Cardiac Secretion of Adrenomedullin in Human Heart Failure

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Abstract

Adrenomedullin (ADM) is a newly discovered endogenous vasorelaxing and natriuretic peptide. Recently, we have reported that plasma ADM is increased in severe congestive heart failure (CHF) in humans and that increased immunohistochemical staining is observed in the failing human ventricular myocardium. The present study was designed to test the hypothesis that the failing human ventricle secretes ADM and that circulating ADM progressively increases with the severity of clinical CHF. Plasma ADM was significantly increased in human CHF (39.8±3.6 pg/ml, $P < 0.001$ vs. normal) as compared with normal subjects (14.4±2.7 pg/ml). Plasma ADM was increased in mild CHF (NYHA class II, 30.1±3.4 pg/ml, $P < 0.01$ vs. normal), moderate CHF (NYHA class III, 31.5±3.0 pg/ml, $P < 0.01$ vs. normal), and severe CHF (NYHA class IV, 66.1±9.4 pg/ml, $P < 0.001$ vs. normal). In 13 patients with CHF in whom plasma samples were obtained from aorta (AO), coronary sinus (CS) and anterior interventricular vein (AIV), there was a significant step-up in plasma ADM between AO and AIV (50.6±9.3 pg/ml and 62.1±11.1 pg/ml, respectively, $P < 0.01$) and between AO and CS (50.6±9.3 pg/ml and 58.6±11.4 pg/ml, respectively, $P < 0.05$). The current study demonstrates that the failing human heart secretes ADM in human CHF suggesting contribution to the increase in plasma ADM, and indicates for the first time an additional endocrine system of cardiac origin which is activated in human CHF and may function in cardiorenal regulation. (*J. Clin. Invest.* 1996. 97: 2370–2376.) Key words: myocardium • heart ventricle • heart failure, congestive • hormones • peptides

Introduction

Adrenomedullin (ADM)[1] is a newly discovered potent endogenous vasorelaxing and natriuretic peptide which was originally isolated from the extracts of human pheochromocytoma (1, 2). Since the isolation of ADM from human pheochromocytoma, accumulating evidence has elucidated that ADM is a novel vasorelaxing and natriuretic peptide which may play an important role in cardiorenal regulation. As ADM has been reported to be present in the heart (3) and kidney (2), and to be secreted from vascular smooth muscle cells (4) and endothelial cells (5), ADM may function as a paracrine and/or autocrine hormone in the regulation of cardiorenal homeostasis. Recently, ADM has been reported to be present in normal human plasma (6), and its plasma concentration has been reported to be increased in patients with hypertension (6) and chronic renal failure (7). More recently, we have reported that plasma concentration of ADM is increased in severe human congestive heart failure (CHF) and that immunohistochemical staining for ADM is more intense in the failing human ventricle as compared with the normal human ventricle (8). Our hypothesis is that failing human ventricle secretes ADM in human CHF.

This study was designed to determine circulating concentration of ADM in clinical stages of human CHF, specifically in mildly symptomatic left ventricular dysfunction and correlate circulating ADM with parameters of cardiovascular hemodynamics. Second, we sought to determine the cardiac secretion of ADM in humans with CHF with a specific goal of determining if like the natriuretic peptide system, the failing human ventricular myocardium functions in the secretion of a cardiorenal acting hormone.

Methods

Study subjects for circulating ADM concentration. 44 patients with CHF (25 men and 19 women, 63.5±1.7 [mean±SEM] years old, not significant vs. control) were studied. The clinical diagnosis of CHF was made on the basis of the clinical history, physical examination, chest roentgenogram, electrocardiogram and echocardiogram in all 44 patients as well as cardiac catheterization data in 36 patients. The patients with CHF were classified by New York Heart Association (NYHA) functional class criteria according to their cardiac symptoms after physical examination and laboratory evaluation. Twelve patients were classified as NYHA class II, twenty one as NYHA class III, and eleven as NYHA class IV. The causes of the ventricular dysfunction in these patients with CHF included idiopathic dilated cardiomyopathy and ischemic cardiomyopathy. All patients with CHF were on treatment, which included digitalis, diuretics, and/or vasodilators. Blood sample for the measurement of plasma ADM was drawn from the aorta (AO) at the time of cardiac catheterization in the supine position in 36 patients with CHF. Blood samples in eight patients with CHF who did not receive diagnostic cardiac catheterization but received physical examination and laboratory evaluation were obtained from the peripheral vein. Serum creatinine in all patients with CHF was 1.3±0.1 mg/ml (not significant vs. control).

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1. *Abbreviations used in this paper:* ADM, adrenomedullin; AIV, anterior interventricular vein; ANP, atrial natriuretic peptide; AO, aorta; CHF, congestive heart failure; CS, coronary sinus.

