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Original Article

The diagnostic value of adrenomedullin and its relation with severity in patients with systolic heart failure

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Abstract

Aim: Adrenomedullin (ADM) is a vasodilator, natriuretic and antiproliferative peptide that lowers blood pressure and inhibits cell migration. The expression of cardiac ADM is increased in heart failure (HF). The objective of this study was to investigate and simultaneously compare the levels of probrain natriuretic peptide (pro-BNP) and ADM as a potential marker in patients with HF.

Material and Methods: In this study, plasma levels of probrain natriuretic peptide and ADM were investigated in 90 subjects with systolic heart failure and 90 healthy controls. The results were compared with appropriate statistical methods.

Results: ADM levels were increased in patients with systolic HF with mean levels of 87.7 (81.4–99.7) pg/mL in HF group and 70.8 (65.2–78.7) pg/mL in healthy controls ($p < 0.001$). Elevated ADM levels in HF were found to demonstrate a positive correlation with New York Heart Association (NYHA) functional classification ($r = 0.94$, $p < 0.001$) and pulmonary arterial systolic pressure (PASP) ($r = 0.44$, $p <0.001$), and a negative correlation with left ventricular ejection fraction (LVEF) ($r = -0.50$, $p < 0.001$) and creatinine clearance (GFR) ($r = -0.21$, $p = 0.045$). The area under the curve for HF was similar for ADM (1.00) and pro-BNP (1.00).

Conclusion: The study showed that ADM may have a diagnostic value in indicating systolic HF. In addition, it was found that ADM levels increased with worsening HF and were positively correlated with NYHA class, pro-BNP and PASP, while ADM levels were negatively correlated with LVEF, GFR.

Keywords: Adrenomedullin; systolic heart failure; probrain natriuretic peptide

INTRODUCTION

Adrenomedullin (ADM) is a hormone found in the circulation that has been investigated in human pheochromocytoma tissue. ADM is secreted from vascular wall and functions as a paracrine and an autocrine or hormone in order to organize blood pressure vascular tonus. ADM is a potent vasodilator, which lowers the blood pressure. ADM exerts its biological activity through a specific receptor activity (modifier protein) and a calcitonin receptor-like receptor. By binding to these receptors, ADM activates a second messenger signal, leading to increased synthesis of nitric oxide and cAMP. In addition, ADM plays an important role in various pathological conditions such as heart failure (HF), hypertension (HT) and myocardial infarction (1-3). Systemic administration of ADM enhances cardiac output and depresses blood pressure in healthy men and patients with HF. Various mechanisms may account for the increase in cardiac output including an enhance in coronary arterial blood flow owing to dilatation of coronary vessels and reduced systemic vascular resistance. ADM activates protein kinase A, increasing myocardial contraction. It may also have a positive inotropic effect on myocardial cells through a mechanism regardless of cAMP in which intracellular calcium levels are enhanced (4-6).

Various cardiovascular diseases that impair cardiac pumping function may lead to HF. It is estimated that the number of patients with HF will reduce, because treatment of the disease improves mortality in HF patients (7). Biomarkers have emerged reflecting pathophysiological processes in the development and progression of HF such as myocardial injury, inflammation and remodeling. HF biomarkers have affected the way HF patients are appreciated and conducted. B-type natriuretic peptide (BNP) and N-terminal pro-BNP are gold standard biomarkers to determine the recognition and prognosis of HF (8,9).

The purpose of this study was to identify the levels of ADM in patients with systolic HF and to evaluate the correlations of ADM with primary clinical parameters such as pulmonary arterial systolic pressure (PASP),

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left ventricular ejection fraction (LVEF), New York Heart Association (NYHA) class and renal functions. In addition, in this study identify value of ADM was evaluated as a marker in comparison with pro-BNP in HF patients.

