

Increased plasma adrenomedullin in patients undergoing percutaneous transluminal coronary angioplasty

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Summary

Objectives: adrenomedullin (ADM) production and secretion have been reported in endothelial cells. The present study was designed to assess whether coronary angiography (CA) and percutaneous transluminal coronary angioplasty (PTCA) affect plasma ADM levels.

Design and methods: we measured plasma concentrations of ADM using a specific radioimmunoassay method in patients undergoing coronary angiography or PTCA before and after a 5-minute procedure. Patients were divided into three groups; group I: normal coronary angiography group (11 males, 10 females; mean age 55.90 ± 11.03 yrs), group II: coronary artery disease (CAD), only coronary angiography performed (14 males, 8 females; mean age 60.95 ± 9.80 yrs), group III: PTCA performed in patients with CAD (35 males, 11 females; mean age 55.89 ± 10.41 yrs).

Results: the plasma ADM levels and left ven-

tricular end diastolic pressures measured before the procedure were similar in the three groups ($p > 0.05$). Plasma ADM levels were 13.98 ± 2.26 , 15.59 ± 6.70 , 17.15 ± 8.47 pg/ml respectively. ADM levels measured after CA showed no significant difference in group I (13.75 ± 1.75 pg/ml) or group II (16.50 ± 7.18 pg/ml) ($p > 0.05$). A marked elevation was observed in group III with ADM levels of 27.31 ± 12.27 pg/ml after PTCA ($p < 0.01$). The ADM levels observed in group III after PTCA were significantly higher than those of group I and group II after coronary angiography ($p < 0.001$).

Conclusion: the results of our study show an increase of ADM after PTCA but not after coronary angiography in patients with or without CAD. We think that the increase of ADM levels may be due to cardiac secretion from endothelial and smooth muscle cells following balloon injury.

Keywords: adrenomedullin; coronary angioplasty

Introduction

Adrenomedullin (ADM), first discovered in 1993 by Kitamura and co-workers, is a potent vasodilator peptide consisting of 52 amino acid residues and one intramolecular disulphide bond [1]. Although ADM was first isolated from pheochromocytoma tissue, it was later observed that ADM could be isolated from plasma and that it was present in various tissues such as cardiac atrium, lung and adrenal medulla [2].

Plasma levels of ADM were found to be higher in patients with essential hypertension, congestive

heart failure, renal failure, liver cirrhosis, mitral stenosis and chronic obstructive pulmonary disease compared with normal controls [3-5]. It was postulated that ADM was synthesised and secreted by human endothelial cells [6] and current evidence suggests that endothelial cells are likely to be the major source of circulating ADM.

This study was designed to assess whether ADM increases in plasma after coronary angiography (CA) and percutaneous transluminal coronary angioplasty (PTCA).

Patients and methods

89 patients who underwent coronary angiography or elective PTCA (60 males, 29 females; mean age 57.15 ± 10.53 yrs) were included in the study. Patients were divided into three groups – group I: control group patients whose coronary angiography were completely normal ($n = 22$; 11 males, 10 females; mean age 55.90 ± 11.03 yrs), group II: coronary artery disease group in whom only coronary angiography and left ventriculography were performed ($n = 22$; 14 males, 8 females; mean age 60.95 ± 9.80 yrs), group III: elective PTCA performed in patients with coronary artery disease ($n = 46$; 35 males, 11 females; mean age 55.89 ± 10.41 yrs).

The study protocol was approved by our institute ethics committee and all patients gave written informed consent for blood sampling. Criteria for exclusion from the study were hypertension, acute coronary syndromes, chronic obstructive pulmonary disease, and renal and hepatic insufficiency.

Blood samples were obtained from the antecubital

veins of all patients just before and five minutes after a coronary invasive procedure in the supine position. We used intravenous heparin routinely 5000 IU in group I and in group II, and 10 000 IU in group III. Blood samples (5 ml) were placed in tubes containing disodium EDTA (1 $\mu\text{g/ml}$) and aprotinin (500 U/ml) and were centrifuged at 3000 rpm at 4°C for 15 minutes. The plasma was decanted and stored at -70°C until analysed.

Plasma concentrations of ADM were measured with a specific radioimmunoassay for human ADM (1–52) as previously described [5]. Values were expressed as mean \pm SD. Comparison of plasma ADM concentrations before and after coronary invasive procedure were evaluated with paired t-test in the same group. Differences in ADM levels between different groups were analysed with the Student's t-test. Pearson's correlation analysis was used to assess the relationship between different changes. A value of $p < 0.05$ was taken as being statistically significant.

Results

There were no differences in age, sex and left ventricular end diastolic pressure between three groups. The amount of contrast medium used during the procedure was 96.52 ± 7.53 ml in group I, 167.18 ± 4.50 ml in group II and 170.15 ± 8.48 ml in group III. The mean plasma ADM level measured before the coronary invasive procedure was 13.98 ± 2.26 pg/ml in group I, 15.59 ± 6.70 pg/ml in group II and 17.15 ± 8.47 pg/ml in group III.

There was no significant difference between the three groups. Although there was no significant change in plasma ADM levels measured before and after coronary angiography in group I and

in group II, there was a significant increase in group III after PTCA ($p < 0.01$). Plasma ADM levels measured just before and 5 minute after coronary invasive procedure were given in Table 1 and Figure 1. The plasma ADM levels measured after PTCA were significantly higher than those of both group I ($p < 0.001$) and group II ($p < 0.001$) after coronary angiography.

There was a positive correlation between left ventricular end diastolic pressure and plasma ADM level ($r = 0.857$, $p < 0.001$). The relationship between left ventricular end diastolic pressure and plasma ADM level is shown in Figure 2.