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Nine patients without cardiac disease or CHF (3 men and 6 women, 55.6±4.8 yr old) in whom diagnostic cardiac catheterization was performed were selected as control subjects. Eight were diagnosed as chest pain syndrome with normal coronary angiogram, and one had abnormality in electrocardiography with normal coronary angiogram. None of them received medication at the time of the study. Serum creatinine in control subjects was 1.0±0.1 mg/ml.

Informed consent was obtained from each patient and his or her family. This study protocol was in agreement with the guidelines of the Institutional Review Board at Mayo Clinic.

Cardiac catheterization. Cardiac catheterization was performed in 36 patients with CHF (NYHA class II, $n = 12$; NYHA class III, $n = 17$; NYHA class IV, $n = 7$) and in all control subjects without cardiac disease ($n = 9$). Systemic arterial blood pressure and left ventricular end-diastolic pressure were measured, and blood sampling for ADM was performed in AO. Among these 36 patients with CHF in whom cardiac catheterization was performed, insertion of a catheter into the anterior interventricular vein (AIV) was possible in 13 patients with CHF (NYHA class II, $n = 4$; NYHA class III, $n = 6$; NYHA class IV, $n = 3$). A 7F Berman-Wedge catheter was placed in the coronary sinus (CS), then the catheter was advanced to the AIV under fluoroscopic guidance with the use of guide wire. The position of the catheter tip in AIV was confirmed by the injection of the contrast medium. In these 13 patients, plasma samples were obtained from AO, CS which receives blood from the whole heart, and AIV which receives blood exclusively from the left ventricle.

Quantification of plasma ADM concentration. Plasma concentration of ADM was measured with a specific radioimmunoassay for human ADM (1-52) as previously described (8). In brief, blood samples for ADM assay were collected in chilled tubes containing EDTA and immediately placed on ice. After centrifugation at 2500 rpm at 4°C for 15 min, the plasma was decanted and stored at −20°C until analysis. Plasma (1 ml) was extracted on C-18 Bond Elute Cartridges and eluted with 75% methanol containing 1% trifluoroacetic acid. Concentrated eluates were then assayed using a specific and sensitive radioimmunoassay for ADM (Phoenix Inc., Mountain view, CA) which was previously described (8). Minimal detectable concentration for the assay is 0.5 pg per tube, and the half-maximal inhibition dose of radioiodinated ligand binding by ADM is 10 pg per tube. Recovery is 72±2%, and intra-assay and interassay variations are 10 and 12%, respectively.

Quantification of plasma atrial natriuretic peptide (ANP) concentration. Blood samples for ANP analysis were collected in chilled EDTA tubes, immediately placed on ice, and centrifuged at 2500 rpm at 4°C for 15 min. Plasma was separated and stored at −20°C until assay. Extracted plasma concentration of ANP was measured by radioimmunoassay to ANP as previously described (9).

Statistical analysis. Results of the values are expressed as mean±SEM. Statistical comparisons between each group were performed by using ANOVA for repeated measures followed by Fisher's least significant difference test of repeated measures when appropriate, and statistical comparisons between groups were performed by using factorial ANOVA followed by Fisher's least significant difference test of repeated measures. The correlations of the plasma concentration of ADM with plasma ANP, serum creatinine and hemodynamic parameters such as left ventricular ejection fraction and left ventricular end-diastolic pressure were performed using linear regression analysis. Statistical significance was accepted for $P < 0.05$.

Results

Hemodynamic data. Table I reports the hemodynamic data in control subjects and in patients with CHF according to NYHA classification. Mean arterial blood pressure in all patients with CHF (91.6±2.8 mmHg) tended to be less in comparison with control subjects, but not significant. Mean arterial blood pressure significantly decreased in NYHA class IV (82.2±3.8 mmHg) as compared with control subjects (98.6±3.7 mmHg, $P < 0.01$) and NYHA class II patients (98.7±5.5 mmHg, $P < 0.05$). Heart rate was increased in all patients with CHF (78.1±2.1 beats/min) as compared with the control subjects (65.6±3.6 beats/min, $P < 0.05$). Heart rate was significantly increased in NYHA class IV (86.9±4.0 beats/min) as compared with control subjects ($P < 0.01$), NYHA class II patients (71.3±4.3 beats/min, $P < 0.05$) and NYHA class III patients (77.4±2.6 beats/min, $P < 0.05$). Left ventricular ejection fraction was significantly decreased in patients with CHF (33.2±3.2%, $P < 0.001$ vs. control) as compared with the control subjects (58.3±1.9%). Left ventricular ejection fraction was decreased in proportion to the severity of NYHA classification (NYHA class II vs. control, $P < 0.05$; NYHA class III vs. control, $P < 0.01$; NYHA class IV vs. control, $P < 0.001$; NYHA class IV vs. II, $P < 0.01$; NYHA class IV vs. III, $P < 0.05$). Left ventricular end-diastolic pressure significantly increased in patients with CHF (23.9±1.4 mmHg, $P < 0.01$ vs. control) as compared with the control subjects (15.2±1.8 mmHg). Left ventricular end-diastolic pressure was increased in proportion

