Molecular forms of adrenomedullin in pericardial fluid and plasma in patients with ischaemic heart disease

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ABSTRACT

Experimental studies have demonstrated that adrenomedullin (AM) has a positive inotropic action and exerts inhibitory effects against ventricular remodelling as an autocrine and paracrine factor. However, there is no clinical evidence for AM acting as a local regulator in the human heart. We measured the levels of various molecular forms of AM, i.e. an active form of mature AM (AM-m), an intermediate inactive form of glycine-extended AM (AM-Gly) and total AM (AM-T = AM-m + AM-Gly), in plasma and pericardial fluid using our newly developed immunoradiometric assay in consecutive 67 patients undergoing coronary artery bypass graft surgery. Pericardial fluid and plasma cAMP, atrial natriuretic peptide and brain natriuretic peptide levels were also measured. The relationships between pericardial fluid AM levels and ventricular functions and other hormone levels were analysed. The level of each molecular form of AM in pericardial fluid was closely correlated with that of the other molecular forms of AM in the fluid. However, levels were not correlated with those in plasma. AM-T levels were slightly higher in pericardial fluid than in plasma (+72%; P < 0.05), whereas AM-m levels and AM-m/AM-T ratios were markedly higher in pericardial fluid than in plasma (AM-m, +994%; AM-m/AM-T ratio, +443%; both P < 0.01). AM-m, AM-Gly and AM-T levels in pericardial fluid were correlated with indices of left ventricular function, and with atrial natriuretic peptide and brain natriuretic peptide levels. Interestingly, AM and cAMP levels were positively correlated in plasma, but negatively correlated in pericardial fluid. In addition, AM-m, AM-Gly and AM-T levels in pericardial fluid were higher in patients with acute coronary syndrome than in those with stable ischaemic heart disease (AM-m, +80%; AM-Gly, +96%; AM-T, +83%; all P < 0.01). These results suggest that AM in pericardial fluid reflects cardiac synthesis, and that enhanced cardiac secretion of AM is associated with left ventricular dysfunction, ventricular overload and myocardial ischaemia. Considering that AM has positive inotropic, coronary vasodilatory and anti-remodelling actions, increased cardiac AM may play a compensatory role in the ischaemic and failing myocardium.

Key words: adrenomedullin, cAMP, ischaemic heart disease, pericardial fluid.

Abbreviations: ACS, acute coronary syndrome; AM, adrenomedullin; AM-Gly, glycine-extended, inactive AM; AM-m, mature, active AM; AM-T, total AM; ANP, atrial natriuretic peptide; BNP, brain natriuretic peptide; IHD, ischaemic heart disease; LVEDP, left ventricular end-diastolic pressure; LVEDVI, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; LVESVI, left ventricular end-systolic volume index.

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INTRODUCTION

Although adrenomedullin (AM), a 52-amino-acid peptide, was originally discovered in human pheochromocytoma tissue [1], subsequent studies have demonstrated that AM peptide and mRNA are widely distributed in various tissues and organs, including the heart [2,3]. Binding studies have demonstrated an abundant concentration of specific AM receptors in the heart [4]. The presence of AM peptide, its mRNA and its receptors in the heart suggests that AM acts as a cardiac autocrine and paracrine factor. Previous studies have demonstrated that AM significantly increases cardiac output in vivo and in vitro [5,6]. We reported previously that AM peptide and mRNA levels are increased in the ventricles of rats with either heart failure or acute myocardial infarction [7–9]. Our laboratory and others have shown that cardiac myocytes and fibroblasts produce and secrete AM [10–13], and that AM inhibits collagen and DNA synthesis in cardiac non-myocytes and inhibits myocyte hypertrophy partly via a cAMP-dependent pathway [13,14]. These results suggest that locally released AM in the heart plays a role in the maintenance of cardiac function and/or in cardiac structural remodelling. In the clinical setting, plasma AM levels are increased in patients with heart failure and after acute myocardial infarction [15–18]. However, there was no clinical evidence for AM acting as a local regulator in the heart. The pathophysiological significance of cardiac AM in acute coronary syndrome (ACS) is not fully understood.