MATERIAL and METHODS

Patients

A total of 150 consecutive patients with systolic HF (LVEF ≤ 45%) who presented to the cardiology and internal medicine clinics and 90 healthy controls were included in the study. Identify of HF was established based on to the ESC Guidelines for the Identify and Therapy of Acute and Chronic Heart Failure criteria (10). Functional capacity of all patients was assessed with NYHA classification. Patients' medical history, concomitant diseases and medical treatments for HF were recorded. Sixty patients with acute coronary syndrome (ACS), cardiogenic shock, acute pulmonary edema, HF with preserved LVEF (> 45%), hepatic failure, acute renal failure, and those with a history of infectious, inflammatory, connective tissue or neoplastic disease were excluded. The remaining 90 subjects were included in the study.

In order to determine PASP and LVEF values, all patients underwent transthoracic echocardiographic examination with Vivid device (Vivid 5, General Electric, Milwaukee, WI, US) implemented by an experienced operator. PASP value was estimated through tricuspid regurgitant jet velocity and LVEF through the modified Simpson's method on two-dimensional echocardiogram (11). To assess renal functions, glomerular filtration rate (GFR) was calculated with Cockcroft-Gault (12).

Following echocardiographic examination, five mL blood was gathered from each patient in test tubes including EDTA and aprotinin after 10 minutes of bed rest in supine position. Sera were stored at −80oC until the time of test. Serum levels of ADM were measured with commercial ELISA kits (Phoenix Pharmaceuticals, US). For ADM, the limit of quantification was 0.23 nmoL/L; the within-run imprecision (CV) was 1.9%, and the between-run imprecision (CV) was 9.8%. Serum pro-BNP levels were measured using commercial kits (Phoenix Pharmaceuticals, US). Performance in the laboratory included a limit of quantitation of 5.0 ng/L, within-run imprecision (CV) of 1.5%, and total imprecision (CV) of 3.0%.

Written informed consent was obtained from all subjects for participation. This study was conducted in line with the ethical principles of the Declaration of Helsinki and approved by the local Ethics Committee of our hospital.

Statistical analysis

Data obtained in this study were evaluated using All the statistical analyses were applied using SPSS version 20.0 (SPSS for Windows, SPSS Inc., Chicago, IL, US). Continuous and categorical values were analyzed between the two group with independent samples Student t test or Mann-Whitney U test. Categorical parameters were assayed using Chi-square or Fischer's exact test. The correlations were analyzed using Pearson's correlation test. The values are stated as mean ± standard deviation (SD) or median and interquartile range (IQR, range from the 25th to the 75th percentile). Comparison of two data sets was performed using Spearman's correlation coefficient. Receiver operating characteristic (ROC) analysis was used to identify diagnostic values. $p<0.05$ values were considered statistically significant.

RESULTS

Demographic data of the patients and control groups are shown in Table 1. The average age of the patients was considerably superior than the controls. The rate of male subjects was considerably superior in HF patients than the controls.

Table 1. Baseline demographic. clinical and laboratory characteristics of the patient and control groups

	Patient (n = 90)	Control (n = 90)	P
Age [years]	64,82 ± 12.14	34.83 ± 11.55	**< 0.001**
Gender: male	66.7%	38.9%	**< 0.001**
Clinical SBP (mm Hg)	127.1 ± 5.6	122.4 ± 7.3	0.08
Clinical DBP (mm Hg)	83.9 ± 4.2	75.6 ± 5.7	0.09
Heart Rate (bpm)	86 ± 4.2	82 ± 3.6	0.11
Ejection fraction [%]	32.2 ± 6.9	60 ± 3.3	**< 0.001**
Pulmonary artery systolic pressure [mm Hg]	41.1 ± 9.2	20 ± 4.8	**< 0.001**
Haemoglobin [g/dL]	11.9 ± 1.9	12.1 ± 2.1	0.15
Haematocrit [%]	36.3 ± 5.5	37.2 ± 5	0.11
Glycated haemoglobin A1c [%]	6.4 ± 0.8	5.7 ± 0.1	**< 0.001**
Glomerular filtration rate [mL/min]	65.3 ± 25.2	112.2 ± 14.4	**< 0.001**
pro-BNP (IQR) [pg/mL]	7445.1(1281–26972)	323.1(235–550)	**< 0.001**
Adrenomedullin (IQR) [pg/mL]	87.7 (81.4–99.7)	70.8 (65.2–78.7)	**< 0.001**

SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; pro-BNP: pro-B-Type Natriuretic Peptide; IQR: Interquartile Range

From etiological perspective, the most common reason of HF was found as ischemia (64.4%), HT (12.2%), diabetes mellitus (DM) (2%), idiopathic dilated cardiomyopathy (16.7%), and valvular disease (3.3%). In the study group, chronic comorbidities were found as HT (58.7%), DM (31.3%), coronary artery disease (63.3%), AF (32.2%) and chronic renal disease (30%). Drugs used for the treatment of HF included furosemide (71.1%), beta blockers (76.7%), ARB (20%), angiotensin receptor blocker (55.6%), ACE inhibitors (70.8%), and digoxin (16.7%). NYHA classes of the patients were found as NYHA II in 54.4%, NYHA III in 37.8% and NYHA IV in 7.8% of the patients.

Mean LVEF in the patient and control groups were 32.2 ± 6.9% and 60 ± 3.3%, respectively (p <0.001). Not surprisingly, the mean LVEF value of the patients was lower than that of the controls. The patient group demonstrated significantly higher PASP values compared to the control group (41.2 ± 9.3 vs 21 ± 4.8 mm Hg, respectively; p <0.001).

For prognostic variables of HF, median pro-BNP values in patients with HF and in the control group were 7445.1 (1281–26972) pg/mL and 323.1 (235–550) pg/mL, respectively. (p<0.001). Median ADM levels were considerably superior compared to healthy subjects (87.7 [81.4-99.7] pg/mL and 70.8 [65.2-78.7] pg/mL) (p <0.001). There was a meaningful correlation between the levels of pro-BNP and ADM in patients with HF (p <0.001, r = 0.96) (Figure 1). A very significant positive correlation was found between NYHA class and ADM levels in the patient group (p <0.001, r = 0.94) (Figure 2). Systolic HF patients were divided into two further groups with respect to NYHA functional classes with a view to appraise ADM levels in different clinical settings. Patients with stable HF (NYHA I–II) (n = 48) were assigned to Group I and those with unstable HF (NYHA III–IV) (n = 42) to Group II. Median ADM levels were found to be considerably superior in Group II compared to Group I (median 95.2, IQR 89.3–99.7 pg/mL vs median 84.3, IQR 81.4–88.7 pg/mL, respectively, p < 0.001).

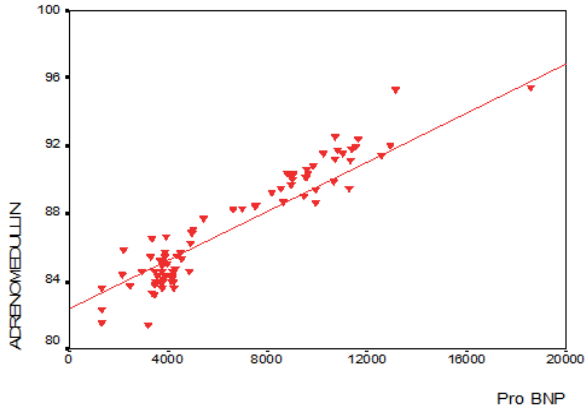

Figure 1. A correlation between pro-B-type natriuretic peptide (pro-BNP) and adrenomedullin level

In addition, there was a negative correlation between ADM levels and LVEF in HF patients (p <0.001, r = –0.50) (Figure 3). On the other hand, there was a distinct positive correlation between ADM levels and PASP in these patients (p <0.001, r = 0.44). The relationship between ADM and GFR was assessed in as much as the well-documented correlation between renal functions and prognosis in HF patients. ADM levels increased as the levels of GFR decrease (p = 0.045, r = –0.21) (Figure 4). No correlation was found between ADM levels and age or gender in both groups.

