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Effects of Atrial Natriuretic Peptide on Left Ventricular Performance in Conscious Dogs Before and After Pacing-Induced Heart Failure[1]

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ABSTRACT

Atrial natriuretic peptide (ANP) has potent vasodilatory and natriuretic actions and may have therapeutic benefit in congestive heart failure (CHF). These benefits may be offset by a negative inotropic effect of ANP seen in isolated preparations. However, ANP's integrated effect on left ventricular (LV) contraction and relaxation, independent of loading conditions, both under normal conditions and after CHF, is not known. We studied six conscious dogs, instrumented to measure LV and left atrial pressures and to determine LV volume from three dimensions. ANP produced significant ($P < .05$) decreases in LV end-systolic pressure (101.2 ± 11.8 versus 91.7 ± 11.2 mm Hg, $P < .05$) in normal dogs and in dogs with CHF (93.1 ± 6.4 versus 87.1 ± 4.4 mm Hg, $P < .05$). ANP also caused significant reductions of the slope of end-systolic pressure-end-systolic volume relation both before (7.0 ± 1.5 versus 6.3 ± 1.5 mm Hg/ml) and after CHF (4.8 ± 1.3 versus 4.4 ± 1.2 mm Hg/ml, $P < .05$). Both before and after CHF, ANP slowed LV relaxation at matched end-systolic pressure. Before CHF, steady-state stroke volume and peak LV filling rate (dV/dt_{max}) were reduced. However, after CHF, the fall in end-systolic pressure more than offset the load-independent LV depression, as stroke volume, the rate LV relaxation, and dV/dt_{max} were increased and minimum LV pressure reduced. ANP has negative effects on LV contractility and relaxation both before and after CHF. However, after CHF, afterload reduction with ANP overcomes its negative effects, resulting in net improvement of LV ejection and relaxation. Thus, the direct cardiodepressant effects of ANP should not limit its usefulness in CHF.

Atrial natriuretic peptide (ANP) is a vasodilatory and natriuretic peptide secreted mainly by atrial myocytes (Kangawa and Matsuo, 1984). ANP (along with a closely related peptide, brain natriuretic peptide) is elevated in patients with congestive heart failure (CHF) (Levin et al., 1998). It seems that ANP's vasodilatory and natriuretic properties, as well as its suppression of sympathetic tone and reduction in the activation of renin-angiotensin system, are beneficial in CHF (Levin et al., 1998). Furthermore, blocking ANP exacerbates the development of CHF in a canine model (Stevens et al., 1995). Thus, inhibiting the degradation of ANP or infusing ANP have been suggested as possible therapies for CHF (Munzel et al., 1992).

ANP produces vasodilation and natriuresis in both the normal circulation and in CHF (Cody et al., 1986; Crozier et al., 1986; Saito et al., 1987). ANP exerts a negative inotropic effect on isolated normal cardiac tissues (Neyses and Vetter, 1989; Tajima et al., 1998). However, ANP does not have a negative inotropic effect on hypertrophied cardiac myocytes (Tajima et al., 1998). It is possible that a similar alteration in ANP's effect on contractile function may also occur in CHF. However, ANP's integrated effects on left ventricular (LV) performance, independent of alterations in loading conditions, both under normal conditions and during CHF, are not known. It is important to understand these effects, especially during CHF, if increasing ANP is to be used as a therapeutic strategy for patients with CHF. Accordingly, we undertook this study to determine the effects of ANP on LV performance in conscious animals both before and after inducing CHF by rapid pacing. LV performance was evaluated using pressure-volume analysis, which provides a load-insensitive evaluation of intact contractile performance.

Materials and Methods

Instrumentation. Six healthy, adult, heartworm-negative mongrel dogs (weight, 25–36 kg) were instrumented under anesthesia after induction with xylazine (2 mg/kg i.m.) and sodium thiopental (6

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ABBREVIATIONS: ANP, atrial natriuretic peptide; CHF, congestive heart failure; LV, left ventricular; LA, left atrial; P_{ED}, end-diastolic pressure; P_{ES}, end-systolic pressure; V_{ED}, end-diastolic volume V_{ES}, end-systolic volume; V_{LV}, LV volume; P-V, pressure volume; SW, stroke work; SV, stroke volume; T, time constant of LV relaxation.

mg/kg i.v.) and maintained with halothane (0.5–2.0%). They were intubated and ventilated with oxygen-enriched room air to maintain arterial oxygen pressure greater than 100 mm Hg and pH between 7.38 and 7.42. A sterile left lateral thoracotomy was performed, and the pericardium was widely opened. Micromanometer pressure transducers (Konisberg Instruments Inc., Pasadena, CA) and polyvinyl catheters (1.1 mm i.d.) for transducer calibration were inserted into the left ventricle through an apical stab wound and into the left atrium via the left atrial (LA) appendage. Three pairs of ultrasonic crystals (5 MHz) were implanted in the endocardium of the left ventricle to measure the anterior to posterior, septal to lateral, and base to apex (long-axis) dimensions, using the method previously described from our laboratory (Cheng et al., 1990, 1992, 1993). Hydraulic occluder cuffs were placed around the inferior and superior venae cavae. A pacing lead was attached to the right ventricle and connected to a programmable pacemaker (model 8329; Medtronic Inc., Minneapolis, MN) implanted s.c.. All wires and tubing were exteriorized through the posterior neck.

