^2 ($p < 0.01$). As during nitroprusside infusion, left ventricular end-diastolic and end-systolic volumes decreased.

Effects on contractile function. Peak positive left ventricular dP/dt was unchanged by either nitroprusside or atrial natriuretic peptide (Table 1). Similarly, neither ejection fraction nor stroke work index changed significantly during infusion of either agent. The results of left ventricular end-systolic pressure-volume analysis are depicted in Figure 1. There was no shift away from the baseline end-systolic pressure-volume relation during atrial natriuretic peptide infusion in Patient 2, a slight leftward shift in Patients 1, 3, 7 and 9 and a slight rightward shift in Patients 4, 5, 6 and 8.

Table 1. Effects of Nitroprusside and Atrial Natriuretic Peptide on Hemodynamics and Indexes of Contractile and Diastolic Function

	Baseline	Nitroprusside	Baseline	Atrial Natriuretic Peptide
Heart rate (beats/min)	90 ± 6	97 ± 5*	90 ± 4	91 ± 5†
Pressures (mm Hg)	90 ± 4	73 ± 3*	89 ± 3	80 ± 2*†
Mean arterial				
Right atrial	8 ± 2	4 ± 1*	10 ± 2	6 ± 2*†
Pulmonary artery	33 ± 3	21 ± 3*	35 ± 3	28 ± 3*†
Pulmonary capillary wedge	24 ± 2	13 ± 3*	24 ± 2	16 ± 3*†
LV end-diastolic	24 ± 2	13 ± 3*	24 ± 2	16 ± 3*†
LV peak systolic	115 ± 8	99 ± 6*	115 ± 6	106 ± 7*†
Cardiac index (liters/min per m^2)	2 ± 0.2	2.4 ± 0.2*	2 ± 0.2	2.4 ± 0.2*
Stroke volume index (ml/m^2)	22 ± 2	26 ± 3*	22 ± 2	26 ± 2*
Stroke work index (g-m/m^2)	20 ± 3	20 ± 2	20 ± 2	23 ± 2
Systemic vascular resistance (dynes-s/cm^5)	1,978 ± 162	1,368 ± 144*	1,935 ± 140	1,491 ± 122*†
Pulmonary vascular resistance (dynes-s/cm^5)	230 ± 40	159 ± 20*	268 ± 50	241 ± 45†
LV peak +dP/dt (mm Hg/s)	1,042 ± 94	982 ± 77	1,054 ± 104	1,023 ± 82
LV peak −dP/dt (mm Hg/s)	1,029 ± 93	1,000 ± 103	1,020 ± 85	998 ± 65
T_L (ms)	70 ± 6	63 ± 9*	75 ± 5	66 ± 6*
T_D (ms)	116 ± 7	89 ± 8*	115 ± 10	106 ± 11†
P_a (mm Hg)	−21 ± 5	−4 ± 5*	−19 ± 6	−14 ± 8
LV end-diastolic volume (ml)	327 ± 29	292 ± 28*	324 ± 30	303 ± 28*†
LV end-systolic volume (ml)	284 ± 27	247 ± 27*	282 ± 27	262 ± 28*†
LV ejection fraction	0.14 ± 0.01	0.16 ± 0.02	0.13 ± 0.01	0.16 ± 0.01
LV peak filling rate (ml/s)	214 ± 25	205 ± 37	198 ± 19	208 ± 30

*$p < 0.05$ versus preceding baseline value, †$p < 0.05$, atrial natriuretic peptide versus nitroprusside. Values are given as mean value ± SEM. dP/dt = first derivative of left ventricular pressure; LV = left ventricular; P_a = pressure asymptote; T_D = derivative time constant; T_L = logarithmic time constant of left ventricular isovolumetric relaxation.

This analysis indicates no consistent inotropic effect of atrial natriuretic peptide at the doses studied.

