

Effects of adrenomedullin on load and myocardial performance in normal and heart-failure dogs

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Received 22 November 1999; accepted in final form 28 March 2000

Lainchbury, John G., Donna M. Meyer, Michihisa Jougasaki, John C. Burnett Jr., and Margaret M. Redfield. Effects of adrenomedullin on load and myocardial performance in normal and heart-failure dogs. *Am J Physiol Heart Circ Physiol* 279: H1000–H1006, 2000.—Myocardial actions of the vasodilator peptide adrenomedullin (ADM) in the intact animal are unknown. Negative and positive inotropic actions have been reported in ex vivo experiments. Myocardial and load-altering actions of ADM in dogs before and after development of heart failure were studied. With controlled heart rate (atrial pacing) and after β -blockade, ADM was administered to five normal dogs in doses of $20 \text{ ng} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ iv, $100 \text{ ng} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ iv, and $200 \text{ ng} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ into the left ventricle (LV). LV peak systolic pressure and end-systolic volume decreased with each dose of ADM. End-systolic pressure decreased with the two higher doses. At the highest dose, arterial elastance and the time constant of LV isovolumic relaxation (τ) decreased, and LV end-systolic elastance (E_{es}) increased. LV end-diastolic pressure and volume were unchanged. In five additional normal dogs receiving only the highest dose of ADM ($200 \text{ ng} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ intra-LV), to control for increased heart rate and sympathetic activation observed with the cumulative infusion, ADM produced arterial vasodilation but no change in E_{es} or τ . In four dogs with pacing-induced heart failure, ADM ($200 \text{ ng} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ intra-LV) was without effect on τ , E_{es} , and systolic or diastolic pressure and volume. In vivo, ADM appears to be a selective arterial dilator without inotropic or lusitropic effects. The vasodilatory actions are attenuated in heart failure.

inotrope; hemodynamics

ADRENOMEDULLIN (ADM) is a recently discovered 52-amino acid peptide that circulates in human plasma (17). Infusion of this peptide results in vasodilation and natriuresis in vivo (11, 21). Plasma concentrations of ADM are increased in a variety of cardiovascular disorders, including hypertension and heart failure (6, 12, 15, 16). These findings suggest that ADM may play a role in the regulation of cardiovascular homeostasis.

The actions of ADM are thought to be mediated, in part, through the second-messenger cAMP and through effects on intracellular calcium homeostasis

(9, 24). Therefore, it is possible that ADM may have inotropic effects. In vitro studies of the myocardial effects of ADM have yielded conflicting results, with experiments in isolated hearts showing a cAMP-independent positive inotropic effect and studies in isolated myocytes showing a negative inotropic effect (8, 28, 29). The effect of ADM on left ventricular (LV) function and the potential therapeutic role of ADM as a vasodilator or inodilator in vivo have not been defined.

To date, no study has directly assessed the effects of ADM on myocardial contractility in vivo in either normal or heart-failure states. Although studies in intact animals have shown an increase in cardiac output and an increase in the maximum rate of change of aortic flow with ADM administration, changes in these variables may be influenced by changes in loading conditions or heart rate rather than by direct positive inotropic effects (3, 22). In addition, the effect of ADM on diastolic myocardial function has not been studied.

This study was designed to document for the first time the effects of ADM infusion on myocardial contractility and diastolic function in conscious normal dogs and dogs with experimental heart failure. A range of doses was used to produce pathophysiological and pharmacological plasma concentrations. Because ADM may possess vasodilatory and inotropic effects, we utilized the end-systolic pressure-volume relationship to assess myocardial effects, as it is a relatively load-insensitive measure of myocardial contractility (14, 25). We hypothesized that ADM would have both vasodilator and positive inotropic effects.

METHODS

Experiments were performed in male mongrel dogs. Dogs weighed between 18 and 24 kg and were fed standard dog chow (Lab Canine Diet 5006; Purina Mills, St. Louis, MO); dogs had free access to drinking water. The study was approved by the Institutional Animal Care and Use Committee of the Mayo Clinic and was conducted in accordance with the Animal Welfare Act.