Data Collection. Studies were performed after full recovery from instrumentation (from 10 days to 2 weeks after surgery) with the dogs lying in a sling. The LV and LA catheters were connected to pressure transducers (Statham P23Db; Gould, Cleveland, OH) calibrated with a mercury manometer. The signal from the micromanometers was adjusted to match that of the catheters. The LA micromanometer was adjusted to match LV pressure at the end of long periods of diastasis. The analog signals were recorded on an eight-channel chart recorder (Astro-Med, West Warwick, RI), digitized with an online analog-to-digital converter (Data Translation Devices, Marlboro, MA) at 200 Hz and stored on a magneto-optical disk memory system.

Experimental Protocol. The effects of ANP were assessed in six dogs before and after the induction of CHF. In two additional instrumented animals, the effect of ANP was assessed after autonomic blockade (metoprolol 0.5 mg/kg plus atropine 0.1 mg/kg, i.v.) and separately with heart rate held constant at 140 beats/min by right atrial pacing. In these two additional instrumented animals, a vehicle (normal saline 3 ml/min) control study was also performed. During the same study period (15 min), the animals received the same amount of saline (6 ml within 2 min, followed by infusion of 3 ml/min, i.v.), and steady-state and caval occlusion data were collected.

Studies in Normal Dogs. Steady-state data and data during transient caval occlusions were recorded at rest while the animals lay in a sling. Three sets of variably loaded pressure-volume (P-V) loops were generated by transient caval occlusions. Then human ANP (Sigma Chemical Co.), 50 μg (dissolved in 6 ml of normal saline), was administered i.v. over 2 min, followed by an i.v. infusion of 0.1 μg/kg/min. Steady-state data were recorded after 5, 10, and 15 min of ANP infusion. Transient caval occlusions were performed at 10 min.

Induction of CHF. After the completion of the baseline study, the pacing rate was adjusted, using the external magnetic control unit, to 200 to 240 beats/min. Three times per week, the pacemaker rate was adjusted below the spontaneous rate. The animal was allowed to equilibrate for 30 min and then the data were collected. After each study, the pacing rate was returned to 200 to 240 beats/min. After pacing for 4 to 5 weeks, when the LV end-diastolic pressure (P_{ED}) during the nonpaced period had increased by more than 15 mm Hg over the prepacing control level, CHF data were obtained. This level of CHF was chosen because the animals had begun to show clinical evidence of CHF: i.e., anorexia, mild ascites, and pulmonary congestion.

Studies in CHF Dogs. Steady-state data and data during transient caval occlusions were collected with the animals lying down after the pacemaker had been turned off for more than 30 min. Then ANP was given and data were collected, using the same protocol as before CHF. In addition, data were collected with higher infusion rates of ANP (0.5 and 1.0 μg/kg/min).

Data Processing and Analysis. The LV volume (V_{LV}) was calculated as a modified general ellipsoid using the following equation:

$$V_{LV} = (\pi/6)D_{AP} \cdot D_{SL} \cdot D_{LA}$$

where D_{AP} is the anterior to posterior LV diameter, D_{SL} is the septal-to-lateral LV diameter, and D_{LA} is the long-axis LV diameter. It was previously demonstrated that this method gives a consistent measure of V_{LV} ($r = 0.97$; standard error of estimate <2 ml) despite changes in LV loading conditions, configurations, and heart rate (Little et al., 1989). To account for respiratory changes in intrathoracic pressure, steady-state measurements were averaged over the 12- to 15-s recording period that spanned multiple respiratory cycles. End-diastole was defined as the relative minimum of LV pressure occurring after the A-wave. End-systole was defined as the upper left corner of the LV P-V loop (Kono et al., 1984). The time of mitral valve opening was defined to be when LV pressure fell below LA pressure. LV P_{ED}, LV end-systolic pressure (P_{ES}), and minimum LV pressure were measured. LV end-diastolic volume (V_{ED}) and end-systolic volume (V_{ES}) were also measured. The mean LA pressure was determined.

The derivative of LV pressure (dP/dt) was calculated using the five-point Lagrangian method (Marble et al., 1981). The maximum dP/dt and minimum dP/dt were determined. Stroke volume (SV) was calculated as V_{ED} minus V_{ES}. LV stroke work (SW) was also calculated by point-by-point integration of the LV P-V loop for each beat, as described by Glower et al. (1985). The effective arterial elastance, E_A, was calculated as LV P_{ES} divided by SV (Sunagawa et al., 1985). Ejection fraction was also calculated as SV divided by V_{ED}.

Analyses of LV P-V Loops During Caval Occlusion. Only caval occlusions that produced a fall in LV P_{ES} of more than 30 mm Hg were analyzed. Premature beats and the subsequent beat were excluded from analysis.

