Comparison of Plasma Levels of Mature Adrenomedullin and Natriuretic Peptide as Markers of Cardiac Function in Hemodialysis Patients with Coronary Artery Disease

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Key Words

Atrial natriuretic peptide · Brain natriuretic peptide ·
Cardiac function · Coronary artery disease ·
Hemodynamics · Mature adrenomedullin

Abstract

Background: It has been suggested that, like ANP and BNP, high plasma levels of mature adrenomedullin (mAM) indirectly reflect the severity of heart failure or renal failure. However, the relationship between mAM levels and hemodynamics and cardiac function has not been examined in hemodialysis (HD) patients with coronary artery disease (CAD). The best marker, among mAM, ANP and BNP, for left-ventricular function in those patients is also unclear. **Patients and Methods:** Plasma levels of mAM, total AM (tAM), ANP and BNP were determined before HD in chronic HD patients with CAD (group 1; $n = 17$) and were compared with those of HD patients without cardiac disease (group 2; $n = 22$). We examined their relationship to hemodynamics and cardiac function in group 1 using data obtained by cardiac catheterization. **Results:** Plasma levels of ANP and BNP were significantly higher in group 1 than in group 2, but there was no

significant difference in plasma levels of mAM and tAM between the two patient groups. Plasma levels of both mAM and tAM significantly correlated with right atrial pressure (RAP), and only plasma tAM levels correlated with pulmonary artery pressure (PAP) and pulmonary artery wedge pressure (PAWP). However, no correlations were found between levels of the two forms of AM and ejection fraction (EF). In contrast, plasma ANP and BNP levels significantly correlated with both PAP and PAWP, and also with EF, although they did not correlate with RAP. The correlation of PAP and PAWP with ANP and BNP levels was closer than that with tAM levels. The most significant correlation was between BNP levels and EF ($r = -0.756$, $p < 0.0001$). **Conclusions:** Our results suggest that the mAM level may be less useful than natriuretic peptide levels as a marker of cardiac function in HD patients with CAD, and that the BNP level might be the best indicator of left-ventricular function. In addition, cardiac disease such as CAD may have a minor impact on mAM levels compared to renal failure.

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0028-2766/02/0924-0832\$18.50/0

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Introduction

Cardiac diseases such as coronary artery disease (CAD) and valvular heart disease are frequently present in patients undergoing hemodialysis (HD) therapy, and the prognosis in such patients is worse than in those without cardiac disease [1]. In the majority of such cases, CAD, including myocardial infarction and angina pectoris, has been reported to be the most important determinant of survival [1]. Previous studies reported that plasma levels of atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) were significantly elevated in proportion with the severity of heart failure in patients with cardiac disease, suggesting that the natriuretic peptides may be good markers for cardiac function [2, 3]. Significantly high levels of these peptides were also demonstrated in patients with chronic renal failure, especially in those on HD [4–7], which may be explained by both the decreased clearance of these peptides and by increased body fluid volume [4–7]. Recently, we have reported that plasma ANP and BNP levels were further increased in HD patients with CAD compared to those without cardiac disease [8]. Our study using cardiac catheterization also showed that plasma ANP and BNP levels correlated well with pulmonary artery pressure (PAP), pulmonary artery wedge pressure (PAWP), left-ventricular end-diastolic pressure (LVEDP) and left-ventricular ejection fraction (LVEF), and that the most significant correlation was between BNP levels and LVEF [8]. These results suggest that cardiac disease such as CAD, as well as renal failure, may have a major impact on plasma ANP and BNP levels and that levels of the two natriuretic peptides could be useful markers for left ventricular function.

