Plasma Adrenomedullin Relation with Doppler-Derived dP/dt in Patients with Congestive Heart Failure

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Summary

Background: Increased circulating adrenomedullin (AM) concentration has been reported in congestive heart failure (HF) and considered as a possible marker of cardiac dysfunction.

Hypothesis: The study was undertaken to assess the relationship between circulating AM concentration and left ventricular (LV) functional state, estimated by echo-Doppler techniques in patients with mild to moderate HF and different degrees of LV dysfunction.

Methods: Plasma AM, B-type natriuretic peptide (BNP), and N-terminal (NT) proBNP levels were measured in 55 patients with HF (New York Heart Association [NYHA] I n = 8, II n = 26, III n = 21) and in 20 controls; dP/dt was calculated by the Doppler tracing of the mitral regurgitation jet.

Results: The study was completed in 51 patients. Adrenomedullin levels were higher than in controls (19.2 ± 1.4 vs. 13.3 ± 0.7 , $p < 0.005$) and elevated in proportion to NYHA functional class. B-type natriuretic peptide and NT-proBNP were 344 ± 67 vs. 12 ± 2 pg/ml and 2196 ± 623 vs. 52 ± 4 pg/ml, respectively ($p < 0.0001$); dP/dt was better related to AM ($r = 0.582$, $p < 0.001$) than to the other peptides. Adrenomedullin was significantly ($p < 0.001$) different between patients grouped according to the dP/dt cut-off predictive of event-free survival.

Conclusions: The combination of depressed contractility and increased AM may provide a clue for further characteriza-

tion of the severity of LV dysfunction in HF, independent of baseline LV ejection fraction.

Key words: congestive heart failure, adrenomedullin, radioimmunoassay, cardiac echo-Doppler.

Introduction

Neurohormonal activation plays a major role in the pathophysiology of congestive heart failure (HF). Between the different neurohormones, B-type natriuretic peptide (BNP) and N-terminal proBNP (NT-proBNP) are the most clinically used indices of left ventricular (LV) dysfunction and prognosis in HF.^{1–3} In the last few years, adrenomedullin (AM), another peptide with endogenous natriuretic and vasodilating activities, has been undergoing intensive investigation.^{4,5} Biological actions of AM, such as dilation of resistance vessels, increased coronary blood flow, positive cardiac inotropic effects, and inhibition of the vasoconstrictive action of endothelin-1 and angiotensin have been described so far.⁶ Renal effects of AM, such as natriuresis, diuresis, and increase in renal blood flow complemented by adrenal actions (inhibition of aldosterone secretion), and central nervous system effects (inhibition of vasopressin release, craving for salt, and thirst) are also well known.^{7,8}

In cardiovascular tissues, AM is regulated by mechanical stressors, inflammatory cytokines, hormones, and metabolic factors.^{9–11} Elevation of plasma AM due to overproduction in response to one or more of these stimuli may explain the raised plasma AM levels present in HF and myocardial infarction and is suggested to be due to secretion by the dysfunctioning myocardium as a possible compensatory mechanism.¹²

In patients with HF, conflicting data have been reported so far on the relation between circulating AM and LV ejection fraction (LVEF), the most commonly used index of LV systolic function. However, the main limitation of LVEF as an index of function is represented by its load dependence.¹³ To overcome this limitation, other indices have been proposed in clinical practice; in particular, the isovolumic phase indices of LV function have been reported to be less load dependent since

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the magnitude of their response to changes in preload, and in particular to afterload, is low.¹⁴ Most of the studies performed so far for the assessment of the isovolumic phase indices of LV function as dP/dt are invasive, requiring high-fidelity micro-manometer-tipped catheters. In recent years, it has been demonstrated that the complete continuous-wave Doppler mitral regurgitant velocity curve allows reconstruction of the ventriculoatrial pressure gradient from mitral valve closure to opening, including LV isovolumic contraction, ejection, and isovolumic relaxation. During systole, left atrial pressure fluctuation is relatively negligible compared with the corresponding LV pressure changes; therefore, the first derivative of the Doppler-derived ventriculoatrial pressure gradient curve (Doppler dP/dt) is able to estimate the LV dP/dt curve.^{15–17}

The aim of the present study was to assess the relationship between circulating AM levels and Doppler dP/dt and LVEF in patients with different degrees of LV dysfunction and to evaluate in this subset of patients the relation between circulating AM levels and other commonly used neurohormones such as BNP and NT proBNP.