Table I. Cardiovascular Hemodynamics and Plasma Concentrations of ADM and ANP in Control Subjects and in Patients with CHF

		CHF			
			NYHA classification		
	Control (n=9)	Total CHF (n=36)	II (n=12)	III (n=17)	IV (n=17)
MAP (mmHg)	98.6±3.7	91.6±2.8	98.7±5.5	92.5±4.2	82.2±3.8*‡
HR (beats/min)	65.6±3.6	78.1±2.1*	71.3±4.3*	77.4±2.6*	86.9±4.0*‡§
LVEF (%)	58.3±1.9	33.2±3.2*	41.6±5.8*	35.1±5.0*	19.2±2.4*‡§
LVEDP (mmHg)	15.2±1.8	23.9±1.4*	22.3±2.3*	22.8±1.5*	31.1±2.8*‡§
ADM (pg/ml)	14.4±2.7	39.8±3.6*	30.1±3.4*	31.5±3.0*	66.1±9.4*‡§
ANP (pg/ml)	29.2±5.9	225.6±44.8*	143.6±43.6*	218.5±66.0*	359.7±129.0*
CR (mg/dl)	1.0±0.1	1.3±0.9	1.3±0.3	1.2±0.6	1.5±0.2*

Values are mean±SEM. *MAP*, mean arterial blood pressure; *HR*, heart rate; *LVEF*, left ventricular ejection fraction; *LVEDP*, left ventricular end-diastolic pressure; *CR*, serum creatinine. *$P < 0.05$ vs. control, ‡$P < 0.05$ vs. NYHA classII, §$P < 0.05$ vs. NYHA class III.

to the severity of NYHA classification (NYHA class II vs. control, $P < 0.05$; NYHA class III vs. control, $P < 0.05$; NYHA class IV vs. control, $P < 0.001$; NYHA class IV vs. II, $P < 0.05$; NYHA class IV vs. III, $P < 0.05$).

Circulating ADM concentrations. Table I also reports the plasma concentrations of ADM in control subjects and in patients with CHF according to NYHA classification. Fig. 1 illustrates the individual values of plasma ADM in control subjects and in patients with CHF according to NYHA classification. Plasma ADM concentration was significantly increased in CHF (39.8±3.6 pg/ml, $P < 0.001$ vs. control) as compared with the control subjects (14.4±2.7 pg/ml). Plasma ADM concentration in CHF patients with each NYHA classification (II, III, and IV) was significantly higher than in control subjects ($P < 0.01$, $P < 0.01$, and $P < 0.001$, respectively). Further, plasma ADM concentration was significantly higher in NYHA class IV (66.1±9.4 pg/ml) as compared with NYHA class II (30.1±3.4 pg/ml, $P < 0.01$) and NYHA class III (31.5±3.0 pg/ml, $P < 0.01$). There was no significant difference in plasma ADM concentration between NYHA class II and NYHA class III (P = not significant between II and III).

Correlation of plasma ADM with cardiac hemodynamics. Fig. 2 illustrates the correlation of plasma ADM with left ventricular ejection fraction and with left ventricular end-diastolic pressure. There was a positive correlation between plasma concentration of ADM and left ventricular end-diastolic pressure ($r = 0.47$, $P < 0.01$) and a weak inverse correlation between plasma concentration of ADM and left ventricular ejection fraction ($r = 0.34$, $P < 0.05$).

Circulating ANP concentrations and correlation with plasma ADM concentrations. Table I also reports the plasma concentrations of ANP in control subjects and in patients with CHF according to NYHA classification. Plasma ANP concentration was significantly increased in CHF patients (225.6±44.8 pg/ml, $P < 0.05$ vs. control) as compared with control subjects (29.2±5.9 pg/ml). Plasma concentration of ANP in CHF patients with each NYHA classification (II, III, and IV) was significantly higher than in control subjects ($P < 0.05$, each). As shown in Fig. 3, there was a positive correlation between plasma ADM concentration and plasma ANP concentration ($r = 0.47$, $P < 0.005$).