Effects on diastolic function. Peak negative left ventricular dP/dt was unchanged during nitroprusside and atrial natriuretic peptide infusion (Table 1). The time constant T_L decreased with both agents, whereas T_D decreased only with nitroprusside. Neither agent affected peak filling rate.

There was insufficient overlap of the diastolic pressure-volume relations during the first baseline period and nitroprusside infusion to allow meaningful assessment of a change in left ventricular distensibility in eight of nine patients. In the remaining patient, who did have sufficient overlap of the diastolic pressure-volume relations, the relation was shifted *upward* during nitroprusside infusion. The diastolic pressure-volume relation during atrial natriuretic peptide infusion overlapped with the relation during the second baseline period in four of the nine patients. In three of these four patients (Patients 1, 4 and 9), the relation shifted downward during atrial natriuretic peptide infusion, whereas there was no shift in Patient 8 (Fig. 2). When left ventricular volume was plotted against left ventricular pressure minus right atrial pressure (an approximation of transmural left ventricular pressure), the downward shifts observed during atrial natriuretic peptide infusion in three patients decreased in magnitude but were not eliminated.

Figure 3 demonstrates that the group mean end-diastolic pressure-volume point during atrial natriuretic peptide infusion was not shifted relative to the exponential end-diastolic pressure-volume relation derived from the data obtained during the baseline and nitroprusside periods.

Side effects. Three patients complained of flushing during the nitroprusside infusion. There were no side effects of atrial natriuretic peptide infusion.

Discussion

Previous studies have assessed the inotropic effect of atrial natriuretic peptide in experimental models. Wangler et al. (20) demonstrated a negative inotropic effect of atrial natriuretic peptide in the isolated perfused heart and attributed the effect to coronary vasoconstriction. In the intact circulation, the direct inotropic action of a substance with vasodilator properties is difficult to separate from effects mediated by alteration of loading conditions. The decrease in stroke volume noted in several studies of atrial natriuretic peptide (6–10,12,13) could be due to an associated decrease in preload. However, in both anesthetized and conscious dogs, Kleinert et al. (11) observed a decrease in cardiac output with no alteration of filling pressure. Similarly, Volpe et al. (7) found that atrial natriuretic peptide decreased cardiac output without significantly changing filling pressure in patients with hypertension. In contrast, Patel and Hintze (21) maintained preload constant during atrial natriuretic