Adrenomedullin (AM), a hypotensive and natriuretic peptide [9], consists of an amidated mature form (mAM) and an intermediate form in human plasma, of which only mAM exerts biological activity [10]. AM functions as a paracrine and/or autocrine factor in the regulation of cardiovascular homeostasis [11], although the clinical significance of mAM is not fully understood. Our recent study showed that, like ANP and BNP, plasma levels of mAM are significantly elevated in patients with chronic renal failure on HD [12] as well as in those with heart failure [13]. These results suggest that mAM may be stimulated by the retention of body fluid in a manner similar to the two natriuretic peptides [2, 4, 6], probably acting as a defensive mechanism in certain pathological conditions, such as heart failure and renal failure, through its vasodilator and natriuretic effects [14]. Previous studies have demonstrated that plasma levels of mAM significantly

correlated with both ANP and BNP, and also with several cardiac parameters such as RAP, PAP and PAWP in patients with heart failure [13, 15]. These results suggest that plasma levels of mAM may indirectly reflect hemodynamics and cardiac function, although whether significant correlations exist between mAM levels and LVEF remains controversial [13, 16]. Thus, determination of plasma mAM levels as well as plasma ANP and BNP levels is considered as a useful non-invasive tool for evaluation of hemodynamics and cardiac function. However, the relationship between mAM levels and hemodynamics and cardiac function has not been examined in HD patients with CAD. Whether mAM levels are superior to ANP and BNP levels as markers of left-ventricular function in those patients is also unclear.

In the present study, we compared plasma levels of mAM in HD patients with CAD to those in HD patients without cardiac disease, and examined the relationship between mAM levels and hemodynamics and left-ventricular function, using data obtained by cardiac catheterization. Furthermore, we compared the usefulness of mAM levels with that of ANP and BNP levels, as a marker of cardiac function.

Patients and Methods

Patients

The study patients comprised two groups: chronic HD patients with CAD (group 1, $n = 17$; 12 men and 5 women) and those without obvious cardiac disease (group 2, $n = 22$; 14 men and 8 women), who had not participated in our previous study [8] (table 1). The underlying renal diseases in the study population included chronic glomerulonephritis (9 in group 1 and 19 in group 2), benign nephrosclerosis (5 and 2, respectively) and idiopathic (3 and 1, respectively). There was no significant difference between patients in the two groups with respect to age, duration of HD, systolic or diastolic blood pressure, cardiothoracic ratio (CTR), blood urea nitrogen, creatinine, albumin or hematocrit. The diagnosis of CAD was made on the basis of clinical histories, physical examinations, chest X-rays, electrocardiograms, and echocardiograms, in addition to the cardiac catheterization data. CAD was defined on cardiac catheterization as more than 75% reduction of luminal diameter of one or more coronary arteries. Among the patients, 9 had effort angina and 8 had an old myocardial infarction. Since the levels of mAM, total AM (tAM), ANP and BNP are usually markedly increased in patients with congestive heart failure [13, 16, 17], acute myocardial infarction [3, 15, 18], cardiac valvular disease [17, 19] and cardiomyopathy [20], patients with these abnormalities were excluded from the study. In group 2, cardiac disease was ruled out based on clinical history, physical examination, and the results of ECG, chest X-ray and echocardiography. In both groups, patients were excluded if they had cardiac arrhythmias, uncontrolled hypertension, diabetes mellitus, chronic pulmonary disease or advanced liver disease. Medications such as antihypertensive agents, platelet aggregation inhibitors, and vasodilators were

Table 1. Characteristics of hemodialysis patients with coronary artery disease (group 1) or without cardiac disease (group 2)

	Group 1 (n = 17)	Group 2 (n = 22)	Significance
Age, years	63 ± 12	56 ± 3	NS
Sex (M/F)	14/3	14/3	NS
HD duration, years	12 ± 9	10 ± 6	NS
Systolic BP, mm Hg	161 ± 22	149 ± 4	NS
Diastolic BP, mm Hg	67 ± 15	79 ± 2	NS
CTR, %	52.6 ± 6.0	49.5 ± 1.0	NS
BUN, mg/dl	54 ± 18	57 ± 12	NS
Creatinine, mg/dl	9.1 ± 2.6	10.7 ± 0.4	NS
Albumin, g/dl	3.9 ± 0.3	3.9 ± 0.1	NS
Hct, %	32.0 ± 7.0	30.2 ± 5.7	NS
Interdialysis weight gain, g	2,762 ± 231	2,633 ± 346	NS