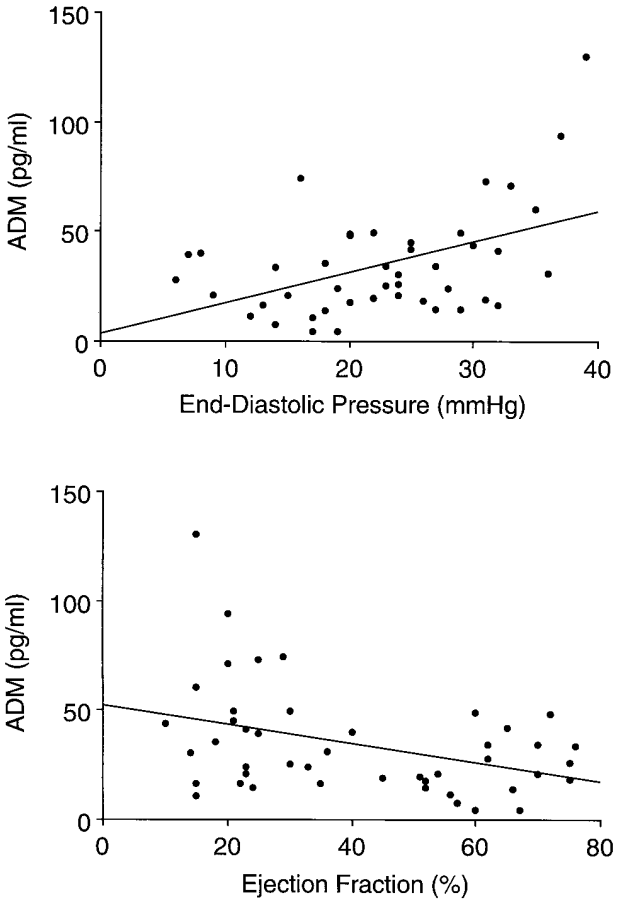

Figure 2. Scatterplots showing the correlation of plasma concentration of ADM with either left ventricular end-diastolic pressure (*upper panel*) or left ventricular ejection fraction (*lower panel*). There was a weak positive correlation between plasma concentration of ADM and left ventricular end-diastolic pressure ($r = 0.47$, $P < 0.01$). There was a weak negative correlation between plasma concentration of ADM and left ventricular ejection fraction ($r = 0.34$, $P < 0.05$).

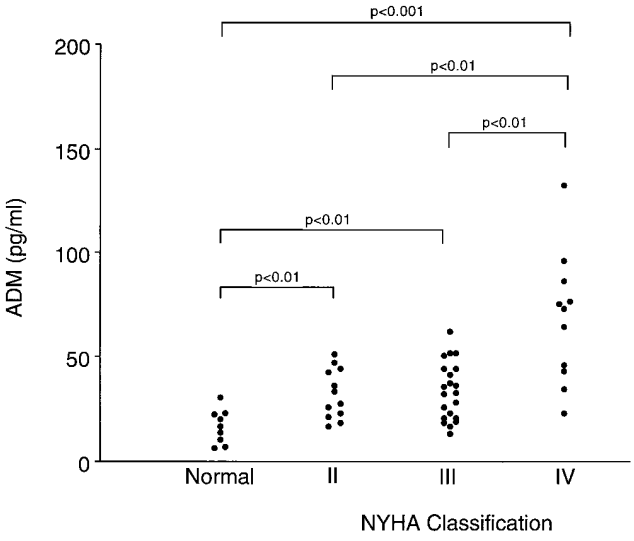

Figure 1. Graph of exact values of ADM concentration in normal control subjects and in patients with CHF according to NYHA classification.

Serum creatinine and correlation with plasma ADM concentrations. There was no significant difference in the serum creatinine between control subjects (1.0±0.1 mg/ml) and patients with CHF (1.3±0.1 mg/ml). However, in some patients with CHF such as NYHA class IV, serum creatinine was slightly increased in the current study. As shown in Table I, the serum creatinine was significantly higher in NYHA class IV than in the normal control subjects. Fig. 4 illustrates the correlation of plasma ADM concentration with serum creatinine. There was a weak positive correlation between serum creatinine and plasma concentration of ADM ($r = 0.285$, $P < 0.05$). Table II reports the plasma concentration of ADM in CHF patients with or without renal dysfunction. Not only plasma ADM concentrations in CHF patients with increased serum creatinine ≥ 1.2 mg/dl, but also those in CHF patients with serum creatinine < 1.2 mg/dl were significantly increased as compared with the normal control subjects. There was no significant difference in plasma ADM concentration between patients with in-