The LV P_{ES}-V_{ES} data during the fall of LV pressure, produced by each caval occlusion, were fit using the least-squares method to:

$$P_{ES} = E_{ES}(V_{ED} - V_{O,ES})$$

where E_{ES} is the slope of linear P_{ES}-V_{ES} relation, representing the LV end-systolic elastance, and $V_{0,ES}$ is the intercept with the volume axis. The volume ($V_{100,ES}$) associated with a P_{ES} of 100 mm Hg was calculated as:

$$V_{100,ES} = V_{O,ES} + 100/E_{ES}$$

The dP/dt_{max} -V_{ED} and SW-V_{ED} relations were quantified by fitting the data from the same beats from each caval occlusion used to evaluate the P_{ES}-V_{ES} relation to:

$$dP/dt_{max} = dE/dt_{max}(V_{ED} - V_{O,dP/dt}) \quad \text{and} \quad SW = M_{SW}(V_{ED} - V_{O,SW})$$

The position of the dP/dt_{max}-V_{ED} and SW-V_{ED} relations were calculated by determining the V_{ED} associated with a dP/dt of 2000 mm Hg/s and SW of 2000 mm Hg · ml:

$$V_{2000,dP/dt} = V_{O,dP/dt} + 2000/(dE/dt_{max})$$

$$V_{2000,SW} = V_{O,SW} + 2000/M_{SW}$$

The slopes and positions in each of the three relations for each condition were evaluated as the mean values of the two or three caval occlusions performed under each condition.

The rate of LV relaxation was analyzed by determining the time constant of the isovolumic fall of LV pressure. LV pressure from the time of minimum dP/dt until mitral valve opening was fit to an exponential equation:

$$P = P_A \exp(-t/T) + P_B$$

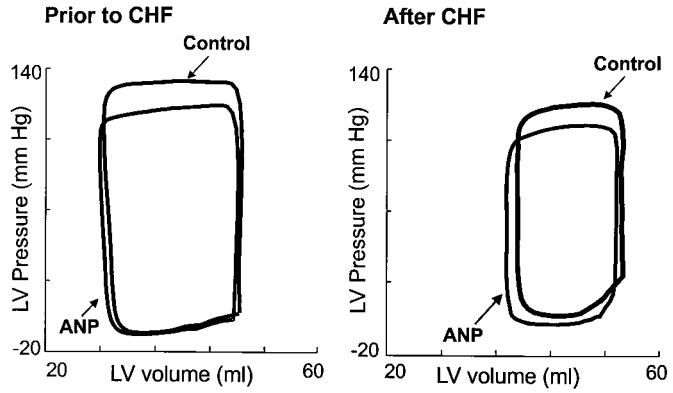

Fig. 1. An example of the average steady-state LV P-V loops obtained before and after pacing-induced CHF. The early diastolic portion of the LV loop was relatively unchanged by ANP in the normal situation. After CHF, ANP shifted the early diastolic portion of the LV P-V loop leftward and downward.

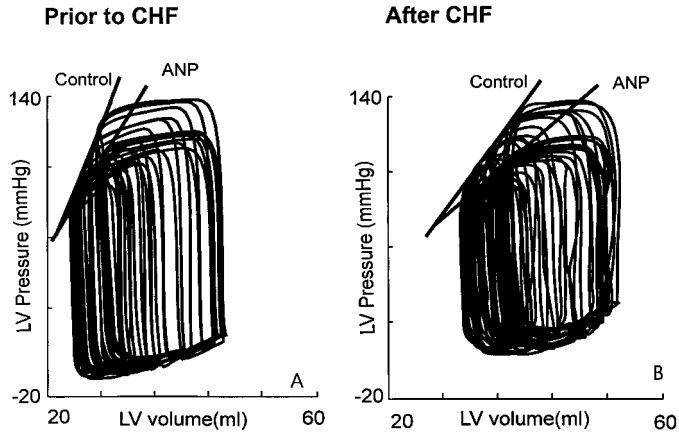

Fig. 2. LV P-V loops produced by transient caval occlusion before (control) and after administration of ANP in the same animal before and after CHF. The LV P_{ES}-V_{ES} relations are indicated by lines. ANP shifted the LV end-systolic P-V relations toward the right with decreased slopes both before and after CHF conditions, indicating a negative inotropic action of ANP.

where P is LV pressure; t is time; and P_A, P_B, and T are constants determined by data. Although the fall of isovolumic pressure is not exactly exponential (Yellin et al., 1986), the T, derived from the exponential approximation, provides an index of the rate of LV relaxation (Gilbert and Glantz, 1989). To account for the load dependence of T, the caval occlusion data was fit to:

$$T = A \cdot P_{ES} + B,$$

where A and B are constants determined by the data. The T associated with a P_{ES} = 85 mm Hg was calculated from the regression equation and compared.

Postmortem Evaluation. At the conclusion of the studies, the animals were sacrificed by lethal injections of sodium thiopental (100 mg/kg, i.v.), and the heart was examined to confirm the proper position of the instrumentation.

