Increased Plasma Adenosine Concentration in the Subacute Phase May Contribute to Attenuation of Left Ventricular Dilation in the Chronic Phase in Patients With Acute Myocardial Infarction

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Background: Changes in the plasma adenosine concentration and the effects on left ventricular (LV) function and remodeling in patients with acute myocardial infarction (AMI) remain unclear.

Methods and Results: In 58 patients with AMI and 14 subjects without cardiac disease (controls), we measured the plasma adenosine concentration by LC-MS/MS. Blood samples were taken from the antecubital vein on days 0, 1, 7, and 14 after AMI, and from the controls on admission. Cardiac echocardiography was performed in the acute (within 7 days) and chronic (6 months) phases of AMI. There were no significant differences in the plasma adenosine concentrations among days 0 (211.5±150.2 nmol/L), 1 (192.7±141.3 nmol/L), 7 (218.8±154.1 nmol/L), and the controls (136.0±50.9 nmol/L). The plasma adenosine concentration increased significantly on day 14 (321.1±195.4 nmol/L) after AMI as compared with days 0, 1 and 7. AMI patients with a greater increase in the plasma adenosine concentration in the subacute phase showed an attenuation of LV dilation in the chronic phase. The plasma adenosine concentration in the acute phase did not affect the LV ejection fraction in the chronic phase.

Conclusions: The plasma adenosine concentration significantly increased 14 days after AMI, which may contribute to attenuation of LV dilation in the chronic phase.

Key Words: Acute myocardial infarction; Left ventricular dilation; Left ventricular ejection fraction; Plasma adenosine concentration

Endogenous adenosine is reported to trigger ischemic preconditioning of the heart. It has also been reported that administration of adenosine or an adenosine analog before prolonged ischemia protects the heart and reduces the size of the myocardial infarct, and that an adenosine A1 receptor agonist improved left ventricular (LV) function and remodeling in dogs with advanced heart failure. These reports suggest that adenosine is a cardioprotective agent. Some have reported that the plasma adenosine concentration is elevated in patients with chronic HF, and that the extent of the increase in plasma adenosine concentration correlated well with the severity of chronic HF as assessed by NYHA classification; however, others have reported that the plasma adenosine concentration did not differ between normal subjects and patients with NYHA class III chronic HF. We recently reported that the plasma adenosine concentration measured by the ESI-MS/MS method was not elevated in patients with chronic HF at any level of severity as assessed by NYHA classification. However, cardiac patients with a lower LV ejection fraction (EF) or dilated LV end-diastolic dimension (LVDd) showed a higher plasma adenosine concentration, suggesting that endogenous adenosine counteracts LV dysfunction and LV dilation in patients with heart disease.

However, changes in the plasma adenosine concentration after acute myocardial infarction (AMI) and the effect of endogenous adenosine on LV function and LV dilation in the chronic phase are still unknown. Therefore, in the present study, we examined whether the plasma adenosine concentration increases after AMI and if endogenous adenosine improves LV function and attenuates LV dilation in the chronic phase 6 months after AMI.

Received October 22, 2018; revised manuscript received December 26, 2018; accepted January 9, 2019; J-STAGE Advance Publication released online February 26, 2019. Time for primary review: 26 days.

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Subjects
The study group comprised 58 patients with AMI (AMI group) and 14 patients without cardiac diseases who were admitted to Gifu University Hospital & Takayama Red Cross Hospital. Patients with normal heart function based on echocardiography and a normal ECG were enrolled as a control group. They underwent echocardiography because of some anterior chest complaints but did not have any cardiovascular diseases. The diagnosis of AMI was based on the presence of prolonged anterior chest pain, ST-segment elevation on ECG, and an occluded coronary artery on coronary angiography. AMI patients were treated with percutaneous coronary intervention followed by standard pharmacological treatment. The patients were enrolled consecutively into the AMI or control group. Of the 58 patients with AMI, 38 were followed up for 6 months after the onset of AMI.