Table 1

Plasma adrenomedullin levels measured before and after coronary invasive procedure.

	group I (n: 21)	group II (n: 22)	group III (n: 46)
left ventricular end diastolic pressure (mm Hg)	12.09 ± 2.84	13.82 ± 6.15	14.22 ± 6.49
adrenomedullin (pg/ml) (before procedure)	13.98 ± 2.26	15.59 ± 6.70	17.15 ± 8.47
adrenomedullin (pg/ml) (after procedure)	13.75 ± 1.75	16.50 ± 7.18	27.31 ± 12.27
p	>0.05	>0.05	<0.01

Figure 1

Mean plasma adrenomedullin levels measured just before (ADM I) and 5 minutes after coronary invasive procedure (ADM II).

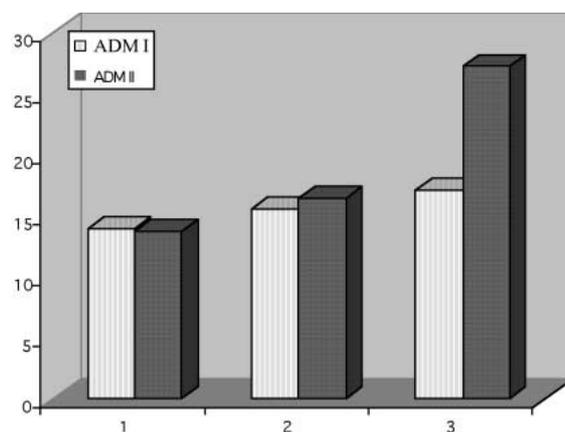


Figure 1

Figure 2

The relation between plasma adrenomedullin levels and left ventricular end diastolic pressure (LVEDP).

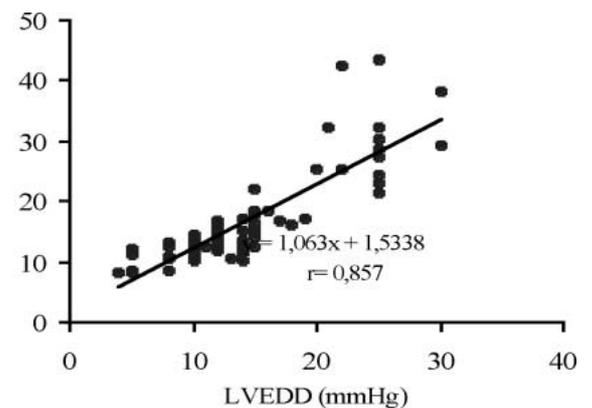


Figure 2

Discussion

In the present study, baseline plasma levels of ADM in the peripheral venous blood of patients with or without coronary artery disease were similar. Coronary angiography did not significantly change plasma ADM levels. Percutaneous coronary angioplasty however, caused a significant increase in plasma ADM levels. Because ADM levels were measured in peripheral venous blood rather than the coronary sinus, this study was not able to demonstrate cardiac ADM secretion directly.

The source of circulating plasma ADM remains unknown. Although ADM mRNA was expressed in several tissues such as lungs, kidneys, brain, liver, adrenal glands and heart, the results of Nishikimi and colleagues' study [7] suggested that these sites might not be the main sources of circulating ADM. In this study, there were no significant differences in plasma ADM levels measured at various sites of systemic venous circulation and it has been reported that plasma ADM does not increase at rest or even during hypertensive attacks in patients with pheochromocytoma. Today vascular tissues are considered to be main source of circulating ADM. Sugo et al. reported that ADM was secreted both by cultured vascular endothelial and smooth muscle cells [8, 9]. It was also shown that ADM is synthesised and secreted by endothelial cells cultured from human umbilical vein [6]. Nakoyama et al. [10] reported that production and secretion of ADM were increased in cultured human coronary artery endothelial cells under hypoxia. It was pointed out ADM increased in the early phase of acute myocardial infarction with or without congestive heart failure and normalised after 1 month. It was found that plasma ADM levels in acute myocardial infarction with congestive heart failure were higher than in patients without congestive heart failure [11]. In addition, it was reported that the plasma ADM level of patients with chronic congestive heart failure was significantly higher than in control subjects [12]. Since left ventricular end diastolic pressures were similar in the three groups of our study, and because other factors that might affect plasma ADM levels were ex-

cluded, we consider that plasma ADM levels measured in the present study reflect the effect of the coronary invasive procedure. While coronary angiography alone appears not to affect plasma ADM levels, the fact that coronary angiography with PTCA increases the level of plasma ADM would suggest that the release of ADM occurs in response to myocardial ischaemia and mechanical injury of coronary endothelial cells during PTCA.

Etoh et al. [13] found a significant increase in plasma ADM levels in the coronary sinus after PTCA. Teteyama and colleagues [14] reported that plasma ADM levels increased after PTCA but not coronary angiography. These two studies support our results.

Although the amount of contrast medium used in group I and in group II was significantly different, the fact that the levels of ADM measured after the procedure were not different make us think that the amount of contrast medium might not affect plasma ADM levels. Since we used similar occlusion times in all patients, the results of this study could not indicate if there was a relationship between occlusion time and the increase in plasma ADM level. As twice the amount of heparin was used in group III compared with groups I and II, it might be inferred that heparin is linked with the increase of plasma ADM, but since no significant rise in ADM levels was observed in groups I and II, despite the use of heparin, suggests indirectly that heparin used during the procedure does not affect plasma ADM levels.

In conclusion, plasma levels of ADM increased after PTCA. This effect may be due to mechanical injury of coronary endothelial cells and myocardial ischaemia.

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