HD = Hemodialysis; BP = blood pressure; CTR = cardiothoracic ratio; BUN = blood urea nitrogen. NS = Not significant.

commonly used as needed. All patients had no residual renal function, and no difference in interdialysis weight gain was observed between the two groups at the start of the HD treatment (table 1). Ultrafiltration was volumetrically controlled in all patients and the rate of fluid removal was recorded hourly during HD. All patients underwent regular sessions of HD for 4 h three times weekly. In all patients, commercial high flux dialyzers with polysulfone or polyester-polymer alloy membranes were used. Heparin was used as an anticoagulant in all patients with an initial loading dose of 1,000 IU followed by continuous infusion of 500 IU/h. The blood flow was usually 150 ml/min, and the dialyzate was bicarbonate-buffered and contained 141 mM sodium. Body fluid was withdrawn and the ultimate goal was to reach a clinically determined dry weight (DW) after dialysis, that is, a condition in which no clinical signs of hypervolemia such as edema, dyspnea, or excessive increase in arterial blood pressure, were evident. This was established under the supervision of an experienced nephrologist. We also studied 11 healthy control subjects (9 men and 2 women; age 29 ± 3 years), who were not on any medication. Informed consent was obtained from each participant prior to initiation of the study.

Study Protocol

Prior to the commencement of dialysis, patients were kept in the supine position in the dialysis room for at least 30 min to stabilize their physical condition. Blood pressure and heart rate were recorded hourly in this position, and body weight was recorded before and after HD. The CTR was determined by one examiner using the chest X-ray film obtained before HD. Plasma mAM, tAM, ANP and BNP levels were determined in blood samples withdrawn from the arterio-venous fistula immediately before the HD session. Before a regularly scheduled HD, all patients of group 1 underwent cardiac catheterization, including left ventriculography and coronary arteriography. LVEDP and LVEF were calculated by the area-length method. At the same time, a Swan-Ganz catheter was inserted into the femoral vein to measure RAP, PAP and PAWP. Cardiac output was calculated by the thermodilution method. Prior to the procedure, blood samples for mAM, tAM, ANP and BNP were also withdrawn from the femo-

ral vein during bed rest. In the control group, blood was drawn from the antecubital vein after a 15-minute rest in the supine position. Blood samples were collected in chilled tubes containing EDTA-2Na and aprotinin, and immediately transported on ice to the laboratory. Plasma was separated by centrifugation and stored at -70°C until analysis. ANP and BNP were determined by commercially available radioimmunoassay kits, namely, Siono-RIA ANP and BNP (Shionogi Co., Osaka, Japan) [8, 12]. Plasma mAM and tAM were measured with radioimmunoassays specific for α -human mAM and tAM, respectively (Shino RIA mature AM kit, RIA AM kit, Shionogi Co.) [12]. The intra-assay coefficients of variation for ANP, BNP, mAM and tAM were 5.6, 5.8, 6.2 and 5.8%, respectively, and their interassay coefficients of variation were 5.6, 6.2, 5.0 and 5.6%, respectively.

Statistical Analysis

All values are presented as mean $\pm$ SD. The unpaired or paired Student's t test was performed to determine the presence of significant differences between the two groups, if appropriate. A value of $p < 0.05$ was considered significant. Correlation coefficients were calculated using linear regression analysis.

Results

Effects of CAD on Plasma Levels of mAM, tAM, ANP and BNP before the HD Session in Groups 1 and 2

Plasma levels of mAM, tAM, ANP and BNP before HD are shown in figure 1. In both groups 1 and 2, mAM levels before HD (group 1: 2.2 ± 0.8 fmol/ml, group 2: 2.4 ± 0.6 fmol/ml) were significantly higher than in control subjects (1.1 ± 0.2 fmol/ml), but no statistical difference was observed between mAM levels of the two patient groups. Similar results were obtained for plasma levels of tAM (group 1: 27.0 ± 12.1 fmol/ml, group 2: $23.6 \pm$

Fig. 1. Plasma concentrations of mature adrenomedullin (mAM), total adrenomedullin (tAM), atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) before hemodialysis (HD), in HD patients with coronary artery disease (group 1) or without cardiac disease (group 2). Dotted bars represent data of normal subjects. Values are expressed as mean $\pm$ SD. * $p < 0.01$, compared with group 2.