Previous studies have shown that two molecular forms of AM, i.e. an active mature form (AM-m) and an inactive intermediate form of glycine-extended AM (AM-Gly), are present in human plasma, and that the major circulating form is AM-Gly [19,20]. Previously reported plasma AM levels are in fact total AM (AM-T) levels, being the sum of AM-m and AM-Gly, because the commonly used RIA employs a polyclonal antibody that does not distinguish between the two forms. To clarify the pathophysiological role of AM, it is important to assess the concentrations of the active and inactive forms of AM. We have therefore developed a new immuno-radiometric assay for measuring the concentrations of the active and inactive forms of AM [21,22].

The pericardial fluid contains abundant levels of various substances produced in the heart [23–25]. In addition, the concentrations of these substances are higher in pericardial fluid than in plasma. Determination of the concentration of AM in the pericardial fluid and plasma of patients with cardiac disease should help to elucidate the role of AM in the maintenance of cardiac function. The purpose of the present study was to: (1) determine whether AM is concentrated in the pericardial fluid, which would suggest that it is released from the heart; (2) compare the concentration of AM-m and its ratio to AM-T between pericardial fluid and plasma; (3) determine the relationship of AM levels with those of atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP), as well as with clinical indices, in patients with ischaemic heart disease (IHD) who were undergoing coronary artery bypass surgery.

METHODS

Patients

We studied 67 consecutive Japanese patients with IHD, aged 48–82 years (mean ± S.D., 67 ± 8 years), who were undergoing coronary artery bypass surgery (52 men, 15 women). Stable IHD was the primary disorder in 46 patients, with ACS in 21 patients. ACS was diagnosed according to recently reported guidelines [26]. All patients were evaluated before the operation by coronary arteriography. Left ventriculography was also performed in all cases, except for seven emergent cases in the ACS group and six patients with stable IHD because of slightly higher creatinine levels (serum creatinine level 170–283 μmol/litre). Left ventricular end-diastolic pressure (LVEDP) was measured. Left ventricular ejection fraction (LVEF), left ventricular end-diastolic volume index (LVEDVI) and left ventricular end-systolic volume index (LVESVI) were calculated using the area–length method. We excluded patients with congestive heart failure, valvular disease, renal failure (serum creatinine level > 283 μmol/litre) and primary lung disease.

The investigation conformed with the principles outlined in the Declaration of Helsinki. Informed consent was obtained from each patient, and the protocol was approved by the ethical committee of our institute.

Sampling of plasma and pericardial fluid

Immediately after incision of the pericardium, undiluted samples of pericardial fluid were obtained without heparinization [24,25]. At the same time, blood was withdrawn from the cannulated brachial artery. Samples were added to sterile chilled tubes containing EDTA (1 mg/ml) and aprotinin (500 kallikrein-inhibitory units/ml) and centrifuged immediately at 1000 g (4 °C) for 10 min and stored in sample tubes at −80 °C.

Assay for AM-m and AM-T

Levels of AM-m and AM-T were measured by immuno-radiometric assays using specific kits (AM mature RIA SHIONOGI and AM RIA SHIONOGI respectively) developed by the Diagnostic Science Department, Shionogi Pharmaceutical Co., Ltd., Osaka, Japan [21,22]. These assay systems use two monoclonal antibodies against human AM, one that recognizes a ring structure of human AM in both kits and another that recognizes the C-terminal sequence in the AM-m kit or AM-(25–36) in the AM-T kit; the assay measures human AM-m or AM-T by sandwiching it between the two antibodies.
without plasma extraction. The assay’s limit of detection of human AM-m or AM-T is 0.5 pmol/l for both kits. The intra-assay and interassay coefficients of variation in several blood samples were 4.4–8.2% and 5.5–8.3% respectively with the AM-m kit, and 3.4–7.3% and 5.3–9.0% respectively with the AM-T kit. The rate of recovery of 5–100 pmol of human AM/litre added to several plasma samples was 91–118% for both kits. The rate of recovery of 20–100 pmol of human AM/litre added to several urine samples was 81–92% for the AM-m kit and 79–104% for the AM-T kit. Reverse-phase HPLC analysis revealed that the major peak of immunoreactive AM in the plasma and urine detected by each immunoradiometric assay kit for AM-m and AM-T was identical to synthetic human AM-(1–52) [21,22]. Levels of AM-Gly were calculated with the formula: AM-Gly = AM-T – AM-m [19].