Instrumentation. Dogs were anesthetized with Pentothal Sodium (20 mg/kg) and isoflurane (0.5–2.5%) and were ventilated with supplemental oxygen. A left lateral thoracotomy

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was performed, and the pericardium was widely opened. A solid-state micromanometer pressure transducer (Konigsberg Instruments, Pasadena, CA) and a silicon fluid-filled catheter for transducer calibration were inserted through the LV apex. Piezoelectric ultrasound dimension crystals (Triton Technology, San Diego, CA, or Sonometrics, London, ON, Canada) were implanted on opposing anterior and posterior endocardial surfaces of the LV to measure the internal short-axis dimension and at the basal epicardial and apical endocardial surface to measure the LV long-axis dimension. Hydraulic occluders were placed on the proximal superior and inferior vena cavae (In Vivo Metrics, Heladsburg, CA). A pacing wire was sutured to the left atrial free wall for use in controlling heart rate during the acute experiments. In dogs used for the heart-failure experiments, a screw-in epicardial pacing lead was placed on the right ventricular (RV) free wall, and a programmable cardiac pacemaker (model 8329 or 5985; Medtronic, Minneapolis, MN) was implanted subcutaneously for chronic RV pacing.

Data collection. Studies were performed after full recovery from the thoracotomy (10–14 days) in the normal dogs and after the pacing protocol was completed in heart-failure animals. All studies were undertaken with the dogs awake and standing quietly in a sling. The LV fluid-filled catheter was connected to a calibrated pressure transducer, and the signal from the micromanometer was adjusted to match that of the fluid-filled catheter. LV dimensions were measured by use of the implanted ultrasonic crystals (3 MHz) and a sonomicrometer. The analog signals of pressure and dimension were processed with an analog-to-digital online data acquisition and control system that allowed online display of all parameters (CA Recorder version 1.1; Data Integrated Scientific Systems, Pinckney, MD).

Experimental protocol. Five normal dogs were studied initially. These normal dogs were given propranolol at 2 mg/kg intravenously (but no other premedication) and paced from the left atrium at ~20 beats/min above their intrinsic heart rate to block effects of vasodilator-induced reflex sympathetic activation and to control heart rate throughout the experimental protocol.

Fifteen minutes after the administration of propranolol and the commencement of atrial pacing, baseline recordings were made. Three steady-state recordings, each of 20-s duration to account for respiratory variation, were made over ~5 min. After completion of the steady-state recordings, at least three sets of variably loaded pressure-volume loops were generated by transient occlusion of the cavae. Hemodynamic variables were allowed to return to baseline between each caval occlusion. After collection of the baseline data, human ADM-(1–52) (Phoenix, Mountain View, CA) was infused at three different doses, each for 30 min: 20 ng · kg⁻¹ · min⁻¹ intravenously, 100 ng · kg⁻¹ · min⁻¹ intravenously, and finally 200 ng · kg⁻¹ · min⁻¹ via the LV fluid-filled catheter. The final dose administered directly into the LV was designed to produce marked elevation of intracoronary ADM concentrations. At the end of each 30-min infusion, steady-state and variably loaded pressure-volume loop recordings were repeated as described above.

Venous blood samples were collected for measurement of plasma ADM and cAMP concentrations at baseline and at the end of each ADM dose. Venous blood samples for measurement of plasma norepinephrine and epinephrine were collected at baseline and at the end of the final ADM dose.

The highest dose of ADM was associated with an increase in plasma norepinephrine and an increase in heart rate above the atrial pacing rate, suggesting reflex sympathetic activation in response to decreases in arterial pressure. Also,

the cumulative infusion of ADM had decreased LV end-systolic pressure dramatically, such that the end-systolic pressure-volume relationship before ADM and after the last dose of ADM showed relatively little overlap. These observations make interpretation of any inotropic and lusitropic effects at the highest dose of ADM difficult. To evaluate potential inotropic or lusitropic responses of the highest dose of ADM in the absence of reflex sympathetic activation and at more similar systolic pressures, five additional normal dogs were studied with only the highest dose of ADM (200 ng · kg⁻¹ · min⁻¹ intra-LV over 30 min) 15 min after administration of propranolol. The decrease in the total dose of ADM and the lack of a prolonged period since propranolol administration were designed to reduce the chance that reflex sympathetic stimulation was responsible for changes in LV function. Data collection was identical to the initial study except that only one dose of ADM was used.

Heart failure was then induced in these five dogs by rapid RV pacing (240 beats/min for 3 wk). This pacing protocol produces a model of severe heart failure (2). For technical reasons, data could only be collected on four dogs in heart failure. At the completion of the pacing protocol, ventricular pacing was stopped, and the dogs were studied with infusion of ADM (200 ng · kg⁻¹ · min⁻¹) into the LV and with atrial pacing to control heart rate but without administration of propranolol. Data were collected at baseline and end of ADM infusion in the same manner as in the previous studies.