Statistical Analysis. LV function parameters, before and after CHF and before and after drug administration, were compared using ANOVA of repeated measures. Subsequent intergroup comparisons were performed using paired *t* tests with a Bonferroni correction for multiple comparisons. Data are expressed as mean ± S.D. *P* values $< .05$ were considered to be significant.

Results

Effects of ANP in Normal Dogs before CHF

Steady-State Measurements. Representatives of LV P-V loops showing the effects of ANP in a normal dog are shown in Fig. 1. Steady-state hemodynamic changes produced with ANP in all six dogs are summarized in Table 1. ANP infused for 10 min evoked significant ($P < .05$) decreases in LV P_{ES} (101.2 ± 11.8 versus 91.7 ± 11.2 mm Hg, $P < .05$), E_A (7.8 ± 1.4 versus 7.2 ± 1.3 mm Hg/ml, $P < .05$), P_{ED}, and mean LA pressure. ANP also produced significant decreases in maximum dP/dt, LV V_{ED}, and stroke volume (14.2 ± 3.2 versus 13.4 ± 2.9 ml, $P < .05$). No significant effects were observed in the time constant of LV relaxation (T; 31.2 ± 4.7 versus 30.7 ± 4.1 ms, P = NS) and minimum LV pressure. Maximum LV filling rate was decreased. Infusion of the same amount of saline without ANP had no effect on heart rate, LV P_{ED}, SV, or LV T. The three LV P-V relations also remained unchanged.

P-V Analysis. The effect of ANP on variably loaded P-V loops in a normal dog is shown in Fig. 2. As shown in Table 2, in normal dogs, ANP produced significant decreases in the slopes of the P_{ES}-V_{ES} relation (7.0 ± 1.5 versus 6.3 ± 1.5 mm Hg/ml, $P < .05$), the dP/dt_{max}-V_{ED} relation (69.5 ± 24.0 versus 54.0 ± 13.1 mm Hg/s/ml, $P < .05$), and the SW-V_{ED} relation (81.2 ± 12.8 versus 73.8 ± 12.3 mm Hg, $P < .05$). There were also significant rightward shifts of all three relations manifested by significant increases in $V_{100,ES}$, $V_{2000,dp/dt}$, and $V_{2000,SW}$ (45.7 ± 5.6 versus 47.6 ± 5.4 ml, $P < .05$). The decreases in slopes and the right shifts of LV P-V

TABLE 1
Effects of ANP on LV steady-state hemodynamics in normal dogs

	Control	ANP 5 min	ANP 10 min	ANP 15 min
Heart rate (beats/min)	107 ± 10.9	110 ± 12.9	101 ± 11.8	101 ± 10.5
Minimum LV pressure (mm Hg)	0.8 ± 1.7	−0.3 ± 1.4	−0.3 ± 1.5	−0.2 ± 1.7
LV end-diastolic pressure (mm Hg)	9.0 ± 2.7	7.2 ± 3.3	6.4 ± 2.6	6.2 ± 2.8
LV end-systolic pressure (mm Hg)	101.2 ± 11.8	93.5 ± 11.0*	91.7 ± 11.2*	89.3 ± 8.7*
LV end-diastolic volume (ml)	40.5 ± 6.7	40.1 ± 7.0	39.6 ± 6.7*	38.9 ± 6.7*
LV end-systolic volume (ml)	26.3 ± 6.0	25.9 ± 5.9	25.7 ± 5.7	25.6 ± 5.7
SV (ml)	14.2 ± 3.2	14.1 ± 3.6	13.4 ± 2.9*	13.6 ± 3.6*
Ejection fraction (%)	35.1 ± 8.7	35.2 ± 8.9	33.8 ± 7.6	35.0 ± 9.7
Mean LA pressure (mm Hg)	6.6 ± 1.7	5.1 ± 1.4*	4.4 ± 1.6*	4.2 ± 1.7*
Maximum dP/dt (mm Hg/s)	2686 ± 503	2585 ± 508*	2583 ± 486*	2508 ± 415*
Minimum dP/dt (mm Hg/s)	−2045 ± 353	−1920 ± 336*	−1867 ± 351*	−1811 ± 270*
Time constant of relaxation (ms)	31.2 ± 4.7	30.2 ± 3.3	30.7 ± 4.1	30.5 ± 4.3
Ea (mm Hg/ml)	7.8 ± 1.4	7.4 ± 1.6	7.2 ± 1.3*	7.3 ± 1.6*
Maximal early filling (ml/s)	129 ± 33	131 ± 36	125 ± 33*	119 ± 31*

Ea, effective arterial elastance.
* $P < .05$ versus control.