**Other assays**
The pericardial fluid and plasma concentrations of ANP and BNP were measured using specific immunoradiometric assay kits (Shionogi Co., Ltd), as reported previously [27]. The pericardial fluid and plasma concentrations of cAMP and cGMP were measured by RIA kits (cAMP and cGMP assay kits; Yamasa Shoyu Co., Chiba, Japan).

**Statistical analysis**
All data are expressed as means ± S.D. unless otherwise indicated. Logarithmic transformation was used to normalize the distribution of pericardial fluid and plasma ANP and BNP concentrations, because these are not normally distributed (by the Kormgrov–Smirnov method). Comparisons of mean values between the two groups were performed using the unpaired or paired Student’s t-test, as appropriate. Correlation coefficients were calculated by linear regression analysis. P values of < 0.05 were considered significant.

**RESULTS**

**Molecular forms of AM and other biochemical factors in pericardial fluid and plasma from patients with IHD**
The clinical characteristics of the patients are presented in Table 1. Figure 1 shows AM-T, AM-Gly and AM-m levels and the AM-m/AM-T ratio in the pericardial fluid and plasma for all patients. AM-T levels were slightly, but significantly, higher in pericardial fluid than in plasma (+72%), whereas there were no significant differences in AM-Gly levels between pericardial fluid and plasma. Interestingly, AM-m levels and the AM-m/AM-T ratio were markedly higher in pericardial fluid than in plasma (AM-m, +994%; AM-m/AM-Gly ratio, +443%). BNP levels were significantly higher in pericardial fluid than in plasma (586 ± 1019 and 199 ± 334 ng/l respectively; P < 0.05), whereas there was no significant differences in ANP levels between pericardial fluid and plasma (38 ± 57 and 65 ± 75 ng/l respectively). There were also no significant differences in cAMP levels between pericardial effusion and plasma (90.5 ± 28.8 and 82.8 ± 27.3 pmol/ml respectively).

**Figure 1** AM-T, AM-Gly and AM-m levels and AM-m/AM-T ratios in pericardial fluid (PF) and plasma from patients with IHD

Values are means ± S.E.M. Significance of differences: *P < 0.05; †P < 0.001 compared with plasma.

**Table 1 Clinical characteristics of the patients in this study**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>67</td>
</tr>
<tr>
<td>Age (years)</td>
<td>67 ± 8</td>
</tr>
<tr>
<td>Gender (male/female)</td>
<td>52/15</td>
</tr>
<tr>
<td>Body surface area (m²)</td>
<td>1.63 ± 0.16</td>
</tr>
<tr>
<td>Diagnosis</td>
<td></td>
</tr>
<tr>
<td>ACS (n)</td>
<td>21</td>
</tr>
<tr>
<td>Stable IHD (n)</td>
<td>46</td>
</tr>
<tr>
<td>Mean aortic pressure (mmHg)</td>
<td>97 ± 14</td>
</tr>
<tr>
<td>LVEDP (mmHg)</td>
<td>17.7 ± 7.3</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>56.4 ± 16.8</td>
</tr>
<tr>
<td>LVESVI (ml/m²)</td>
<td>86 ± 50</td>
</tr>
<tr>
<td>LVEFVI (ml/m²)</td>
<td>40 ± 10</td>
</tr>
</tbody>
</table>

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and in plasma for all patients. The levels of each molecular form of AM in the pericardial fluid were closely correlated with those of the other molecular forms of AM in this fluid (Figures 2A–2C). In addition, each molecular form of AM in plasma was also closely correlated with other molecular forms of AM in plasma (Figures 2D–2F).
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Figure 4  Relationships between levels of the various molecular forms of AM in pericardial fluid, and LVEF and LVEDP in patients with IHD

Table 2  Correlation coefficients between levels of the various molecular forms of AM in plasma and indices of left ventricular function in patients with IHD