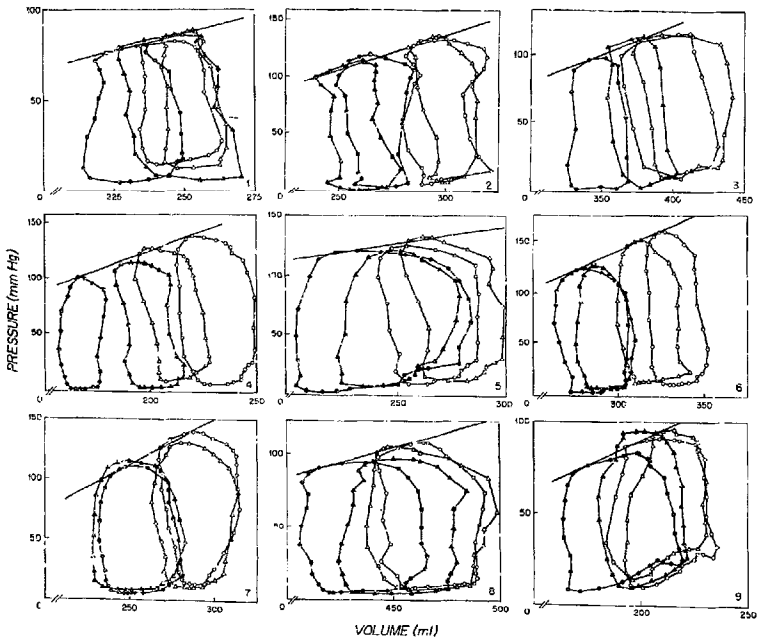

Figure 1. Left ventricular pressure-volume loops in nine patients during the first (○——○) and second (△——△) baseline periods and during nitroprusside (●——●) and atrial natriuretic peptide (▲——▲) infusions. The solid line indicates the end-systolic pressure-volume relation determined from the two baseline loops and the nitropresside loop, as described in the text. Four patients (Patients 1, 3, 7 and 9) had slight leftward shifts away from the end-systolic pressure-volume relation during atrial natriuretic peptide infusion and four patients (Patients 4, 5, 6 and 8) had slight rightward shifts. One patient (Patient 2) had no shift from the baseline end-systolic pressure-volume relation during peptide infusion.

peptide infusion by aortic occlusion in conscious dogs, and observed no change in peak left ventricular dP/dt.

Because of the influence of load on many measures of ventricular systolic performance, we utilized the left ventricular end-systolic pressure-volume relation, a relatively load-independent measure of contractile function (22,23), to assess the inotropic effect of atrial natriuretic peptide in patients with heart failure. We found that atrial natriuretic peptide did not consistently shift the relation between end-systolic pressure and volume leftward (indicating a positive inotropic effect) or rightward (indicating a negative effect) in these patients. Rather, we observed small shifts that seemed randomly distributed leftward (four patients) and rightward (four patients) from the baseline end-systolic pressure-volume relation. The sensitivity of our technique for detecting inotropic effects is evident from previous studies showing a leftward shift of the end-systolic pressure-volume relation in eight of nine patients treated with the phosphodiesterase inhibitor enoximone (25) and a rightward shift in 12 of 14 patients treated with the calcium channel blocker nicardipine (26). In the present study, the relation between end-systolic pressure and volume during atrial natriuretic peptide infusion was indistinguishable from that predicted for a pure vasodilator with no effect on contractile function.

Lack of inotropic effect of atrial natriuretic peptide. Because of the time constraints inherent in a left heart cathe-

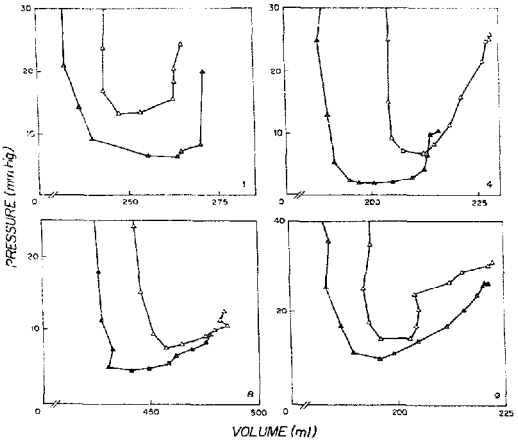

Figure 2. Left ventricular diastolic pressure-volume relations during the second baseline period (△——△) and during atrial natriuretic peptide administration (▲——▲) in four patients. Patients 1, 4 and 9 (**upper left and right panels and lower right panel**, respectively) had a downward shift of the passive portion of the relation with atrial natriuretic peptide, indicating an improvement in left ventricular distensibility; Patient 8 (**lower left panel**) had no shift.

terization study, we did not independently vary afterload during atrial natriuretic peptide infusion, and thus did not attempt to construct the full end-systolic pressure-volume relation on atrial natriuretic peptide. We therefore cannot draw conclusions regarding the slope and volume intercept of the relation during infusion of the peptide. The relative effects of inotropic interventions on the slope and intercept of the end-systolic pressure-volume relation depend on the model studied (35,36). We reasoned instead that a positive inotropic effect would result in a smaller end-systolic volume for any given end-systolic pressure and that a negative inotropic effect would be associated with a larger end-systolic volume for any pressure. We cannot exclude the possibility, however unlikely, that the slope and intercept of the end-systolic pressure-volume relation on atrial natriuretic peptide changed in such a way that it intersected the baseline relation at a point very close to that obtained for each patient during infusion of the peptide.