Data analysis. Steady-state recordings were averaged over the 20-s recording period to account for respiratory variation.

LV volume was calculated as a modified ellipsoid model with the use of the following equation

$$V_{LV} = \left(\frac{\pi}{6}\right) \cdot SA^2 \cdot LA$$

where V_{LV} is volume of LV, SA is short-axis LV dimension, and LA is long-axis LV dimension. This method of volume calculation gives consistent measures of LV volume despite changes in loading conditions and inotropic state (4). Stroke volume was calculated as LV end-diastolic volume minus LV systolic volume. Ejection fraction (in %) was calculated as stroke volume divided by end-diastolic volume and multiplied by 100. End diastole was defined as the relative minimum of LV pressure after the A wave. End systole was defined as the top left corner of the pressure-volume loop, identified by use of the iterative technique (18).

Effective arterial elastance (E_a) was calculated as end-systolic pressure divided by stroke volume (27). This variable combines compliance, characteristic impedance, and resistive properties of the vasculature.

Calculated first derivative of pressure development over time (dP/dt) was derived from LV pressure by the five-point Lagrangian fit (20). The rate of LV relaxation was analyzed by determination of the time constant of the isovolumic fall of LV pressure (τ). The time from peak negative dP/dt to 5 mmHg above LV end-diastolic pressure was fit to an exponential equation: $P = P_0 e^{-t/\tau}$, where P is LV pressure, P_0 is LV pressure at peak negative dP/dt , t is time, and τ is a constant determined by the data (23).

Only caval occlusions that produced a fall in end-systolic pressure of at least 30 mmHg were analyzed. Premature beats and two subsequent beats were excluded from the analysis. The LV end-systolic pressure and volume data during the fall in LV pressure, caused by each caval occlusion, were fit by use of the least squares technique to the equation $P_{es} = E_{es}(V_{es} - V_0)$, where P_{es} is end-systolic

Table 1. *Effects of multiple doses of ADM on hemodynamic parameters in normal dogs*

	Baseline	ADM		
		20 ng/kg iv	100 ng/kg iv	200 ng/kg intra-LV
LV peak systolic pressure, mmHg	133 ± 7	126 ± 8*	121 ± 7*	110 ± 9*
LV end-systolic pressure, mmHg	120 ± 5	114 ± 7	107 ± 8*	84 ± 8*
LV end-systolic volume, ml	25 ± 8	23 ± 8*	23 ± 8*	21 ± 7*
Arterial elastance, mmHg/ml	15 ± 3	15 ± 3	12 ± 1	7 ± 1*
LV end-diastolic pressure, mmHg	7.3 ± 1.3	4.3 ± 1.4	5.2 ± 1.8	5.1 ± 1.2
LV end-diastolic volume, ml	34.6 ± 4.5	31.6 ± 4.6	33.0 ± 4.3	33.2 ± 3.3
Heart rate, beats/min	142 ± 3.4	142 ± 4.2	142 ± 4.6	161 ± 3.0*
τ , ms	29.4 ± 1.6	27.0 ± 1.6	27.0 ± 2.0	23.4 ± 1.4*
E_{es} , mmHg/ml	8.8 ± 1.2	9.0 ± 1.4	8.9 ± 2.7	10.6 ± 2.0*
V_0 , ml	9.0 ± 7.1	9.1 ± 7.4	8.8 ± 5.4	11.4 ± 6.5*

Values are means ± SE; $n = 5$ dogs. ADM, adrenomedullin; LV, left ventricular; τ , time constant of LV isovolumic relaxation, assuming non-zero asymptote; iv, intravenous administration; E_{es} , end-systolic elastance; V_0 , LV volume at zero pressure. * $P < 0.05$ vs. baseline.

pressure, E_{es} is slope of the linear end-systolic pressure-volume relationship (representing the LV end-systolic elastance), V_{es} is volume at end systole, and V_0 is intercept with the volume axis. The slope of the end-systolic pressure-volume relationship (E_{es}) is sensitive to changes in contractile state but relatively insensitive to changes in loading conditions.

Plasma assays. Venous blood samples were collected into EDTA and immediately placed on ice. After centrifugation at 2,500 rpm for 10 min, the plasma was decanted and stored at -20°C until analysis.