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Plasma AM-T</th>
<th>Plasma AM-Gly</th>
<th>Plasma AM-m</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEF</td>
<td>$r = 0.31$, $P &lt; 0.05$</td>
<td>$r = 0.31$, $P &lt; 0.05$</td>
<td>$r = 0.34$, $P &lt; 0.05$</td>
</tr>
<tr>
<td>LVESVI</td>
<td>$0.19$, NS</td>
<td>$0.25$, NS</td>
<td>$0.18$, NS</td>
</tr>
<tr>
<td>LVEDVI</td>
<td>$0.01$, NS</td>
<td>$0.01$, NS</td>
<td>$0.01$, NS</td>
</tr>
<tr>
<td>LVEDP</td>
<td>$0.08$, NS</td>
<td>$0.07$, NS</td>
<td>$0.16$, NS</td>
</tr>
</tbody>
</table>

However, levels of each of the molecular forms of AM in plasma were not correlated with those in pericardial fluid (Figure 3).

Figures 4(A)–4(F) show the relationships between levels of the molecular forms of AM in pericardial fluid and indices of left ventricular function in patients with IHD. Levels of AM-T, AM-Gly and AM-m in pericardial fluid were all correlated with LVEF and LVEDP, but the correlation coefficients were relatively higher for AM-T and AM-Gly than for AM-m. Levels of the various molecular forms of AM in pericardial fluid were also correlated with LVESVI (AM-T, $r = 0.41$; AM-Gly, $r = 0.44$; AM-m, $r = 0.28$; all $P < 0.05$) and LVEDVI (AM-T, $r = 0.33$; AM-Gly, $r = 0.29$; AM-m, $r = 0.28$; all $P < 0.05$). However, levels of the molecular forms of AM in plasma were weakly correlated with LVEF, but not with LVEDP, LVEDVI or LVESVI (Table 2). In addition, levels of AM-T, AM-Gly and AM-m in pericardial fluid were correlated with ANP and BNP levels in pericardial fluid (Figures 5A–5F).

Interestingly, levels of the molecular forms of AM in pericardial fluid were negatively correlated with cAMP levels in pericardial fluid (Figures 5G–5I), but not with those in plasma (plasma cAMP: AM-T, $r = 0.06$; AM-Gly, $r = 0.19$; AM-m, $r = -0.06$). In contrast, plasma AM-T, AM-Gly and AM-m levels were positively correlated with plasma cAMP levels (AM-T, $r = 0.44$; AM-Gly, $r = 0.43$; AM-m, $r = 0.44$; all $P < 0.01$). Pericardial fluid cAMP levels were not correlated with plasma cAMP levels ($r = 0.11$). Thus levels of the molecular forms of AM and of cAMP in pericardial fluid and in plasma are differently regulated.

Levels of the molecular forms of AM in pericardial fluid and plasma of patients with ACS

The characteristics of the groups of patients with ACS and with stable IHD are presented in Table 3. There were no significant differences in age, gender or body mass index between the two groups. However, an intra-aortic balloon pump was used only in the ACS group. With regard to cardiac function, there were no differences in LVEDP, LVEF, LVEDVI or LVESVI between the two groups.

The levels of the molecular forms of AM in the pericardial fluid and plasma of patients in the ACS and stable IHD groups are presented in Figure 6. AM-T, AM-m and AM-Gly levels were higher in the ACS group than in the stable IHD group in both pericardial fluid and plasma, whereas there were no differences between the two groups in the AM-m/AM-T ratios in pericardial fluid or plasma.

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Table 3  Clinical characteristics and biochemical markers in pericardial fluid and plasma in groups of patients with ACS or stable IHD