4.0 fmol/ml, control subjects: 9.1 ± 2.1 fmol/ml). As described previously [8], ANP and BNP levels were significantly higher in both groups (group 1: 261 ± 210 pg/ml and 772 ± 966 pg/ml, group 2: 123 ± 44 pg/ml and 261 ± 44 pg/ml, respectively) compared to the control values (ANP: 18.6 ± 9.9 pg/ml, BNP: 7.7 ± 7.6 pg/ml). ANP and BNP levels in group 1 were significantly higher than in group 2 ($p < 0.05$), and BNP levels were markedly higher than those of ANP, especially in group 1.

Correlations among mAM, tAM, ANP and BNP before HD in Groups 1 and 2

The results of correlation analyses among mAM, tAM, ANP and BNP before the HD session are shown in table 2. Significant correlations existed between the two forms of AM as well as between the two natriuretic peptides in both groups. In group 1, tAM levels correlated

significantly with ANP and BNP levels ($p < 0.05$), but no correlations were observed between mAM levels and levels of the two natriuretic peptides. As shown in our recent report [12], levels of both mAM and tAM correlated significantly with BNP levels in group 2, whereas they did not correlate with ANP levels. The correlation of BNP with mAM was closer than that with tAM ($p < 0.005$ vs. $p < 0.05$).

Correlation between mAM, tAM, ANP and BNP before HD and Various Cardiac Parameters Measured by Cardiac Catheterization in Group 1

Table 3 shows the correlations between mAM, tAM, and natriuretic peptides and LVEF and hemodynamic parameters. Plasma levels of mAM and tAM weakly but significantly correlated with RAP, but only tAM levels correlated with PAP and PAWP. Plasma levels of both

Table 2. Correlations among mAM, tAM, ANP and BNP in hemodialysis patients with coronary artery disease (group 1) or without cardiac disease (group 2)

	Regression coefficient	p value
<i>Group 1</i>		
mAM vs. tAM	0.715	0.0013
mAM vs. ANP	0.104	0.6918
mAM vs. BNP	0.114	0.6629
tAM vs. ANP	0.512	0.0355
tAM vs. BNP	0.592	0.0124
ANP vs. BNP	0.882	<0.0001
<i>Group 2</i>		
mAM vs. tAM	0.790	<0.0001
mAM vs. ANP	0.340	0.3001
mAM vs. BNP	0.602	<0.005
tAM vs. ANP	0.201	0.5079
tAM vs. BNP	0.418	<0.05
ANP vs. BNP	0.820	<0.0001

ANP = Atrial natriuretic peptide; BNP = brain natriuretic peptide; mAM = mature adrenomedullin; tAM = total adrenomedullin.

mAM and tAM did not correlate with LVEDP and LVEF. In contrast, plasma ANP and BNP levels correlated significantly with PAP and PAWP, and also with LVEF, although they did not correlate with RAP [8]. The correlation of PAP and PAWP with ANP and BNP levels was closer than that with tAM levels. The most significant correlation was between BNP levels and LVEF ($r = -0.756$, $p < 0.0001$).

Correlation between mAM, tAM, ANP and BNP and the Severity of CAD Evaluated by Cardiac Catheterization

Table 4 shows the plasma levels of those peptides and the hemodynamics data including LVEF levels measured by echocardiography, according to the severity of CAD evaluated by cardiac catheterization. Seven patients had single-vessel and 10 had multivessel CAD. We found that LVEF measurements obtained by echocardiography were consistent with those obtained by cardiac catheterization. The LVEF levels in HD patients with severe CAD were significantly lower than in those with mild CAD, although there was no difference in the hemodynamics data other than LVEF between the two patient groups. We noted no correlations between the levels of both mAM and tAM and the severity of CAD. ANP levels tended to correlate with the severity of CAD, but it was not statistically sig-

Table 3. Correlations between natriuretic peptides and left-ventricular function or hemodynamics measured by cardiac catheterization in hemodialysis patients with coronary artery disease