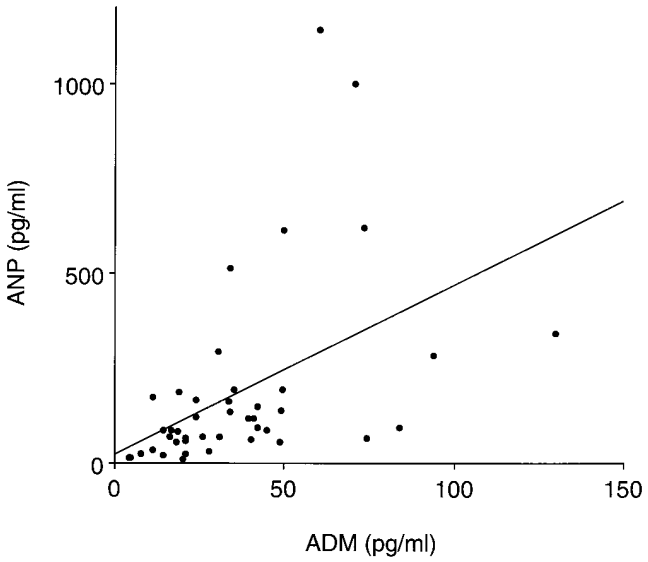

Figure 3. Scatterplots showing the correlation of plasma concentration of ADM with ANP. There was a weak positive correlation between plasma ADM and plasma ANP ($r = 0.47$, $P < 0.005$).

creased serum creatinine ≥1.2 mg/dl and those with serum creatinine < 1.2 mg/dl. (Table II).

Cardiac secretion of ADM. Among 36 patients with CHF in whom cardiac catheterization was performed, insertion of a catheter into the AIV was possible in 13 patients (Table III). These patients with CHF had decreased left ventricular ejection fraction (28.0±5.0%) and increased left ventricular end-diastolic pressure (23.7±2.4 mmHg) as compared with the normal control subjects. Blood sampling was performed in AO, CS and AIV. Fig. 5 illustrates the difference of the plasma concentration of ADM between CS and AO, Δ (CS-AO), and that

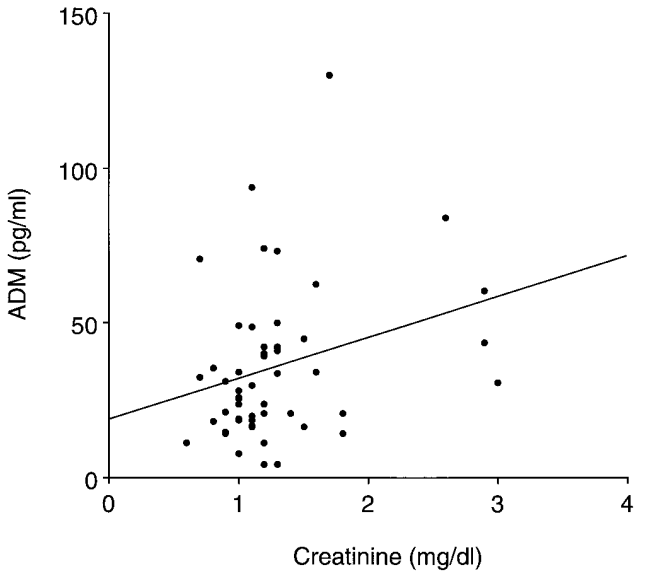

Figure 4. Scatterplots showing the correlation of plasma concentration of ADM with serum creatinine. There was a weak positive correlation between plasma concentration of ADM and serum creatinine ($r = 0.285$, $P < 0.05$).

Table II. Plasma Concentration of ADM with or without Renal Dysfunction in Patients with CHF and in All Subjects

	Number	ADM
		pg/ml
Patients with CHF	44	39.8±3.6*
Serum creatinine ≥ 1.2 mg/dl	19	43.8±5.3*
Serum creatinine < 1.2 mg/dl	25	34.8±3.9*
Normal control	9	14.4±2.7

Values are mean±SEM. There was no significant difference in plasma ADM concentration between patients with increased serum creatinine > 1.2 mg/dl and those with serum creatinine < 1.2 mg/dl. *$P < 0.05$ vs. normal control.

of ADM between AIV and AO, Δ (AIV-AO) in 13 patients with CHF. There was a significant step-up in plasma concentration of ADM between AO (50.6±9.3 pg/ml) and AIV (62.1±11.1 pg/ml, $P < 0.01$ vs. AO) and between AO and CS (58.6±11.4 pg/ml, $P < 0.05$ vs. AO). However, no significant difference in plasma ADM concentration was observed between CS and AIV. The amounts of ADM secreted from the ventricle as calculated by arteriovenous difference of plasma ADM concentration, Δ (AIV-AO) tended to increase in proportion to the increase in left ventricular end-diastolic pressure ($r = 0.54$, $P = 0.056$), and in proportion to the decrease in left ventricular ejection fraction ($r = 0.37$, $P = 0.21$).