<table>
<thead>
<tr>
<th>Parameter</th>
<th>ACS (n = 21)</th>
<th>Stable IHD (n = 46)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>66 ± 8</td>
<td>67 ± 9</td>
<td>NS</td>
</tr>
<tr>
<td>Gender (male/female)</td>
<td>16/5</td>
<td>36/10</td>
<td>NS</td>
</tr>
<tr>
<td>Body surface area (m²)</td>
<td>1.64 ± 0.20</td>
<td>1.63 ± 0.13</td>
<td>NS</td>
</tr>
<tr>
<td>Use of IABP (n)</td>
<td>13</td>
<td>0</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Aortic pressure (mmHg)</td>
<td>91 ± 13</td>
<td>98 ± 14</td>
<td>NS</td>
</tr>
<tr>
<td>LVSDP (mmHg)</td>
<td>21.4 ± 6.0</td>
<td>16.8 ± 7.4</td>
<td>NS</td>
</tr>
<tr>
<td>LVESD (%)</td>
<td>53 ± 18</td>
<td>58 ± 16</td>
<td>NS</td>
</tr>
<tr>
<td>LVESVI (m²/m²)</td>
<td>89 ± 31</td>
<td>86 ± 55</td>
<td>NS</td>
</tr>
<tr>
<td>LVSDVI (m²/m²)</td>
<td>42 ± 21</td>
<td>39 ± 33</td>
<td>NS</td>
</tr>
<tr>
<td>Pericardial fluid ANP (ng/ml)</td>
<td>66 ± 64</td>
<td>23 ± 26</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Plasma ANP (ng/ml)</td>
<td>86 ± 41</td>
<td>55 ± 65</td>
<td>NS</td>
</tr>
<tr>
<td>Pericardial fluid BNP (ng/ml)</td>
<td>1022 ± 1416</td>
<td>354 ± 630</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Plasma BNP (ng/ml)</td>
<td>269 ± 326</td>
<td>164 ± 336</td>
<td>NS</td>
</tr>
<tr>
<td>Pericardial fluid cAMP (pmol/ml)</td>
<td>83.3 ± 28.5</td>
<td>94.0 ± 28.6</td>
<td>NS</td>
</tr>
<tr>
<td>Plasma cAMP (pmol/ml)</td>
<td>88.2 ± 30.1</td>
<td>80.2 ± 25.7</td>
<td>NS</td>
</tr>
</tbody>
</table>

Table 3 shows the biochemical indices in the pericardial fluid and plasma for the ACS and stable IHD groups. Pericardial fluid ANP and BNP levels were higher in the ACS group than in the stable IHD group, but there were no differences in plasma ANP and BNP levels between the two groups. Nor were there any differences in pericardial fluid or plasma cAMP levels between the two groups.

DISCUSSION

The human AM precursor consists of 185 amino acids, with a putative signal peptide [28]. Active AM is produced from the precursor by a two-step enzymic reaction. First, the AM precursor is converted into AM-Gly, a 53-amino-acid peptide that represents an intermediate, inactive form of AM. Subsequently, inactive AM-Gly is converted into the active form, AM-m, a 52-amino-acid peptide with a C-terminal amide structure, by enzymic amidation [19]. Both forms of AM-m and AM-Gly circulate in human plasma, and the major circulating form is AM-Gly [19,20]. The present study has revealed an AM-m/AM-T ratio in plasma of 0.06–0.07, which is consistent with previous studies [20,29]. The reasons for this lower AM-m/AM-T ratio in the plasma, compared with the pericardial fluid, are considered to be as follows: (1) AM-m produced in the tissues binds and acts in situ, and little AM-m is released...
Adrenomedullin in pericardial fluid

Figure 6  AM-T, AM-Gly and AM-m levels, and AM-m/AM-T ratios, in pericardial fluid and plasma from patients with ACS and stable IHD

Values are means ± S.E.M. Significance of differences: *P < 0.05, †P < 0.01 compared with plasma.

into the circulation; (2) AM-Gly has low biological activity and cannot bind to the receptor on the cells, and therefore AM-Gly produced in the cells is almost all released into the circulation; and (3) the half-life of AM-m in plasma is shorter than that of AM-Gly, because AM-m, but not AM-Gly, is extracted in the pulmonary circulation [20]. As the origin of plasma AM is now thought to be the vascular wall [30], the decreased AM-m/AM-T ratio in plasma may be explained by autocrine and paracrine actions of AM in the vascular wall or by the longer half-life of AM-Gly in the circulation.