		Regression coefficient	p value
RAP	vs. mAM	0.515	0.0414
	vs. tAM	0.547	0.0283
	vs. ANP	0.360	0.1714
	vs. BNP	0.328	0.2155
PAP	vs. mAM	0.378	0.1484
	vs. tAM	0.648	0.0066
	vs. ANP	0.744	0.0009
	vs. BNP	0.759	0.0006
PAWP	vs. mAM	0.309	0.2450
	vs. tAM	0.491	0.0500
	vs. ANP	0.541	0.0306
	vs. BNP	0.565	0.0227
LVEDP	vs. mAM	-0.017	0.9495
	vs. tAM	0.435	0.0925
	vs. ANP	0.622	0.0076
	vs. BNP	0.631	0.0067
LVEF	vs. mAM	0.087	0.7499
	vs. tAM	-0.386	0.1392
	vs. ANP	-0.598	0.0112
	vs. BNP	-0.756	0.0004

For abbreviations, see table 2. RAP = Right atrial pressure; PAP = pulmonary artery pressure; PAWP = pulmonary artery wedge pressure; LVEDP = left-ventricular end-diastolic pressure; LVEF = left-ventricular ejection fraction.

nificant, as shown in our previous report [8]. In contrast, BNP levels in patients with severe CAD were significantly higher than in patients with mild CAD.

Discussion

This study is the first to demonstrate the lack of significant difference in plasma levels of mAM before a HD session between HD patients with CAD and those without cardiac disease, suggesting that cardiac disease such as CAD had a minor impact on mAM levels compared to the impact of renal failure. From the data obtained by cardiac catheterization, our results also indicate that the mAM level may be less useful than ANP and BNP levels as a marker for cardiac function in HD patients with CAD, and that the BNP level might be the optimal indicator for left ventricular function.

Table 4. Plasma levels of mAM, tAM, ANP and BNP and the hemodynamics data according to the severity of coronary artery disease evaluated by cardiac catheterization in hemodialysis patients with coronary artery disease

	mAM fmol/ml	tAM fmol/ml	ANP pg/ml	BNP pg/ml	RAP (1 ~ 10) mg Hg	PAP (9 ~ 16) mm Hg	PAWP (1 ~ 10) mm Hg	LVEDP (3 ~ 12) mm Hg	LVEF (60 ~ 80) %	LVEF (UCG) (60 ~ 80) %
1 vessel (n = 7)	2.2 ±0.9	26 ±10	189 ±50	430 ±267	5 ±2	19 ±8	13 ±7	16 ±10	67 ±13	63 ±18
2 or 3 vessels (n = 10)	2.1 ±0.8	28 ±14	311 ±264	1,082 ⁺ ±1,108	5 ±3	18 ±8	10 ±4	14 ±7	56 ⁺ ±16	52 ⁺ ±14
Group 2 (n = 22)	2.4 ±0.6	23 ±4	123 ±44	261 ±44						

For abbreviations, see tables 2 and 3. 1 vessel = Hemodialysis patients with involvement of a single coronary artery; 2 or 3 vessels = hemodialysis patients with involvement of two or three coronary arteries; group 2 = hemodialysis patients without cardiac disease. UCG = Echocardiography. Values are expressed as mean ± SD. ⁺ p < 0.05, compared with the 1-vessel group.

It has been suggested that, like ANP and BNP, volume overload may be a stimulus for synthesis and secretion of AM by vascular endothelial [21] and smooth muscle cells [22], despite the differences in their intracellular signaling systems [9, 23–26]. In addition, it has been reported that the failing ventricular myocardium itself may be a source of increased AM production [27, 28]. Thus, it is probable that mAM acts as a defensive mechanism through its vasodilator and natriuretic effects in certain pathological conditions such as heart failure and renal failure [13, 29], in a manner similar to the two natriuretic peptides. We have recently demonstrated the presence of significantly high plasma levels of ANP and BNP in HD patients with CAD compared with those without cardiac disease, indicating that CAD and renal failure have an additive effect on plasma ANP and BNP levels [8]. In the present study, we demonstrated the presence of significantly high plasma levels of mAM in HD patients compared to those in healthy subjects, consistent with previous findings [12, 29–33]. However, in our present study, we observed no additive effects of CAD and renal failure on plasma mAM levels, suggesting that regulation of AM secretion/metabolism may be distinct from that of the natriuretic peptides. We cannot explain the reason for this; however, it could possibly be due to a smaller amount of AM secreted from the failing heart compared with that of natriuretic peptides [27]. Based on the fact that the majority of our patients had a relatively preserved left-ventricular function, a state of volume overload rather than cardiac dysfunction may have contributed to the elevated plasma mAM levels observed in our study. Our results suggest