Materials and Methods

Patient Population

We studied 55 consecutive patients with mild to moderate chronic congestive HF (35 idiopathic, 14 postischemic, 6 other). Of these, 49 were outpatients and 6 inpatients admitted to our Institute for routine coronary arteriography. All patients had been in stable clinical condition for at least 3 months. Exclusion criteria were acute coronary syndrome or acute inflammation (within 6 months), significant peripheral occlusive artery disease, neoplastic disease, and renal failure (serum creatinine value above 1.5 mg/dl). Eight patients were in New York Heart Association (NYHA) class I, 26 in class II, 21 in class III. Patients were on homogeneous optimal medical treatment (furosemide, angiotensin-converting enzyme [ACE] inhibitors, carvedilol, spironolactone for patients in NYHA class III), continued at the time of the study for ethical reasons. Each patient underwent a baseline history, physical examination, and transthoracic echocardiogram.

Twenty subjects of comparable age and gender, with no history of cardiovascular disease and normal regional and global LV function assessed by two-dimensional echocardiography and under no medical treatment, served as control group.

The present investigation conforms with the principles outlined in the Declaration of Helsinki (*Br Med J* 1964; ii:177). The study was approved by the local Ethical Committee, and all patients provided informed consent.

Examination by Doppler Echocardiography

A transthoracic two-dimensional echocardiogram and Doppler examination were performed in all patients by commercially available echocardiographic equipments: Acuson Sequoia (Acuson Corporation, Mountain View, Calif., USA)

or Hewlett-Packard 5500 (Philips, Medical System, Andover, Mass., USA). The mitral regurgitation jet was interrogated with continuous-wave Doppler from an apical four-chamber view using a sweep speed of 100 mm/s. Care was taken to align the imaging beam to the direction of the regurgitant jet. Scale and baseline were adjusted to maximize the spectral sign at the beginning of the Doppler interrogation. Left ventricular dimensions were obtained from the parasternal long-axis view; LV volumes and derived EF were calculated from apical four-chamber and two-chamber views by the biplane summation method.¹⁸

Continuous-wave Doppler spectra of the mitral regurgitation jet were analyzed off line by the built-in software of the echocardiographic equipments. Doppler-derived dP/dt was calculated as follows: the two points on the mitral regurgitation jet corresponding to 1 m/s and 3 m/s were identified; according to the modified Bernoulli equation, these points correspond to LV-left atrial gradients of 4 mmHg and 36 mmHg, respectively; therefore, dP/dt was $(36-4) \text{ mmHg/dt in s} = 32 \text{ mmHg/dt}$. Three dP/dt measurements were averaged in patients in sinus rhythm, five consecutive measurements in patients in atrial fibrillation.

Plasma Samples

Blood samples (8–10 ml) were obtained within 3 days from the echo Doppler examination; in the case of inpatients, blood was drawn the morning of discharge. Samples were placed into ice-chilled disposable polypropylene tubes containing aprotinin, 500 KIU/ml, and ethylene diamine tetraacetic acid (EDTA), 1 mg/ml. Plasma samples were rapidly separated by centrifugation for 15 min at 4°C and then stored frozen at –20°C in aliquots.

Assay Method

After sample extraction, plasma AM was measured by radioimmunoassay (RIA) method (human adrenomedullin 1–52, Phoenix Pharmaceuticals, Belmont, Calif., USA), with some modifications. For this, 2 ml of plasma were acidified with 2 ml of 1% trifluoroacetic acid (TFA), and after centrifugation at 1500 g for 10 min, loaded on activated Sep-Pak C18 cartridges (Waters Associated, Milford, Mass., USA). The columns were washed three times with 3 ml of 1% TFA, and AM was eluted with 3 ml of a solution containing 60% acetonitrile in 1% TFA. The eluate was dried and the dry residue was resuspended with 300–500 µl of the assay buffer and 100 µl was used for the immunometric assay. The extraction recovery was evaluated by adding known amounts of ¹²⁵I-AM (125-I-iodotyrosyl rat AM, sp.a 2000 Ci/mmol, Amersham Pharmacia Biotech, Buckinghamshire, UK) to a plasma pool before the extraction procedure.