The protocol was approved by the Ethics Committee of Gifu University Graduate School of Medicine (approval no. 27-394). All patients provided written informed consent before the study commenced. The investigation conformed with the principles outlined in the Declaration of Helsinki (BMJ 1964; ii: 177). The public trial registry number was R000026665.

Evaluation of LV Function and Dilation
Echocardiography (iE33, PHILIPS, Tokyo, Japan) was performed to measure the LVEF (i.e., LV systolic function) and LVDd within 7 days (acute phase) and at 6 months (chronic phase) after the onset of AMI.

Measurement of Plasma Adenosine Concentration
For AMI patients, blood samples (1 mL each) were taken from the antecubital vein for measurement of the plasma

### Table 1. Patients’ Characteristics and Drugs Used

| Characteristics | CTRL (n=14) | AMI (n=58) (on. admission) | P value |
|-----------------|------------|----------------------------|--------|
| Age (years)     | 65.5±6.9  | 68.5±12.3                  | 0.24   |
| Sex (M/F)       | 9/5        | 44/14                      | 0.59   |
| HTN, n (%)      | 8 (57.1)   | 34 (58.6)                  | 0.84   |
| HL, n (%)       | 2 (14.3)   | 34 (58.6)                  | 0.007  |
| DM, n (%)       | 5 (35.7)   | 18 (31.0)                  | 0.99   |
| Smoking, n (%)  | 2 (14.3)   | 20 (34.5)                  | 0.25   |
| CKD, n (%)      | 6 (42.9)   | 27 (46.6)                  | 0.96   |
| TC (mg/dL)      | 203±43.4   | 185±33.7                   | 0.31   |
| LDL-C (mg/dL)   | 83±54.5    | 113±31.3                   | 0.20   |
| HDL-C (mg/dL)   | 66±21.9    | 46±10.8                    | 0.010  |
| TG (mg/dL)      | 84.5 (70–230) | 103 (65–153)            | 0.70   |
| HbA1c (%)       | 6.0 (5.5–6.5) | 5.9 (5.6–6.3)            | 0.82   |
| CRE (mg/dL)     | 0.9±0.28   | 0.9±0.28                   | 0.89   |
| BNP (pg/mL)     | 25.4 (9.8–47.6) | 62.9 (22.6–152.0)     | 0.006  |
| CRP (mg/dL)     | 0.06 (0.02–0.29) | 0.10 (0.05–0.24) | 0.35 |
| EF (%)          | 67.9±5.51  | 51.4±10.79                 | <0.001 |
| LVDd (mm)       | 46.1±5.53  | 48.2±6.66                  | 0.28   |

Drugs used

| Drug          | CTRL (n=14) | AMI (n=58) (on. admission) | P value |
|---------------|------------|----------------------------|--------|
| ACEI, n (%)   | 0 (0)      | 1 (1.72)                   | 0.44   |
| ARB, n (%)    | 6 (42.9)   | 21 (36.2)                  | 0.88   |
| CCB, n (%)    | 7 (50.0)   | 17 (29.3)                  | 0.25   |
| BB, n (%)     | 1 (7.1)    | 3 (5.2)                    | 0.72   |
| Diuretics, n (%) | 1 (7.1) | 6 (10.3)         | 0.89   |
| MRA, n (%)    | 0 (0)      | 1 (1.7)                    | 0.44   |
| NTG, n (%)    | 0 (0)      | 4 (6.9)                    | 0.72   |
| Nicorandil, n (%) | 0 (0) | 0 (0)                  | >0.99  |
| Statin, n (%) | 2 (14.3)   | 15 (25.9)                  | 0.57   |
| Aspirin, n (%) | 1 (7.1)    | 8 (13.8)                   | 0.82   |
| Clopidogrel, n (%) | 0 (0) | 5 (8.6)                   | 0.58   |
| Insulin, n (%) | 3 (21.4)   | 1 (1.7)                    | 0.025  |
| Metformin, n (%) | 1 (7.1) | 2 (3.4)                   | 0.90   |
| DPP-4 inhibitors, n (%) | 3 (21.4) | 6 (10.3)       | 0.50   |