that cardiac disease such as CAD had a minor impact on mAM levels compared to renal failure and that volume overload may have a major impact on mAM levels.

Previous studies have shown that plasma levels of both mAM and tAM correlated significantly with cardiac parameters such as RAP, PAP and PAWP in patients with heart failure, suggesting that mAM may be a useful marker for hemodynamics and cardiac function [13, 16]. In the present study in HD patients with CAD, we demonstrated for the first time that the correlation of PAP and PAWP with ANP and BNP levels was closer than that with tAM levels, and that levels of both mAM and tAM failed to correlate with LVEDP and LVEF. Furthermore, there was a significant correlation between levels of the two natriuretic peptides and LVEDP or LVEF, with the most significant correlation noted between BNP levels and LVEF ($r = -0.756$, $p < 0.0001$), as described previously [8]. Our results also showed that BNP levels well reflected the severity of CAD, but no correlation was found between the two forms of AM and the severity of CAD. These results strongly indicate that mAM levels may be less useful than natriuretic peptide levels as markers of cardiac function in HD patients with CAD, and that BNP levels could be the best indicators of left ventricular function. Our finding of a lack of significant correlation between mAM levels and LVEF may be consistent with a previous study in patients with heart failure [13], although this remains controversial [16]. This may be explained by the differences in the primary cause of heart failure or by the severity of left-ventricular dysfunction in the patients studied, in addition to the differences in the

pathological conditions between the previous studies (patients with heart failure) [13, 16] and ours (HD patients with CAD). Another implication from our present study is that plasma levels of mAM, but not those of ANP, correlated with RAP, suggesting that plasma levels of mAM may be useful markers of volume status in HD patients with cardiac disease such as CAD. As described in our recent study [8], the absence of a significant correlation between ANP levels and RAP may be explained by the fact that the levels of RAP obtained in our study were almost within the normal range (less than 10 mm Hg), and elevated ANP levels may be reflected by PAWP levels rather than those of RAP.

Our present study revealed significant correlations between the two forms of AM as well as between the two natriuretic peptides in HD patients with CAD, which is consistent with our recent findings in HD patients without cardiac disease [12] and the previous results in patients with heart failure [13, 29]. Previous studies showed that mAM and tAM significantly correlated with ANP and BNP in relation to the severity of diseases such as heart failure [13, 16] and hypertension [34]. In the present study, plasma levels of tAM correlated significantly with levels of both ANP and BNP in HD patients

with CAD, whereas no correlation was observed between mAM levels and natriuretic peptide levels. These results differed from those for HD patients without cardiac disease (group 2), in whom both mAM and tAM significantly correlated with BNP levels but not with ANP levels [Suda et al., in press]. We cannot explain the reason, but it could reflect differences in the associated pathological conditions. Further studies are required to clarify the clinical significance of mAM in certain pathological conditions, where cardiac disease and renal failure coexist.

We conclude that the mAM level may be less useful than natriuretic peptide levels as a marker of cardiac function in HD patients with CAD, and that the BNP level could be the best indicator of left-ventricular function. Unlike the two natriuretic peptides, plasma mAM levels may closely reflect volume status rather than cardiac performance status.

Acknowledgments

The authors are grateful to Akiko Sugimoto for technical assistance. This work was supported by grants from the Ministry of Education, Science and Culture of Japan (A.O., No. 11671065), and the Renal Anemia Foundation, Japan (A.O., M.T.).

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