Plasma BNP was measured by an IRMA method (Shionoria BNP manufactured by Shionogi & Co., Ltd., Osaka, Japan), which does not require a preliminary step of extraction or purification of plasma samples. This method has been reported previously in detail in the literature.^{19,20}

N-terminal proBNP was evaluated with a fully automated electrochemiluminescent assay (ECLIA) on Elecsys® 2010 analyzer (Roche Diagnostics, Mannheim, Germany), as recently reported in detail.²¹

Statistical Analysis

All sample concentrations and other data for quality control of the RIA system were calculated by a previously described computer program; the interpolation of the dose-response curves was computed using a four-parameter logistic function.²² The unpaired Student's *t*-test was used to compare the results of the two independent groups studied. Since AM, BNP, and proBNP values are not normally distributed in the population, both the original and the logarithmic transformation of data were used for statistical analysis. DP/dt, considered as dependent variable, and AM, BNP, and NT-pro BNP as independent variables, were also analyzed in a linear multiple regression analysis. The results are expressed as mean $\pm$ standard error of the mean (SEM).

Results

The study was completed in 51 of 55 patients; four patients were excluded because of the lack of a well-defined mitral regurgitation jet curve at Doppler examination.

Clinical and echocardiographic characteristics of the study population are reported in Table I.

TABLE I Clinical and echocardiographic characteristics of the study population

No. of patients	51
Age (years)	65 $\pm$ 1
Sex	
M = 36	
F = 15	
Cause	
DCM = 32	
CAD = 13	
Other = 6	
NYHA class	
I = 5	
II = 26	
III = 20	
EDD (mm)	68 $\pm$ 10
EDS (mm)	55 $\pm$ 2
LVEF %	32 $\pm$ 1
dP/dt (mmHg/s)	514 $\pm$ 21

All values are expressed as mean $\pm$ standard error of the mean.

Abbreviations: M = male, F = female, DCM = idiopathic cardiomyopathy, CAD = ischemic cardiomyopathy, NYHA = New York Heart Association, EDD = left ventricular end-diastolic dimension, ESD = left ventricular end-systolic dimension, LVEF = left ventricular ejection fraction.

Plasma AM and BNP were assessed in all 51 patients, while NT-proBNP was assessed in 36 of 51 patients. No difference was found between in- and outpatients as far as the three analyzed markers are concerned.

The average plasma AM concentration in patients with HF was higher than that in controls (19.2 $\pm$ 1.4 vs. 13.3 $\pm$ 0.7 pmol/l, mean $\pm$ SEM, $p < 0.005$) and significantly higher in NYHA class III than in NYHA class I–II patients ($p < 0.001$) (Fig. 1). In patients with HF, the average plasma BNP and NT-proBNP concentrations versus controls were 344 $\pm$ 67 vs. 12 $\pm$ 2 pg/ml and 2196 $\pm$ 623 vs. 52 $\pm$ 4 pg/ml, respectively ($p < 0.0001$). A mild correlation was observed between AM plasma levels and BNP and NT-proBNP ($r = 0.4$, $p < 0.05$ and $r = 0.3$, $p < 0.05$, respectively).

When the relationship between indices of LV function and AM, BNP, and NT-proBNP levels was analyzed, a significant correlation in the overall population was found between dP/dt and all the peptides ($r = 0.574$ for AM, $p < 0.001$; $r = 0.48$ for BNP, $p < 0.005$; and $r = 0.47$ for NT-proBNP, $p = 0.005$) (Fig 2). A significant relationship was also found between BNP, NT pro-BNP, and LVEF ($r = 0.474$, $p < 0.05$, and $r = 0.465$, $p < 0.05$, respectively). No relationship could be found between AM and LVEF ($r = 0.269$, $p = 0.07$).

When dP/dt, LVEF, and end-systolic dimension (considered as dependent variables) and AM, BNP, and NT-proBNP (considered as independent variables) were analyzed by means of multivariate regression analysis, AM significantly and independently contributed to the regression for dP/dt ($p < 0.05$), but not to EF or end-systolic dimension. On the other hand, BNP and NT-proBNP only contributed to the regression for EF ($p < 0.05$) (Table II).

When patients were divided in two subgroups according to dP/dt values (Group I $n = 34 < 600$ mmHg/s, Group II $n = 17 > 600$ mmHg/s), a significant difference in AM was observed between the two groups: 22.4 $\pm$ 1.8 in Group I versus 13.0 $\pm$ 1.1 pmol/l in Group II, $p < 0.001$ (Fig 3).