Cardiac secretion of ANP and comparison to ADM. Among 13 patients with CHF in whom insertion of a catheter into the AIV was performed, plasma ANP concentrations in AO, CS and AIV were also measured (Table III). There was a significant step-up in plasma concentration of ANP between AO (264.4±106.6 pg/ml) and AIV (500.9±133.1 pg/ml, $P < 0.05$ vs. AO) and between AO and CS (586.0±130.1 pg/ml, $P < 0.05$ vs. AO). However, no significant difference in plasma ANP

Table III. Cardiovascular Hemodynamics and Plasma Concentrations of ADM and ANP in AO, CS and AIV in 13 Patients with CHF

		Control	CHF
		(*n*=9)	(*n*=13)
MAP (mmHg)		98.6±3.7	86.9±4.9
HR (beats/min)		65.6±3.6	77.9±3.4*
LVEF (%)		58.3±1.9	28.0±5.0*
LVEDP (mmHg)		15.2±1.8	23.7±2.4*
ADM (pg/ml)	AO	14.4±2.7	50.6±9.3*
	CS	NA	58.6±11.4‡
	AIV	NA	62.1±11.1‡
ANP (pg/ml)	AO	29.2±5.9	264.4±106.6*
	CS	NA	586.0±130.1‡
	AIV	NA	500.9±133.1‡

Values are mean±SEM. *MAP*, mean arterial pressure; *HR*, heart rate; *LVEF*, left ventricular ejection fraction; *LVEDP*, left ventricular end-diastolic pressure; *NA*, not available. *$P < 0.05$ vs. control, ‡$P < 0.05$ vs. AO in CHF.

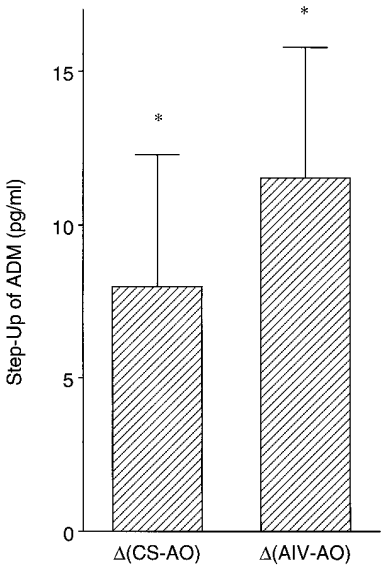

Figure 5. Step-up of ADM concentration in CS and AIV. Δ (CS-AO), the difference in the plasma ADM concentration between the CS and the AO; Δ (AIV-AO), the difference in the plasma ADM concentration between the AIV and the AO. $*P < 0.05$ vs. aortic concentration of ADM.

concentration was observed between CS and AIV. The percent differences of step-up in plasma hormone concentration between CS and AO were calculated as [(CS-AO) / AO] × 100, and the percent differences of step-up in plasma hormone concentration between AIV and AO were calculated as [(AIV-AO) / AO] × 100. Fig. 6 illustrates the percent differences of step-up in the plasma concentration of ADM and ANP between CS and AO, Δ (CS-AO), and between AIV and AO, Δ (AIV-AO). The percent differences of step-up in the plasma concentration of ANP between CS and AO and between AIV and AO were 319±120 and 206±70%, respectively, while those in the plasma concentration of ADM were 20±8% and 25±14%, respectively.

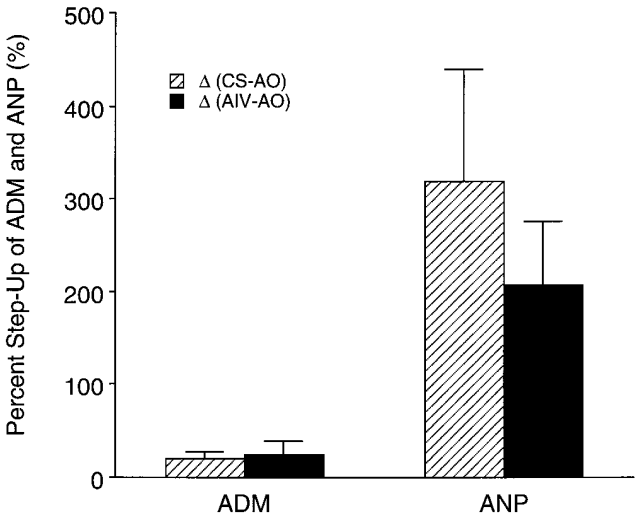

Figure 6. Bar graphs showing percent differences of step-up in the plasma concentrations of ADM and ANP between CS and AO, Δ (CS-AO), and between AIV and AO, Δ (AIV-AO).

Discussion

ADM is a novel 52–amino acid peptide that has potent vasorelaxing and natriuretic actions (1, 2). The current study confirms that the plasma concentration of circulating ADM is increased in patients with CHF as compared with those in normal subjects (8, 10), extending previous studies in the determination of ADM elevation in mild CHF (NYHA class II) and moderate CHF (NYHA class III) as well as severe CHF (NYHA class IV). More importantly, the current study demonstrates for the first time the secretion of ADM by the failing human ventricular myocardium.