TABLE 2
Effects of ANP on LV P_{ES}-V_{ES}, dP/dt_{max}-V_{ED}, and SW-V_{ED} relations in normal dogs

	P_{ES}-V_{ES} Relation			dP/dt_{max}-V_{ED} Relation			SW-V_{ED} Relation		
	E_{ES}	$V_{O,ES}$	$V_{100,ES}$	dE/dt_{max}	V_O, dp/dt	V_{2000}, dp/dt	M_{SW}	$V_{O,SW}$	$V_{2000,SW}$
	mm Hg/ml	*ml*	*ml*	*mm Hg/s/ml*	*ml*	*ml*	*mm Hg*	*ml*	*ml*
Control	7.0 ± 1.5	9.6 ± 4.0	24.5 ± 4.6	69.5 ± 24.0	−6.9 ± 13.8	24.0 ± 9.0	81.2 ± 12.8	20.5 ± 2.9	45.7 ± 5.6
ANP	6.3 ± 1.5*	8.6 ± 3.9	25.3 ± 4.7*	54.0 ± 13.1*	−3.8 ± 11.3	35.0 ± 5.3*	73.8 ± 12.3*	20.0 ± 3.5	47.6 ± 5.4*

* $P < .05$ versus control.

relations with ANP administration indicate that it caused a significant decline of LV contractile performance in normal dogs.

Effect of Pacing-Induced CHF

As summarized in Tables 1 and 3, after the development of CHF, the mean P_{ED} increased from 9.0 ± 2.7 to 28.6 ± 5.3 mm Hg ($P < .05$). The minimum LV pressure (0.8 ± 1.7 versus 7.3 ± 3.5 mm Hg, $P < .05$) and mean LAP (6.6 ± 1.7 versus 18.1 ± 5.1 mm Hg, $P < .05$) were also increased. The LV V_{ES} and V_{ED} increased, whereas SV was decreased. The T of LV relaxation increased (31.2 ± 4.7 versus 39.2 ± 5.0 ms, $P < .05$). The LV contractility was also significantly impaired, as indicated by the decreases in the slopes and produced rightward shifts of the P-V relations.

Effects of ANP in Dogs with CHF

Steady-State Data Measurements. Representatives of LV P-V loops showing the effects of ANP in a CHF dog are shown in Fig. 1. Steady-state hemodynamic responses produced with ANP in all six dogs are summarized in Table 3. After CHF, the same dosage of ANP that was given in normal dogs (50 μg loading plus 0.1 μg/kg/min infusion for 10 min) produced significant decreases in P_{ES} (93.1 ± 6.4 versus 87.1 ± 4.4 mm Hg, $P < .05$) and E_A (8.4 ± 2.4 versus 7.4 ± 2.1 mm Hg/ml, $P < .05$). ANP did not affect the heart rate at this concentration. In contrast to the results in normal dogs, ANP caused significant increases in SV and the maximum LV filling rate with decreases in T (39.2 ± 5.0 versus 36.7 ± 4.4 ms, $P < .05$) and in minimum LV pressure (7.3 ± 3.5 versus 5.7 ± 3.5 mm Hg, $P < .05$). ANP did not cause decreases in P_{ED} and mean LA pressure at this concentration. Increased dosages of ANP infusion also produced significant decreases in P_{ES}, E_A, T, and minimum LV pressure, and a similar increase in SV. These doses of ANP revealed significant decreases in P_{ED} and mean LA pressure (Table 3).

P-V Analysis. The effect of ANP (50 μg loading plus 0.1 μg/kg/min infusion for 10 min) on variably loaded P-V loops in a CHF dog is shown in Fig. 2. The changes of LV P-V relations by the three dosages of ANP are summarized in Table 4. After CHF, ANP (0.1 μg/kg/min), the identical dose used in normal dogs, caused significant decreases in the slopes of the LV P_{ES}-V_{ES} relation (4.8 ± 1.3 versus 4.4 ± 1.2 mm Hg/ml, $P < .05$), the dP/dt_{max}-V_{ED} relation (51.8 ± 18.5 versus 42.2 ± 12.3 mm Hg/s/ml, $P < .05$), and the SW-V_{ED} relation (61.6 ± 6.6 versus 56.3 ± 6.5 mm Hg, $P < .05$). There were also significant rightward shifts of all three relations, manifested by significant increases in $V_{100,ES}$ (37.6 ± 17.9 versus 38.8 ± 18.2 ml, $P < .05$), $V_{2000,dp/dt}$ and $V_{2000,SW}$ (63.8 ± 16.9 versus 65.7 ± 17.5 ml, $P < .05$). The higher doses of ANP produced similar results.

Effects of ANP on LV Relaxation

ANP produced upward shifts of the LV T-P_{ES} relations both before and after CHF (Fig. 3). Thus, at a P_{ES} of 85 mm Hg, T was prolonged from 26.2 ± 4.1 to 30.3 ± 4.7 ms ($P < .05$) with ANP infusion in normal dogs. After CHF, ANP lengthened T at 85 mm Hg from 28.8 ± 12.8 to 36.8 ± 8.2 ms ($P < .05$).