Corroborative evidence for the lack of an inotropic effect of atrial natriuretic peptide comes from the observation that left ventricular stroke work index, ejection fraction and peak positive dP/dt did not change significantly during infusion of the peptide. However, these ejection phase and isovolumetric indexes of contractile function are sufficiently load de-

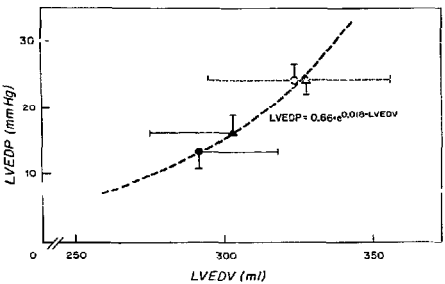

Figure 3. Effects of nitroprusside (●) and atrial natriuretic peptide (▲) on the relation between left ventricular end diastolic pressure (LVEDP) and left ventricular end-diastolic volume (LVEDV). The end-diastolic pressure-volume relation is modeled as an exponential curve (**dashed line**) fitted to the first (○) and second (△) baseline and nitroprusside (●) end-diastolic pressure-volume points. The left ventricular end-diastolic pressure-volume point during atrial natriuretic peptide administration was not shifted away from this relation.

JACC Vol. 20, No. 1
July 1992:98–106

pendent that conclusions from them must be drawn with caution. An alternative method of evaluating the inotropic effect of an agent independent of changes in loading conditions is the intracoronary infusion technique. Applying this method in patients with normal left ventricular systolic function, Herrmann et al. (37) found that atrial natriuretic peptide had no inotropic effect when administered in doses that did not alter loading conditions.

Effect of atrial natriuretic peptide on diastolic function. In most studies, the administration of atrial natriuretic peptide to animals and humans has resulted in a decrease in filling pressures, whether systolic function is normal (3,14) or depressed (3,14–18). Although venodilation or fluid shifts to the extravascular compartment, or both, may account for the decrease in filling pressures, it is also possible that an improvement in diastolic myocardial properties contributes to this effect. Meulemans et al. (19) demonstrated that atrial natriuretic peptide induces early relaxation of isolated cat papillary muscles. Herrmann et al. (37) found that atrial natriuretic peptide shortened the time constant of isovolumetric relaxation in patients with normal ventricular function. Because patients with heart failure due to systolic dysfunction may also have abnormalities of diastolic function (28,38), it is possible that the overall improvement in ventricular function brought about by atrial natriuretic peptide in these patients is due in part to a beneficial effect on diastolic myocardial performance.

Evaluation of diastolic function in humans is difficult because available indexes assess different aspects (relaxation, filling, stiffness) of diastolic function. Furthermore, indexes of diastolic function, like indexes of systolic function, may be affected by loading conditions (27,39–41). In fact, previous studies (28,40,42) have demonstrated beneficial effects of the "pure" vasodilator nitroprusside on indexes of diastolic function in patients with heart failure. We reasoned that a direct effect of atrial natriuretic peptide on diastolic myocardial properties would be manifested as an effect beyond that of nitroprusside, and therefore compared the influences of these two agents on indexes of diastolic function.

Left ventricular peak negative dP/dt was unchanged with administration of nitroprusside or atrial natriuretic peptide. Both T_L and T_D decreased with nitroprusside, whereas only T_L decreased significantly with atrial natriuretic peptide. Thus, the effect of atrial natriuretic peptide on indexes of relaxation was no greater than that of nitroprusside. We attribute the decrease in T_L with both agents to a downward translation of the ventricular pressure curve, which obligates a shortening of the time constant of relaxation in a model that constrains the pressure asymptote to be zero (43). A similar finding of a decrease in T_L with no effect on T_D during atrial natriuretic peptide infusion was reported by Herrmann et al. (37) in patients with normal left ventricular function. Changes in loading conditions with reduction of left ventricular end-systolic volume may also affect isovolumetric relaxation in patients with heart failure, accounting for the fall in T_D with nitroprusside (28,41). Peak filling rate was unchanged with both nitroprusside and atrial natriuretic peptide. It is possible that a tendency toward improved filling with both medications was counterbalanced by the concomitant decrease in pulmonary capillary wedge pressure, which reflects the driving force for early diastolic filling (27,44).