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BB, β-blocker; BNP, B-type natriuretic peptide; CCB, calcium-channel blocker; CKD, chronic kidney disease; CRE, creatinine; CRP, C-reactive protein; DM, diabetes mellitus; EF, ejection fraction; HbA1c, hemoglobin A1c; HTN, hypertension; HL, hyperlipidemia; LVDd, left ventricular end-diastolic dimension; MRA, mineralocorticoid receptor antagonist; NTG, nitroglycerine; TC, total cholesterol; TG, triglyceride.
Adenosine and LV Remodeling

Adenosine concentration on days 0, 1, 7 and 14 after the onset of AMI. We defined days 0, 1, and 7 (within 7 days) as the acute phase and day 14 as the subacute phase of AMI. Blood samples were collected into sterile tubes containing EDTA, immediately placed on ice, and then centrifuged at 10,000g for 15 min. Plasma was then collected and frozen at −83°C until further analysis. Blood samples are conventionally collected in tubes containing dipyrindamole, 2′-deoxycoformycin and EDTA to block the degradation of adenosine. However, it was recently confirmed that blood collection without dipyrindamole and 2′-deoxycoformycin combined with measurement of the plasma adenosine concentration using the highly sensitive ESI-MS/MS method combined with Hydrophilic interaction chromatographic (HILIC) separation mentioned below, yields relatively accurate levels of adenosine in plasma. Therefore, in the present study, we used tubes containing only EDTA to collect blood samples.

Plasma adenosine concentrations were measured using a Prominence HPLC system (Shimadzu, Japan) equipped with a 3200 QTRAP MS/MS system with a Turbo V source and an ESI probe (AB SCIEX, Canada). HILIC separation was performed on a Tosoh TSKgel Amide-80 column (3μm, 150×2.0 mm i.d.) with a mobile phase consisting of water and acetonitrile (linear gradient: 100–90% acetonitrile over 12 min followed by 90–30% over 8 min) at a flow rate of 0.2 mL/min at 40°C. We recently developed an ESI-MS/MS method to determine adenosine in human plasma combined with HILIC separation after simple pretreatment consisting of deproteinization and ultrafiltration. This method gives highly sensitive and reproducible multiple-reaction monitoring signals of adenosine (m/z: 268.1/136.1) and 15N5-adenosine (m/z: 273.1/141.1) as an internal standard under positive ESI conditions without ionic suppression caused by matrix compounds in human plasma. The calibration curve was linear across the examined dynamic range from 10 to 500 nmol/L (r=1.000). The relative standard deviations of the MS/MS responses with 6 trials were 2.17%, 2.71%, 2.24%, and 1.82% for plasma samples containing 10, 50, 100, and 500 nmol/L adenosine, respectively. The detailed analytical procedures and validation for the ESI-MS/MS method have been published.

Blood Biochemical Analysis

Blood biochemical analyses for creatine kinase (CK), aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), creatinine (CRE), blood urea nitrogen (BUN), C-reactive protein (CRP), hemoglobin A1c (HbA1c), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), and B-type natriuretic peptide (BNP; Shionoria BNP RIA kit; Shionogi, Osaka, Japan) were performed.

Drugs used and complications in patients were examined.

Statistical Analysis

The data are shown as mean±1 standard deviation. Categorical data are summarized as percentages and were compared with a chi-square test or Fisher’s exact test. The normality of data distributions was tested using the Kolmogorov-Smirnov test. The significance of the differences between groups for variables that were normally distributed was determined by an unpaired Student’s t-test. Otherwise, a Mann-Whitney U test was used to compare the differences between groups. Effects of drugs on echocardiographic parameters were assessed by univariate analysis. P<0.05 was considered significant. All statistical
analyses were performed using Stat View version 5.0 (SAS Institution Inc., Cary, NC, USA).

Results

Patients’ Characteristics and Drugs Used

Patients’ characteristics and drugs used are shown in Table 1. The incidence of HL was greater in the AMI group than in the control group. BNP was higher and HDL-cholesterol was lower in the AMI group than in the control group. EF was lower in the AMI group than in the control group. The incidence of drugs used, such as insulin, was lower in the AMI group than in the control group.