Effects of ANP during Atrial Pacing and after Autonomic Blockade

As displayed in Fig. 4B, when heart rate was held constant by right atrial pacing, ANP produced a similar decrease in LV P_{ES} (108 ± 9.9 versus 93 ± 8.6 mm Hg) and without marked change in T (32.7 ± 2.1 versus 31.5 ± 1.3 ms). ANP

TABLE 3
Effects of ANP on LV steady-state hemodynamics in CHF dogs after a 10-min infusion

	Control	ANP		
		0.1	0.5	1.0
			μg/kg/min	
Heart rate (beats/min)	119 ± 13.2	113 ± 14.7	107 ± 15.7	108 ± 14.6
Minimum LV pressure (mm Hg)	7.3 ± 3.5	5.7 ± 3.5*	5.6 ± 3.1*	5.5 ± 2.7*
LV end-diastolic pressure (mm Hg)	28.6 ± 5.3	27.4 ± 6.0	27.1 ± 5.2*	26.0 ± 5.9*
LV end-systolic pressure (mm Hg)	93.1 ± 6.4	87.1 ± 4.4*	85.0 ± 5.2*	85.5 ± 5.4*
LV end-diastolic volume (ml)	52.3 ± 18.0	52.4 ± 18.3	52.0 ± 17.9	51.7 ± 18.3*
LV end-systolic volume (ml)	40.6 ± 16.7	39.9 ± 17.0*	39.6 ± 17.0*	39.2 ± 16.8*
SV (ml)	11.8 ± 3.1	12.5 ± 3.2*	12.4 ± 3.1*	12.5 ± 3.4*
Ejection fraction (%)	23.8 ± 7.7	25.4 ± 8.4*	25.5 ± 8.8*	25.6 ± 8.4*
Mean LA pressure (mm Hg)	18.1 ± 5.1	17.3 ± 4.6	15.0 ± 4.6*	14.0 ± 3.7*
Maximum dP/dt (mm Hg/s)	1855 ± 200	1748 ± 183*	1668 ± 212*	1702 ± 255*
Minimum dP/dt (mm Hg/s)	−1673 ± 119	−1563 ± 147*	−1520 ± 146*	1549 ± 164*
Time constant of relaxation (ms)	39.2 ± 5.0	36.7 ± 4.4*	36.2 ± 4.4*	36.3 ± 4.8*
Ea (mm Hg/ml)	8.4 ± 2.4	7.4 ± 2.1*	7.3 ± 2.2*	7.3 ± 2.2*
Maximal early filling dV/dt (ml/s)	185 ± 35	198 ± 39*	196 ± 33*	196 ± 36*

Ea, effective arterial elastance.
* $P < .05$ versus control.

TABLE 4
Effects of ANP on LV P_{ES}-V_{ES}, dP/dt_{max}-V_{ED}, SW-V_{ED} relations in CHF dogs

	P_{ES}-V_{ES} Relation			dP/dt_{max}-V_{ED} Relation			SW-V_{ED} Relation		
	E_{ES}	$V_{O,ES}$	$V_{100,ES}$	dE/dt_{max}	V_O, dp/dt	V_{2000}, dp/dt	M_{SW}	$V_{O,SW}$	$V_{2000,SW}$
	mm Hg/ml	*ml*	*ml*	*mm Hg/s*	*ml*	*ml*	*mm Hg*	*ml*	*ml*
Control	4.8 ± 1.3	15.3 ± 12.4	37.6 ± 17.9	51.8 ± 18.5	11.7 ± 9.8	54.5 ± 20.2	61.6 ± 6.6	31.0 ± 15.0	63.8 ± 16.9
ANP 0.1 (μg/kg/min)	4.4 ± 1.2*	14.6 ± 12.6	38.8 ± 18.2*	42.2 ± 12.3*	7.8 ± 11.6	58.2 ± 20.6*	56.3 ± 6.5*	29.8 ± 14.8*	65.7 ± 17.5*
ANP 0.5 (μg/kg/min)	4.3 ± 1.3*	14.7 ± 12.2	39.7 ± 18.9*	42.3 ± 13.9*	8.4 ± 12.4	59.3 ± 22.5*	56.0 ± 5.5*	29.8 ± 15.3*	65.8 ± 17.1*
ANP 1.0 (μg/kg/min)	4.2 ± 1.3*	12.6 ± 10.7*	38.9 ± 17.9*	42.3 ± 14.7*	7.7 ± 13.4	59.7 ± 23.6*	56.0 ± 4.4*	29.8 ± 14.7*	65.7 ± 16.3*

* $P < .05$ versus control.