FIG. 1 Distribution of adrenomedullin (AM) plasma levels (after logarithmic transformation) as a function of clinical severity. Each box consists of five horizontal lines displaying the 10th, 25th, 50th (median), 75th, and 90th percentiles of the variable. All values above the 90th percentile and below the 10th percentile are plotted separately. NYHA = New York Heart Association.

FIG. 2 (A) Correlation between adrenomedullin (AM) plasma values (after logarithmic transformation) and dP/dt. (B) Correlation between B-type natriuretic peptide (BNP) plasma values (after logarithmic transformation) and dP/dt. (C) Correlation between N-terminal (NT) pro-BNP plasma values (after logarithmic transformation) and dP/dt.

Discussion

The present findings confirm that AM plasma levels are elevated in patients with mild to moderate chronic HF and different degrees of LV systolic dysfunction.²³

In contrast to many other cardiac peptides, plasma AM has a multitissue origin, as it is derived not only from the vasculature and heart but also from the adrenal medulla and lung;²⁴ therefore, the importance of assessing AM in HF relies on the assumption that increased concentrations of this peptide may reflect not only the cardiac response but also the systemic response to cardiac dysfunction,⁶ thus providing a more “total body” index in this condition. Studies^{25, 26} published so far have demonstrated a relationship between the most widely used natriuretic peptides in clinical practice — BNP and NT-proBNP — with LVEF. In our population, as well, a relationship between BNP, NT-proBNP, and LVEF was documented. Some investigators have shown a significant although weak relationship between AM levels and LVEF, while other studies could not report such a relationship, either in HF²⁷ or in post-myocardial infarction.^{28, 29} These reports concluded that AM could not be a good marker for the hemodynamic status in HF.³⁰ In our population, no significant relationship was found between AM and LVEF; on the other hand, such a relationship was found with dP/dt. A possible explanation for this result may be the fact that LVEF is heavily influenced by preload and afterload. By contrast, dP/dt is less load dependent, especially as far as afterload is concerned; thus, it could theoretically represent a more accurate index of the contractile state of the heart

in patients with different degrees of baseline dysfunction and in different clinical conditions.³¹

Doppler-derived dP/dt can be easily calculated in patients with HF by conventional Doppler echocardiography, since most of these patients show some degree of mitral regurgitation secondary to annular dilatation and/or chordal tethering. In our consecutive patients, only four were withdrawn because of the lack of a well-defined Doppler mitral regurgitation curve at ultrasound examination. Moreover, echocardiography represents the technique of choice for the diagnosis and follow-up of patients with HF³² and only a few additional minutes are required to obtain this information. Assessment by dP/dt has been shown to bear also prognostic implications. Kolia *et al.*³³ derived a cut-off of 600 mmHg/s to predict an event-free survival in patients with congestive HF, showing that a dP/dt > 600 mmHg/s defines a subgroup of patients at low risk of developing major events (death, transplant, or LV assist device). In our population, AM levels were significantly lower in patients with a dP/dt > 600 mmHg/s, independent of baseline EF.

To our knowledge, this is the first time that AM plasma determinations have been related to indices of LV systolic function different from LVEF. Patients in stable clinical conditions and with mild to moderate HF have been enrolled in the study in order to avoid all possible confounding factors in natriuretic plasma level determinations such as acute water retention, de-

TABLE II Multivariate analysis

	dP/dt	LVEF	ESD
lnAM	0.02	0.99	0.78
lnBNP	0.42	0.03	0.47
lnNT-proBNP	0.86	0.04	0.81

Abbreviations: LVEF = left ventricular ejection fraction, ESD = left ventricular end-systolic dimensions, ln = natural logarithm, AM = adrenomedullin, BNP = B-type natriuretic peptide, NT = N-terminal.

FIG. 3 Plasma adrenomedullin (AM) levels in patients with dP/dt values < 600 mmHg/s and > 600 mmHg/s.

rangements in renal function, or acute changes in treatment. Although the results of this study deserve confirmation in a bigger population of patients, they suggest that the combination of plasma AM assay together with Doppler-derived dP/dt may provide further clues for understanding the complex relationship between hemodynamic status and neurohormonal condition of patients with chronic HF.

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