AM mRNA is expressed not only in the adrenal gland, but also in the heart, kidney and lungs [1]. We demonstrated previously that the mRNA and peptide levels of AM are increased in the failing rat myocardium [5]. In addition, Yoshihara et al. [9] recently reported that ventricular AM levels in the pressure- and volume-overloaded failing myocardium are well correlated with the degree of fetal cardiac gene expression, suggesting that the cardiac AM level is a marker of the failing heart. In addition, we measured tissue AM levels in the pericardium by the immunoradiometric assay used in the present study, and confirmed that AM immunoreactivity was not detected in pericardial tissue (T. Nishikimi, unpublished work), suggesting that pericardial fluid AM is derived from the ventricle. In the present study, we observed that AM-m levels and the AM-m/AM-T ratio were markedly increased in pericardial fluid compared with plasma. A similar pattern is found for BNP, which is of ventricular origin. In addition, we have shown that pericardial fluid AM-T and AM-Gly levels are better correlated with indices of left ventricular function than are pericardial fluid AM-m levels. These results raise the possibility that pericardial AM reflects the cardiac production of AM, and that AM-T or AM-Gly may be a better marker for cardiac function than AM-m. Although the reason for this is not known at present, levels of AM-T or AM-Gly better reflect the entire cardiac production of AM, because AM-m is consumed as an autocrine and paracrine factor in the ventricle [10,14].

It remains unclear how endogenous cardiac AM functions in the ischaemic ventricle. AM has been reported to increase myocardial contractility in vivo [8] and to exert a direct inotropic effect in vitro [9]. Thus AM in pericardial fluid may function as an endogenous positive inotropic substance to oppose deterioration of cardiac performance as a defence mechanism. To support this notion, we found in the present study that AM levels were negatively correlated with cAMP levels in the pericardial fluid, although plasma AM levels were positively correlated with plasma cAMP levels. In heart failure, plasma cAMP increases along with the increases in noradrenaline and AM [16]. In contrast with the plasma, down-regulation of β-adrenergic receptors in
the failing heart leads to a decrease in cAMP production in the heart [31]. Previous studies have demonstrated that AM increases intracellular cAMP levels in cardiac myocytes and non-myocytes [10,12,14]. Taken together, these results suggest that increased cardiac AM levels may be involved in compensatory mechanisms in the failing heart.

Previous studies have shown that plasma AM-T levels are increased in patients with ACS compared with normal control subjects [17,18]. Furthermore, we have reported that cardiac AM synthesis is increased in the infarcted and non-infarcted myocardium in rats following acute myocardial infarction, and that ventricular AM levels are correlated with infarct size and LVEDP [6]. In the present study we observed that levels of the various molecular forms of AM in the pericardial fluid and plasma were increased in patients with ACS compared with those with stable IHD. The mechanisms by which ACS results in increased AM remain unknown. Previous studies have demonstrated that various cytokines markedly increase AM mRNA expression in cultured vascular smooth muscle cells and endothelial cells [32,33]. Moreover, we reported that interleukin-1β and tumour necrosis factor-α enhance AM mRNA expression in cardiac myocytes and fibroblasts [11]. It has been demonstrated that cytokines are activated in acute myocardial infarction [34]. Although we have not demonstrated a direct relationship between cytokines and AM in the present study, these previous results suggest that increased cytokine levels in ACS may stimulate AM synthesis in the ventricle. The pathophysiological role of increased cardiac AM in ACS remains unknown. AM dilates the coronary artery not only by decreasing the Ca²⁺ concentration, but also by decreasing Ca²⁺ sensitivity [35,36]. In human coronary arterioles, AM elicits vasodilatation in part through production of nitric oxide and in part through activation of K⁺ channels [37]. These results suggest that cardiac AM may function as an endogenous vasodilatory peptide to oppose deterioration of myocardial ischaemia. Further studies are necessary to elucidate the exact pathophysiological role of cardiac AM in IHD.

The present study was subject to certain limitations. Since we did not study the relationship between cardiac AM mRNA levels and pericardial fluid AM levels, the latter may not necessarily reflect increased cardiac AM production. Although several experimental studies have shown that the cardiac production of AM is increased in proportion to the severity of left ventricular dysfunction [8,9], and a few clinical studies have revealed that plasma AM levels in the coronary sinus are increased in proportion to the severity of heart failure [7,38], it is difficult to prove that increased pericardial AM levels are due to increased cardiac production in human subjects. The metabolism and clearance of AM may be changed in these conditions.

In conclusion, we have found that enhanced cardiac AM secretion is associated with indices of left ventricular function, pericardial fluid ANP, BNP and cAMP levels and myocardial ischaemia in patients with IHD. Given the biological action of AM, these findings suggest that increased cardiac synthesis of AM may play a compensatory role in the ischaemic and failing human myocardium.

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