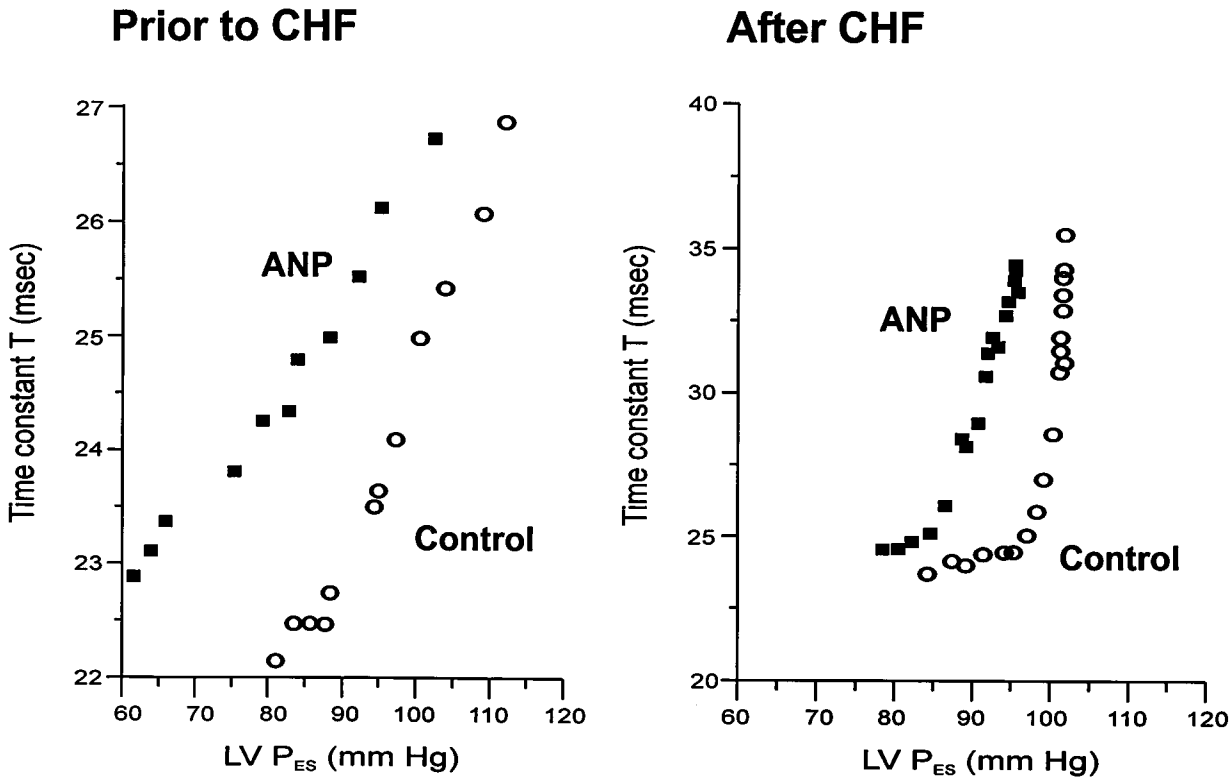

Fig. 3. LV T-P_{ES} relations during vena caval occlusions in a normal dog and in the same dog after pacing-induced CHF. Both before and after CHF, ANP produced an upward shift of the relations, so that at constant pressure, the T is increased, indicating slower relaxation with ANP. Under normal conditions, the fall in P_{ES} offsets the upward shift of the T-P_{ES} relation. Thus, there is little change in steady-state T with ANP. After CHF, T is more sensitive to changes in P_{ES}, so the ANP-induced reduction in P_{ES} more than offsets the upward shift of the LV T-P_{ES} relations; therefore, steady-state T is reduced with ANP.

also produced similar decreases and rightward shift of 3 LV P-V relations (Fig. 4). Similar observations were obtained after autonomic blockade (Fig. 4C).

Discussion

In this study, we assessed the effect of exogenous ANP on LV systolic and diastolic performance in conscious animals. We used P-V analysis to separate ANP's effects on LV function from load-induced alterations. We found that ANP depresses the contractile performance of the intact LV in conscious animals both before and after CHF. Our results before CHF are consistent with previous findings in normal isolated myocytes (Tajima et al., 1998; Neyses and Vetter, 1989) and in isolated papillary muscles (Meulemans et al., 1988). The depression of normal contractile function by ANP seems to be mediated by cGMP and involves an alteration in Na^+/H^+ exchange, leading to intracellular acidification (Tajima et al., 1998). ANP's suppression of activation of the sympathetic and renin-angiotensin systems may also contribute to the mild depression of LV contractile performance we observed in our conscious animals. However, the negative inotropic effect of ANP was still present after autonomic blockade. In addition, ANP's effects were not caused by a change in heart rate. Heart rate tended to decrease slightly with ANP, but these changes did not reach statistical significance. Furthermore, the effects of ANP were seen when heart rate was held constant by right atrial pacing (Fig. 4 and Table 5).

Tajima et al. (1998) found that ANP's negative inotropic effects were absent in hypertrophied rat myocytes. This find-