Plasma ADM and cAMP were measured by specific radioimmunoassay, as previously described (12, 26). Plasma epinephrine and norepinephrine were measured by high-pressure liquid chromatography (Mayo Medical Laboratory, Rochester, MN).

Statistics. All data are presented as means ± SE. Comparisons within the multiple-dose normal group were made by one-way ANOVA for repeated measures followed by a post hoc analysis with Dunnett's test or a test for linear trend. Comparisons within and between the single-dose normal and heart-failure groups were made with the use of t -tests. Statistical significance was accepted as $P < 0.05$.

RESULTS

All dogs tolerated the protocol, and all results are included in the analyses.

Normal dogs with multiple doses of ADM. Steady-state hemodynamic measurements at baseline and at the end of each ADM dose are shown in Table 1.

LV peak systolic pressure and end-systolic pressure decreased in a dose-dependent fashion with ADM infusion. LV peak systolic pressure was significantly

reduced compared with baseline with all doses of ADM, whereas LV end-systolic pressure was significantly reduced by the two higher doses of ADM. LV end-systolic volume was decreased significantly and in a dose-dependent fashion with each dose of ADM. E_a was significantly decreased with the highest dose of ADM. Heart rate increased above the atrial pacing rate with the highest dose of ADM.

LV end-diastolic pressure and end-diastolic volume were unchanged by ADM infusion. τ , the time constant of LV isovolumic relaxation, decreased with the highest dose of ADM.

E_{es} was significantly increased with the highest dose of ADM but was unchanged by the lower infusion doses. V_0 increased with the highest dose of ADM. Figure 1 shows representative variably loaded pressure-volume loops from one dog at baseline and with the highest ADM infusion rate. Figure 1 demonstrates the increase in the slope of the end-systolic pressure-volume relationship with ADM administration at the 200-ng \cdot kg $^{-1}$ \cdot min $^{-1}$ dose into the LV. However, because of the marked decrease in systolic pressure with the cumulative dose of ADM, there was relatively little overlap in the end-systolic pressures at which the slopes of the end-systolic pressure-volume relationships were compared.

Plasma concentrations of ADM and cAMP at baseline and with each infusion dose are shown in Table 2. ADM plasma concentrations increased dose dependently with infusion of ADM ($P < 0.05$ by ANOVA and $P < 0.05$ with post hoc test for linear trend). Plasma

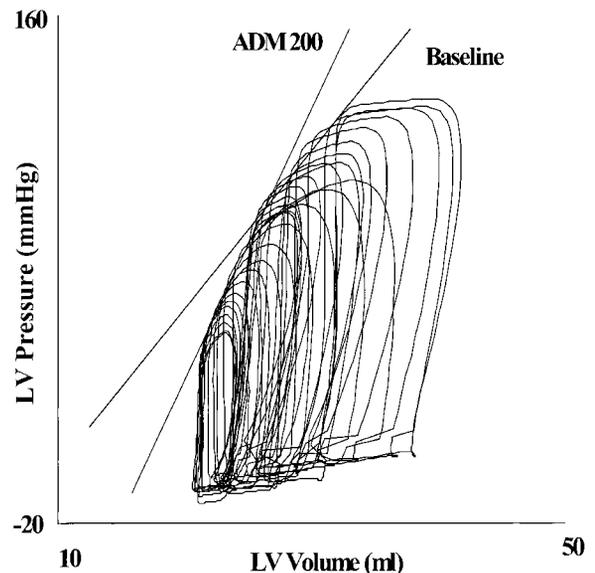


Fig. 1. Example of variably loaded pressure-volume loops from 1 dog obtained at baseline and with adrenomedullin (ADM) infusion at 200 ng \cdot kg $^{-1}$ \cdot min $^{-1}$ (ADM 200) into the left ventricle (LV; after preceding doses of 20 and 100 ng \cdot kg $^{-1}$ \cdot min $^{-1}$ iv). The slope of the line connecting the end-systolic points is the end-systolic elastance. The increase in slope of this line from baseline to ADM infusion (200 ng/kg into the LV) suggests an increase in LV contractility; however, the end-systolic pressure-volume relationships are compared over markedly different pressure ranges, making interpretation of the apparent inotropic response difficult.