The current study confirms the increase in plasma concentrations of ADM in humans with CHF. The significance of this elevation will require further studies elucidating the biological actions of exogenously administered ADM to humans and/or utilization of ADM receptor antagonists in CHF. Nonetheless, neurohumoral activation is known to take place and play an important role in the progression of ventricular dysfunction (11). Specifically, activation of natriuretic and vasorelaxing factors such as ANP (9) and brain natriuretic peptide (12) may function to oppose the co-activation of local and circulating vasoconstrictive and sodium-retaining factors like norepinephrine, angiotensin II and endothelin (13). The current study is consistent with the concept that ADM which mediates its biological actions via generation of cAMP (14, 15) could also play a compensatory role in CHF to enhance myocardial contractility via cAMP. As ADM has natriuretic and vasorelaxing actions, ADM may also play a compensatory role in the kidney to maintain sodium balance during the early stage of ventricular dysfunction in the maintenance of optimal intravascular volume and cardiac filling pressures despite ventricular dysfunction (16). Lastly, one could speculate that exogenous ADM may have a therapeutic role in patients with CHF.

To date, the mechanism of circulating ADM elevation in human CHF remains undefined. Synthesis, secretion, metabolism and clearance of ADM have not been elucidated. At present, precise sites of possible increased release of ADM have not been defined in patients with CHF. Previous investigators have measured plasma concentration of ADM from various sites in humans without ventricular dysfunction, and found that there was no step-up of ADM in the coronary circulation excluding the heart as a major site for release (17). Recently, we have shown that immunohistochemical ADM is significantly increased in the ventricular myocytes from severely failing hearts obtained at cardiac transplantation than those from normal hearts (8). As ventricular production of the natriuretic peptides, ANP and brain natriuretic peptide secondary to ventricular dilatation and myocyte hypertrophy are markedly augmented in patients with CHF (12, 18, 19), it is tempting to speculate that the failing ventricular myocyte may be a source of increased ADM production. To test this hypothesis, blood sampling was performed in the AIV, CS and AO simultaneously in 13 patients with mild to severe CHF in the present study. Because the AIV is known to drain the ventricle, the difference between AIV and AO [Δ (AIV-AO)] reflects the amount of secretion from the ventricle (12). In contrast, CS drains most of the heart including atria and ventricles, and the

difference between CS and AO [Δ (CS-AO)] indicates secretion from the whole heart. In the current study, there was a significant step-up in the concentration of ADM between AO and AIV and between AO and CS, however, there was no significant difference in ADM concentration between AIV and CS. This finding establishes for the first time that the failing ventricle contributes to the increased release of ADM in human CHF and that ADM is secreted mainly from the ventricle and not by the atrium in patients with CHF. Although the first paper in which plasma ADM concentration was measured in various sites including CS failed to demonstrate the heart as site of ADM release (17), the investigators did not examine plasma ADM concentration of CS nor AIV in patients with CHF. In the present study, we examined plasma concentration of ADM in patients with CHF, and found that ADM concentrations in CS and AIV are significantly increased in these patients.

ANP is a cardiac hormone secreted from the heart. The present study confirmed that plasma concentration of ANP is increased in patients with CHF as compared with the control subjects. Furthermore, there was a positive correlation between plasma concentration of ADM and that of ANP ($r = 0.47$, $P < 0.005$). However, the percent differences of step-up in the plasma concentration of ANP between CS and AO (319±120%) and between AIV and AO (206±70%) were much greater than those for ADM (20±8% and 25±14%, respectively). Thus, although the current study raises the possibility that the failing heart contributes to the increased concentration of ADM in patients with CHF, the amount of ADM secreted from the heart that contributes to the general circulation is considered to be less than that of ANP. It should however be noted that ADM appears to be a more potent natriuretic peptide than ANP (2, 20) and therefore smaller increases in circulating ADM may have greater actions than similar increases in plasma ANP in the regulation of sodium excretion.

In the present study, plasma ADM concentration was significantly higher in NYHA class IV as compared with NYHA class II and NYHA class III. There was a weak inverse correlation between plasma concentration of ADM and left ventricular ejection fraction ($r = 0.34$, $P < 0.05$) and a weak positive correlation between plasma concentration of ADM and left ventricular end-diastolic pressure ($r = 0.47$, $P < 0.01$). These findings suggest that ADM may be increased in proportion to the severity of left ventricular dysfunction. Indeed, the amounts of ADM secreted from the ventricle tended to increase in proportion to the increase in left ventricular filling pressure ($r = 0.54$, $P = 0.056$) and in proportion to the decrease in left ventricular ejection fraction ($r = 0.37$, $P = 0.21$). The increase in wall tension or stretch may stimulate the production and secretion from the ventricle in patients with CHF. However, the weakness of these relationships suggests that other mechanical and/or humoral mechanisms may be important in the elevation of plasma ADM in human CHF.