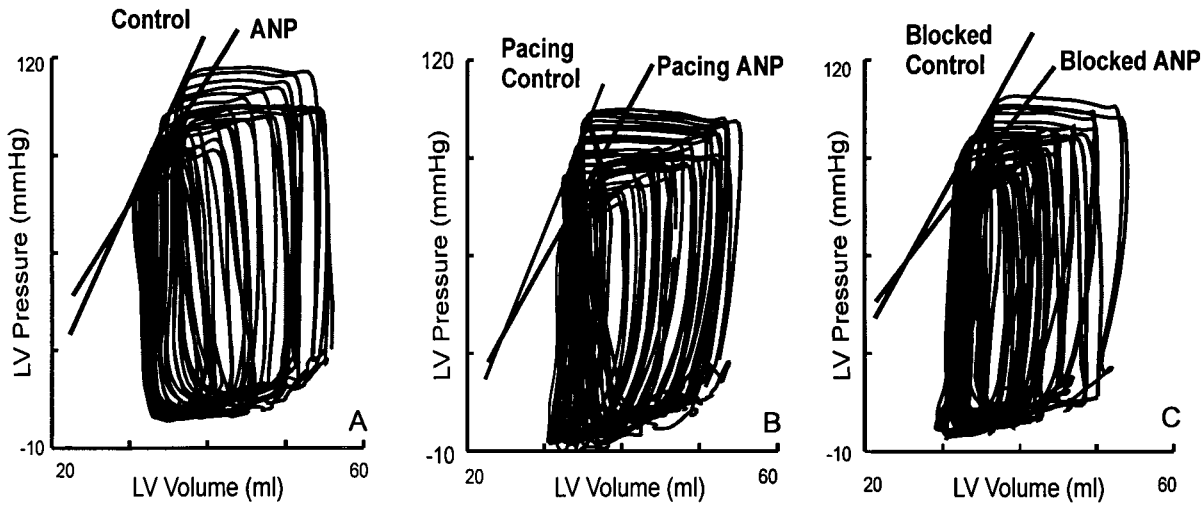

Fig. 4. Variably loaded P-V loops obtained before and after ANP. ANP produced similar depression (rightward shift, decreased slope) when the heart rate was held constant with right atrial pacing, and after autonomic blockade.

TABLE 5
Hemodynamic changes with ANP (n = 2)

	Reflexes Intact	Paced at 140	Autonomic Blockade
		bpm	
Heart rate (bpm)	−9 ± 2	0	3 ± 2
LV end-systolic pressure (mm Hg)	−11 ± 2	−12 ± 6	−10 ± 4
Time constant of relaxation (ms)	−1.2 ± 2.1	−1.6 ± 1.2	−1.8 ± 1.0
E_{ES} (mm Hg/ml)	−1.6 ± 0.4	−1.2 ± 0.2	−1.5 ± 0.5
dE/dt_{max} (mm Hg/s)	−10.5 ± 4.2	−31.5 ± 5.8	−6.3 ± 2.3
M_{SW} (mm Hg)	−8.3 ± 1.6	−10.3 ± 4.7	−8.5 ± 3.8

ing, as well as altered renal and vasodilatory responses (Kohzuki et al., 1989; Wada et al., 1994) with chronic ANP activation, suggests that the response to ANP may be altered in disease states with sustained elevation of ANP. In contrast, we found that the infusion of ANP continued to produce a negative inotropic effect after the induction of CHF by rapid pacing. However, ANP's modest negative inotropic effect in CHF was more than offset by the reduction in arterial load produced by ANP's vasodilation. Thus, the steady-state SV was enhanced by ANP after CHF.

ANP has been found to induce early relaxation of isolated cat and rat papillary muscles (Meulemans et al., 1988). This effect seems to be mediated by cGMP that is produced by endothelial release of nitric oxide, although other mechanisms are also possible (Winquist et al., 1984; Winaver et al., 1995). We evaluated LV relaxation by assessing the T of LV isovolumic pressure fall at constant systolic load (P_{ES} = 85 mm Hg) (Fig. 3). In contrast to the findings in isolated papillary muscles, we found that LV relaxation (at constant load) was slowed by ANP both before and after CHF.

Under normal conditions, the direct depression of LV relaxation by ANP was balanced by the reduction in arterial load produced by ANP's vasodilatory action; there was little change in the time course of LV pressure fall and minimum LV pressure, although peak LV filling was reduced. The load sensitivity of relaxation is enhanced in CHF (Little, 1992). Consistent with this concept, we found that after CHF, the decrease in systolic pressure produced by ANP more than offset the direct depression of relaxation. Thus, after CHF, steady-state relaxation was enhanced by ANP. In addition, after CHF, ANP produced a downward shift of the early diastolic portion of the steady-state P-V loop (Fig. 1), so that minimum LV pressure was reduced and peak LV filling rate (dV/dt_{max}) was increased after CHF.

Because ANP is increased severalfold in CHF, the response to a further increase in ANP might be attenuated, compared with before CHF. For example, Wada et al. (1994) found that vasodilatory action of ANP was decreased in dogs with severe tachycardia-induced CHF. In contrast, we found that vasodilatory and cardiodepressant effects of an infusion of ANP were not attenuated in CHF. Although we used the same animal model, we cannot be certain that the severity of CHF was equivalent. We cannot be certain that the results in our animal model of CHF will apply to all patients with clinical CHF; however, our results suggest that increasing ANP by infusion or blocking its degradation may be beneficial in CHF.

In conclusion, we found that ANP produces arterial vasodilation and a load-independent depression of LV contractile function and relaxation both in normal conscious animals and after pacing-induced CHF. However, the contractile depression and slowing of relaxation after CHF are more than offset by ANP's arterial vasodilation so that steady-state SV, relaxation, and early diastolic function are enhanced. Thus, cardiac depression by ANP should not limit its usefulness as a therapeutic strategy in CHF.

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