Table 2. Plasma ADM and cAMP concentrations in response to ADM infusion in normal dogs

	Baseline	ADM		
		20 ng/kg iv	100 ng/kg iv	200 ng/kg Intra-LV
ADM, pg/ml	9.2 ± 0.4	31.5 ± 6.5	140.6 ± 46.3	322.6 ± 151.5
cAMP, pmol/ml	17.9 ± 4.9	12.8 ± 4.6	18.8 ± 3.1	22.6 ± 5.2

Values are means ± SE; n = 5 dogs. ADM concentrations increased dose dependently with ADM infusion (P < 0.05 by ANOVA and post hoc test for linear trend). cAMP tended to increase with ADM infusion (P = 0.053 by ANOVA).

concentrations of cAMP tended to increase with the higher doses of ADM but did not reach statistical significance (P = 0.053 by ANOVA).

Norepinephrine concentrations were increased at the end of the protocol compared with baseline (407 ± 37 vs. 236 ± 15 pg/ml, P = 0.01). Epinephrine concentrations were not significantly changed by ADM infusion (113 ± 29 vs. 84 ± 22 pg/ml, P = 0.2).

Normal dogs with high-dose ADM only. The results of the infusion of ADM at 200 ng · kg⁻¹ · min⁻¹ into the LV, given without other preceding doses and in closer temporal proximity to β-blockade, are shown in Table 3.

Importantly, no change in heart rate was observed with ADM infusion. LV peak, end-systolic pressure, and E_a decreased significantly with ADM infusion. LV end-systolic volume tended to decrease but was not significantly smaller. LV end-diastolic pressure and end-diastolic volume were unchanged by ADM infusion. τ and E_{es} were also unchanged. Representative pressure-volume loops at baseline and with ADM infusion are shown in Fig. 2; no change in the slope of the end-systolic pressure-volume relationship is seen with ADM infusion, and there is good overlap of the end-systolic pressures at which the slopes of the end-systolic pressure-volume relationships are compared.

ADM infusion resulted in a significant increase in plasma ADM (increase with infusion 827 ± 242 pg/ml, P < 0.05 for increase) but no change in cAMP (increase with infusion 3.2 ± 3.9 pmol/ml).

Heart-failure dogs. After the induction of heart failure by rapid ventricular pacing, baseline LV peak

Table 3. Effects of a single dose of ADM on hemodynamic parameters in normal dogs

	Baseline	ADM (200 ng/kg intra-LV)
LV peak systolic pressure, mmHg	139 ± 6	123 ± 6*
LV end-systolic pressure, mmHg	125 ± 6	96 ± 5*
LV end-systolic volume, ml	20 ± 3	17 ± 2
Arterial elastance, mmHg/ml	9.3 ± 1.3	4.9 ± 0.6*
LV end-diastolic pressure, mmHg	6.1 ± 0.9	8.9 ± 1.5
LV end-diastolic volume, ml	35 ± 5	38 ± 4
Heart rate, beats/min	144 ± 5	149 ± 3
τ, ms	28 ± 2	26 ± 2
E _{es} , mmHg/ml	6.5 ± 1.0	6.4 ± 1.0
V ₀ , ml	-2.0 ± 5.01	-0.5 ± 0.3

Values are means ± SE; n = 5 dogs. *P < 0.05 vs. baseline.

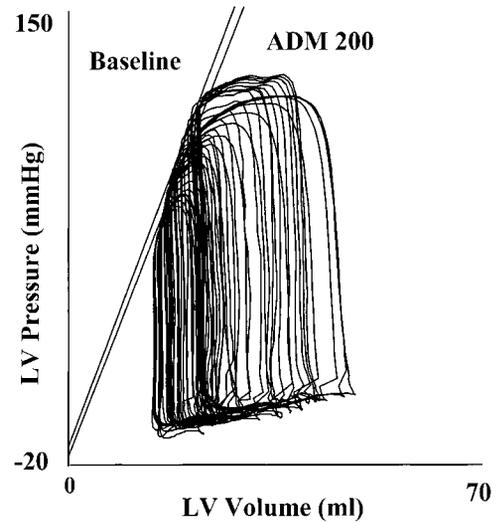


Fig. 2. Examples of pressure-volume loops from 1 dog at baseline and after receiving a single infusion of ADM at 200 ng · kg⁻¹ · min⁻¹ into the LV. When pressure-volume relationships are compared over similar pressure ranges, there is no change in the slope of the end-systolic pressure-volume relationship (end-systolic elastance; E_{es}), suggesting no inotropic effect.

systolic pressure and end-systolic pressure were decreased compared with baseline in normal dogs, and end-diastolic pressure was increased (P < 0.05 for all; Tables 3 and 4).