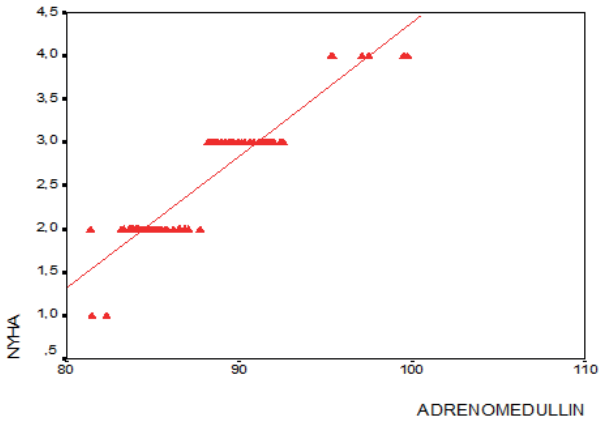

Figure 2. A correlation between New York Heart Association (NYHA) class and adrenomedullin level

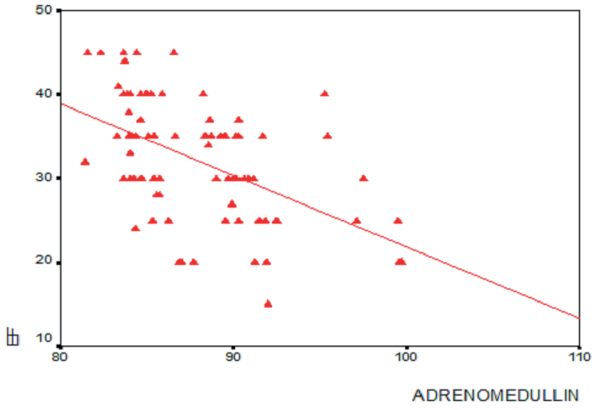

Figure 3. A correlation between left ventricular ejection fraction (LVEF) and adrenomedullin level

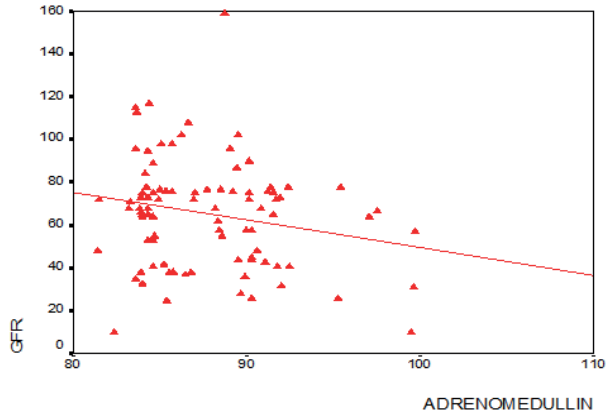

Figure 4. A correlation between glomerular filtration rate (GFR) and adrenomedullin level.

ROC analysis was performed in as much as compare the diagnostic values of ADM and pro-BNP levels in HF. Accordingly, sensitivity of ADM was calculated as 100% and specificity as 100% at the level of 80.05 pg/mL. Area under the curve (AUC) was 1.00 (95% confidence interval [CI] $p < 0.001$). Sensitivity of pro-BNP was calculated as 100% and specificity as 100% at the level of 1285 pg/mL (Figure 5).

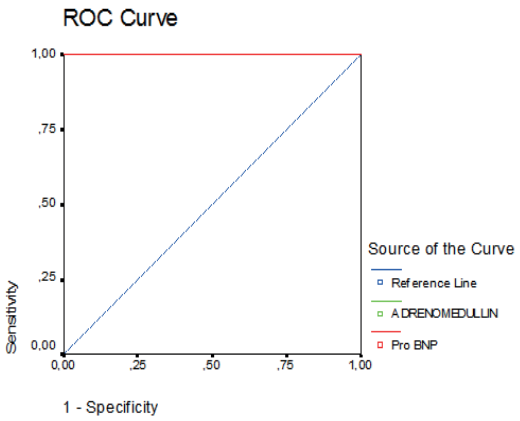

Figure 5. A comparison of adrenomedullin and pro-B-type natriuretic peptide (pro-BNP) levels using receiver operation curve (ROC) analysis

DISCUSSION

The present study indicated that plasma ADM and pro-BNP levels are enhanced in patients with systolic HF. ADM levels showed a negative relation with GFR and LVEF while showing a positive relation with pro-BNP, NYHA and PASP.