Overall left ventricular distensibility throughout diastole is best assessed by the pressure-volume relation. Marked decreases in ventricular volume prevented comparison of diastolic pressure over a common range of volume for the first baseline and nitroprusside periods in eight patients and for the second baseline and atrial natriuretic peptide periods in five patients. Of the four patients in whom the position of the diastolic pressure-volume relation during atrial natriuretic peptide infusion could be compared with that during the second baseline period, a downward shift of the relation was observed in three. This effect was lessened but not abolished when the pressure-volume relations were replotted by using estimated transmural pressure. In a previous study (28) of patients with heart failure, similar downward shifts during administration of nitroprusside were also not completely abolished after "correction" for right atrial pressure. Because coronary blood flow increases in patients with coronary stenosis (45) and is not significantly altered by atrial natriuretic peptide in patients with heart failure (17), we cannot attribute the residual improvement to a decrease in coronary turgor. The effect of atrial natriuretic peptide on the relation between *end*-diastolic pressure and volume was not significantly different from that of nitroprusside.

Overall, the effects of atrial natriuretic peptide on indexes of diastolic myocardial function were similar to those of nitroprusside. Thus, we found no specific influence of the peptide on myocardial contractile or diastolic function in patients with heart failure. Additional evidence for the lack of direct myocardial actions of atrial natriuretic peptide comes from the radioautographic localization studies of Bianchi et al. (46), in which the peptide was found to bind to the endothelial cells of the rat heart but not to ventricular myocytes.

Limitations of the study. The limitations imposed by the time constraints inherent in a left heart catheterization study have already been acknowledged. Several other limitations of this study need to be considered. First, although cardiac medications were withheld for 12 to 24 h before study, it is conceivable that residual effects of these drugs could modify the effects of atrial natriuretic peptide on the myocardium. Second, it is possible that a change in autonomic tone occurring during either atrial natriuretic peptide or nitroprusside infusion may have affected myocardial contractile or diastolic function, or both. Although we did not measure plasma catecholamine concentrations in this study, previous studies (47) in which nitroprusside was administered to patients with heart failure did not reveal a change in sympathetic tone as measured by plasma norepinephrine and epinephrine levels. However, heart rate did increase slightly with nitroprusside in our study group. Third, the study

patients had severe left ventricular systolic dysfunction. It is possible that atrial natriuretic peptide would affect left ventricular contractile or diastolic function in patients with less profound heart failure.

Finally, studies (48,49) in conscious animals have suggested that pharmacologic manipulations of ventricular loading conditions with agents such as nitroprusside may alter the end-systolic pressure-volume relation despite autonomic blockade. We have attempted to achieve steady state alteration in loading conditions in patients with heart failure by balloon occlusion of the inferior vena cava in lieu of nitroprusside infusion, but have been unable to lower arterial pressure sufficiently by this method to reliably construct the end-systolic pressure-volume relation. The development of methods to reliably determine ventricular volumes on a beat to beat basis in patients with heart failure may allow the use of mechanical techniques to construct the end-systolic pressure-volume relation.

Conclusions. The administration of atrial natriuretic peptide to patients with heart failure due to systolic dysfunction results in improved pump performance, manifested as an augmentation of forward output and a decrease in filling pressures. This improvement is not associated with a change in myocardial contractile function. Changes in indexes of diastolic function with atrial natriuretic peptide infusion are similar to those that occur with nitroprusside, and are most likely mediated by an alteration in loading conditions rather than a direct effect on myocardial diastolic properties. We conclude that the beneficial effects of atrial natriuretic peptide on ventricular function in patients with chronic heart failure result from favorable changes in ventricular load without alterations in myocardial properties.

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