The effects of ADM infusion at 200 ng · kg⁻¹ · min⁻¹ into the LV in pacing-induced heart failure are shown in Table 4.

None of the hemodynamic variables measured changed significantly with ADM infusion. The changes from baseline in end-systolic pressure and E_a with ADM infusion were significantly less in the heart-failure dogs than in the normal dogs studied with the single dose of ADM (P < 0.05 for both).

Figure 3 shows pressure-volume loops from a dog with pacing-induced heart failure at baseline and with ADM infusion. No significant change in the slope of the end-systolic pressure-volume relationship is seen with ADM infusion, suggesting no inotropic effect.

ADM infusion resulted in a significant increase in plasma ADM (increase with infusion 2,529 ± 847

Table 4. Effects of a single dose of ADM on hemodynamic parameters in heart-failure dogs

	Baseline	ADM (200 ng/kg intra-LV)
LV peak systolic pressure, mmHg	105 ± 7	103 ± 8
LV end-systolic pressure, mmHg	87 ± 6	81 ± 7
LV end-systolic volume, ml	46 ± 19	46 ± 19
Arterial elastance, mmHg/ml	33 ± 14	35 ± 16
LV end-diastolic pressure, mmHg	27 ± 9	29 ± 5
LV end-diastolic volume, ml	59 ± 22	63 ± 22
Heart rate, beats/min	173 ± 7	182 ± 3
τ, ms	29 ± 2	28 ± 1
E _{es} , mmHg/ml	4.0 ± 1.3	3.9 ± 1.3
V ₀ , ml	8.1 ± 0.6	2.7 ± 1.9

Values are means ± SE; n = 4 dogs.

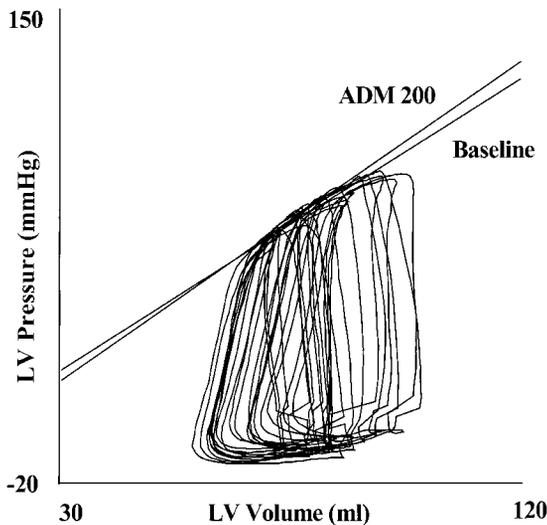


Fig. 3. Example of pressure-volume loops from a dog with pacing-induced heart failure at baseline and after receiving a single infusion of ADM at $200 \text{ ng} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ into the LV. No change in the slope of the end-systolic pressure-volume relationship (E_{es}) is noted with ADM infusion, suggesting no inotropic effect.

pg/ml, $P < 0.05$ for increase) and a small but significant increase in cAMP (increase with infusion 8.8 ± 1.6 pmol/ml, $P < 0.05$ for increase).

DISCUSSION

These studies are the first to address in vivo the direct myocardial actions of ADM infusion. The results confirm the arterial vasodilating actions of ADM at pathophysiological and pharmacological doses and suggest that these actions are attenuated in heart failure. ADM was without effect on preload and diastolic function and did not demonstrate inotropic actions in normal or heart-failure dogs.

In the first group of normal dogs, only the last and highest dose of ADM infused into the LV resulted in an increase in E_{es} , a relatively load-insensitive measure of myocardial contractility. However, a number of factors other than a direct inotropic response are likely to explain the observed increase in E_{es} . An increase in heart rate (above the atrial pacing level) and an increase in plasma norepinephrine were observed with this highest dose of ADM and suggested reflex sympathetic activation. Although these studies were conducted in the presence of β -blockade, marked sympathetic activation may have overcome the competitive blockade of the β -adrenergic receptor. The effect of sympathetic activation and a treppe effect from increased heart rate may have explained the positive inotropic response observed with the highest dose. In addition, the end-systolic pressure-volume relationship can have significant curvilinearity in the range of pressures observed in normal conscious dogs, and caution is necessary if pressure-volume relationships are compared over markedly different pressure ranges, as was the case at the highest dose of this prolonged (>90 min) infusion (2, 13). Finally, no dose-response effect of

ADM on E_{es} was observed, and this also suggests that a direct inotropic effect is unlikely. Therefore, we made an effort to control these factors in the additional group of five normal dogs studied with the highest dose of ADM alone. In these dogs, no inotropic response was observed.