ADM is a vasodilator, natriuretic and anti-proliferative peptide that lowers blood pressure and inhibits cell migration. It is well recognized which plasma degrees of ADM enhance in pathophysiologic circumstances such as HF, ACS, HT, renal failure and septic shock (13). Studies in the literature have indicated which plasma grades of ADM enhance with more serious symptoms in patients with HF (14–17). Previous studies have reported a negative correlation between ADM concentrations and ejection fraction while a direct relationship was found with pulmonary capillary wedge pressure, atrial natriuretic peptide, pro-BNP and plasma renin activity (8,9). In a study by Sato et al. from Japan with HF patients, it was demonstrated that the increase in ADM levels had a direct correlation with PASP, pulmonary wedge pressure and NYHA, while there was a negative correlation with LVEF (18). Our study demonstrated that ADM was negatively proportional with LVEF but showed a direct correlation with pro-BNP and PASP.

In 2010, BACH study investigated the recognition values of mid-regional pro-atrial natriuretic peptide (MR-proANP) and mid-regional pro-adrenomedullin (MR-proADM) were investigated in patients presenting by shortness of breath. In this study, MR-proANP was indicated to be a diagnostic value at least as high as BNP, and MR-proADM was demonstrated to have a powerful prognostic determinant of surviving (19). We demonstrated in our study that ADM may have a diagnostic value as high as pro-BNP in HF patients. Haehling et al. investigated the degrees of MR-proADM, a non-active precursor of ADM, in patients with HF (20). In that study, there was a positive correlation between the levels of MR-proADM and NYHA classes, and increases in levels of MR-proADM were associated with enhanced mortality in 1-year follow-up of 501 patients with chronic cardiac failure. Another study also reported that ADM had a prognostic worth in patients with systolic HF compared to cardiac natriuretic peptides (21). It has been reported that MR-proADM may also be used as a marker for the diagnosis, seriousness and treatment response of patients with pulmonary hypertension (22). Another study demonstrated that plasma ADM was associated with edema, orthopnea, hepatomegaly, and jugular venous pressure in patients with new-onset and deteriorative HF (23). Similarly, we demonstrated in our study that ADM showed an effective performance comparable to pro-BNP in the recognition of HF, and it had a diagnostic value at least as good as pro-BNP.

Study limitations

This study had some limitations. Absence of a matching control group for gender and age was a limitation of the study. However, it should also be taken into consideration that no correlation could be demonstrated between age and gender and ADM levels in the study group. Because ADM levels were measured only at the time of admission, we could not assess ADM levels in response to treatment due to the lack of serial measurements. Another limitation, clinical situations such as renal failure and DM may affect the level of adrenomedullin, which do not exclude from in our study. Finally, we could not evaluate the prognostic role of ADM in systolic HF because of the cross-sectional design of this study.

CONCLUSION

Results from this study indicated that ADM levels can be used as a diagnostic indicator in the diagnosis of systolic HF. In addition, it was found that ADM levels increased with worsening HF and were associated with NYHA class, pro-BNP and PASP, while ADM levels were negatively associated with LVEF and GFR. Moreover, further studies are needed for the potential contribution of ADM to the prediction of prognosis of systolic and diastolic HF, and its role in the diagnosis of systolic HF.

Competing interests: The authors declare that they have no competing interest.

Financial Disclosure: There are no financial supports.

Ethical approval: This study protocol was approved by the local ethics committee (decision year and no: 2010/45).

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