NYHA functional classification is a simple and useful criteria in the evaluation of patients with CHF. NYHA is dependent on the patient's symptoms, and is notoriously inaccurate as compared with the objective determination of exercise capacity by stress exercise test. In this study, there was no significant difference in plasma ADM concentration between NYHA class II and NYHA class III. Left ventricular end-diastolic pressure values in NYHA class III patients were not different from those observed in NYHA class II. Distinction between NYHA class II and NYHA class III may be obscure and lack objectivity, and this may be the reason why left ventricular end-diastolic pressure values as well as ADM values for NYHA class III patients are not different from those seen in NYHA class II in this study.

In this study, blood samples for the measurement of plasma ADM were drawn from the AO at the time of cardiac catheterization in 36 patients. On the other hand, blood samples in eight patients with CHF who did not receive diagnostic cardiac catheterization were obtained from the peripheral vein. It is not known whether plasma ADM concentration in the AO is equivalent to that in the peripheral vein. Previous investigations have examined plasma concentration of ADM in inferior vena cava, superior vena cava and AO, and reported that there is no significant step-up of ADM concentration between AO (17.5±10.0 pg/ml) and superior vena cava (21.0±10.4 pg/ml) or between AO (17.5±10.0 pg/ml) and inferior vena cava (20.7±13.0 pg/ml) (17). In a preliminary study, we measured plasma concentration in AO and a peripheral vein simultaneously in a small number of patients with CHF ($n = 4$), and found that ADM in the peripheral vein (68.4±12.5 pg/ml) is slightly higher than those in the AO (61.9±12.5 pg/ml), but not significantly. Thus, we analyzed only aortic ADM data between normal control subjects and patients with CHF omitting the eight patients in whom aortic samples were not obtained, and found that the aortic ADM concentration is increased in patients with CHF (39.4±4.2 pg/ml, $P < 0.001$ vs. control) as compared with normal control subjects (14.4±2.7 pg/ml). Although the venous level was slightly higher than the AO level in the previous study (17) and our preliminary study, the plasma difference of ADM between AO and peripheral vein did not influence the result of the present study.

Since the previous investigators reported that plasma concentration of ADM is increased in patients with chronic renal failure (7), one might think that the elevation of ADM is associated with a decrease of clearance of ADM in the kidney. Recently, other investigators reported that plasma ADM concentrations are positively correlated with serum creatinine and inversely correlated with glomerular filtration rate in patients with hypertension (21). The hypertensive patients with increased creatinine (≥ 1.2 mg/dl) or with decreased glomerular filtration rate (≤ 80 ml/min) had higher concentrations of ADM than those of the normotensive subjects or borderline hypertensive patients (21). In the present study, although there was a weak positive correlation between serum creatinine and plasma concentrations of ADM ($r = 0.285$, $P < 0.05$), plasma ADM concentrations in CHF patients with increased creatinine more than 1.2 mg/dl were not significantly changed as compared with those in CHF patients with creatinine less than 1.2 mg/dl. Therefore, the elevation of plasma concentration of ADM in patients with CHF may be in part but not mainly due to the reduction in renal function.

In this study, plasma ADM concentration was increased in patients with CHF, even though the patients were on treatment, which included digitalis, diuretics, and/or vasodilators. To date, it is not known whether medications have influences on plasma concentration of ADM. Recently, investigators measured plasma ADM concentration in patients with hypertension before and after effective anti-hypertensive drug therapy, and found that despite blood pressure control with anti-hypertensive therapy, plasma ADM concentration in these patients with hypertension was not changed (21). Further studies are

needed to clarify the effect of medication on plasma ADM concentration in patients with CHF.

The conventional view of the heart is that it is a mechanical pump which functions to maintain cardiovascular homeostasis. The current investigation is further evidence for an additional function in heart failure. Specifically, the heart may also function as an endocrine organ as advanced by Braunwald et al. in 1964 (22). In the current study, the cardiac secretion of ADM is demonstrated and joins previous investigations which established the cardiac release of norepinephrine and the natriuretic peptides in heart failure. While these humoral factors may also have paracrine and autocrine actions upon the heart, they may have important systemic actions.

In summary, this study demonstrates that circulating ADM is increased in human CHF. Specifically, plasma ADM is increased in mild CHF with further increases in severe CHF. The current study also indicates the possibility that the failing ventricle contributes to the increased concentration of ADM in patients with CHF. These studies support a potential diagnostic as well as pathophysiological role for ADM in the neurohumoral activation which characterizes human CHF and indicates the ventricle as a site of ADM secretion.

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