In vitro studies have reported both positive and negative inotropic effects of ADM (8, 28, 29). Differences in experimental design may explain the contradictory results in these studies. Positive inotropic responses independent of cAMP were noted by Szokodi et al. (28, 29) in isolated perfused hearts, whereas Ikenouchi et al. (8) noted a negative inotropic effect in isolated myocytes that was at least partially mediated by nitric oxide. Our results suggest that, in vivo, ADM is without inotropic effects, even at doses that achieve pharmacological plasma ADM concentrations in normal and heart-failure dogs.

A small decrease in τ was seen with the highest dose of ADM in the first group of normal dogs receiving the three doses of ADM. This measure of LV relaxation is sensitive to afterload, sympathetic tone, and changes in heart rate. Thus the effects of any intervention on τ need to be interpreted in light of the changes in these parameters (5). In the normal dogs studied only with the highest dose of ADM, in which decreases in systolic pressure tended to be lower and heart rate was unchanged, no effect on τ was seen. This lack of effect on diastolic function was also noted in heart failure.

Importantly, in the absence of a specific ADM antagonist, our results obtained in normal dogs and extending to a model of heart failure provide the most direct evaluation of the myocardial actions of ADM in vivo. Previous in vivo studies have reported changes in such variables as maximum rate of change of aortic flow and cardiac output, but these variables are not reliable measures of contractility, being influenced by changes in loading conditions and heart rate (3, 22). No previous studies have reported the effects of ADM on diastolic function.

The vasodilator action of ADM is well established. We noted a dose-dependent decrease in systolic pressure in the normal dogs and a significant decrease in E_a with the highest dose of ADM. However, this action appears to be significantly attenuated in heart failure. These results are in keeping with a study of the vasodilatory effects of ADM in skeletal muscle arteries in normal and heart-failure subjects (21). In that study, the vasodilatory effect was to some extent mediated by nitric oxide, and impaired production of nitric oxide in heart failure may explain some of the attenuated effect. Our results also suggest that ADM is predominantly an arterial vasodilator, as we did not observe changes in variables reflecting preload such as LV end-systolic volume and pressure.

The pathophysiological importance of the elevated ADM plasma concentrations observed in heart failure is currently unclear, although these increased concentrations are of prognostic significance. The current study reports significant hemodynamic effects of ADM

infusion at the lowest dose in normal dogs. The plasma concentrations achieved with this dose are in the range of those observed in dogs with experimental heart failure and suggest that these concentrations are pathophysiologically relevant (10). We infused a high dose of ADM in dogs with heart failure and observed no hemodynamic effects; in heart failure, the effects of ADM may be limited by activation of counter-regulatory vasoconstrictor systems. Definitive statements on the pathophysiological significance of circulating ADM in heart failure await the development of a specific antagonist.

We do not address the mechanism of action of ADM. In vitro and in vivo studies have suggested that cAMP-independent mechanisms mediated via activation of protein kinase C and nitric oxide may be important (21, 29). The small increase in cAMP seen in our study would also be consistent with cAMP-independent mechanisms playing a major role in the inotropic and other hemodynamic effects of ADM. In addition, the lack of lusitropic effect would support non-cAMP pathways mediating the effects observed, as increases in cAMP produced by β -adrenergic agonists or phosphodiesterase inhibitors are associated with decreases in τ (7, 19).

In conclusion, although definitive elucidation of the importance of this peptide in the regulation of myocardial function awaits the development of a specific antagonist, this study provides a comprehensive assessment of the myocardial and load-altering actions of ADM in normal and heart-failure dogs. Our results confirm that ADM is an arterial vasodilator but that this action is attenuated in heart failure and that in vivo ADM does not have inotropic actions and is without effect on preload or LV relaxation.

We thank Denise Heublein and Gail Harty for expert technical assistance.

This work was supported by a National American Heart Association Grant-in-Aid, the Miami Heart Research Institute, the Joseph P. and Jeanne M. Sullivan Foundation, and the Mayo Foundation. J. G. Lainchbury was supported by a Health Research Council of New Zealand Training Fellowship in Clinical Research.

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