Plasma Adenosine Concentrations

On day 0, the plasma adenosine concentration was not significantly different between the AMI group (211.5±150.2 nmol/L) and control group (136.0±50.9 nmol/L) (Figure 1A). The plasma adenosine concentration in AMI patients did not increase on day 1 (192.7±141.3 nmol/L) or day 7 (218.8±154.1 nmol/L) but significantly increased on day 14 (321.1±195.4 nmol/L) compared with days 0, 1, and 7 (Figure 1A). The changes in the plasma adenosine concentration described during days 0–14 in the AMI group (Figure 1A) were typical of most of the AMI patients, although some patients exhibited a peak plasma adenosine concentration on other days (i.e., day 0, 1, 7, or 14). Therefore, we determined the maximum plasma adenosine concentration (Max adenosine) of each patient regardless of the day after AMI onset, and compared it with the plasma adenosine concentrations in the control group. Max adenosine in the AMI group was significantly greater than in the control group (P<0.01; Figure 1B). Peak CK (PCK) and the sum of CK (∑CK) are reported to be indicators of myocardial infarct size,10 so we measured CK at 8 points during days 0–2. The highest value of CK was defined as PCK. When AMI patients were divided into 2 groups (PCK <1,000 IU and PCK ≥1,000 IU), Max adenosine was not different between them (P=0.750; Figure 2A). ∆Adenosine (Max adenosine - minimum plasma adenosine concentration) was not different between the group with PCK ≥1,000 IU and the group with PCK <1,000 IU (P=0.440; Figure 2D).

Figure 2. (A) Maximum plasma adenosine concentration (MAX adenosine) in AMI patients with peak CK (PCK) <1,000 IU and those with PCK ≥1,000 IU. (B) ∆adenosine in AMI patients with PCK <1,000 IU and those with PCK ≥1,000 IU. (C) MAX adenosine in AMI patients with ∑CK <30,000 IU and those with peak ∑CK ≥30,000 IU. (D) ∆adenosine in AMI patients with ∑CK <30,000 IU and those with peak ∑CK ≥30,000 IU. AMI, acute myocardial infarction; CK, creatine kinase.
Adenosine and LV Remodeling

Adenosine and LV Remodeling

∆adenosine between the patients with positive ∆EF (263.7±182.2 nmol/L) and negative ∆EF (313.6±108.6 nmol/L) (Figure 4D).

LV Dilation and Plasma Adenosine Concentration

Of the 58 AMI patients subjected to acute-phase analysis (days 0–7 after onset), 38 were followed until 6 months after AMI (chronic phase) to measure the LVDd. LV dilation, which indicates HF, is generally assessed by an increase in LVDd between the acute and chronic phases. The difference between LVDd in the acute and chronic phases (LVDd in the chronic phase - LVDd in the acute phase) was defined as ∆LVDd. Max adenosine tended to inversely correlate with ∆LVDd (P=0.181) (Figure 5A). ∆adenosine also tended to inversely correlate with ∆LVDd (P=0.122) (Figure 5B). We divided the patients into 2 groups: a positive ∆LVDd group (LVDd increased in the chronic phase, ∆LVDd >0, suggesting progression to LV dilation) and a negative ∆LVDd group (LVDd decreased in the chronic phase or remained unchanged from the acute phase, ∆LVDd ≤0, suggesting attenuation of LV dilation). Max adenosine was significantly higher (P=0.036) in the negative ∆LVDd group (458.0±208.1 nmol/L) than in the positive ∆LVDd group (324.7±154.7 nmol/L) (Figure 5C).

Factors Affecting LVEF and LV Dilation

In the univariate analysis, many factors that may be asso-
release is accelerated by a short period of myocardial ischemia such as ischemic preconditioning. However, changes in the plasma adenosine concentrations in patients with AMI caused by chronic myocardial ischemia, but not to short periods of ischemia, are still unknown. In the present study, there was no significant difference in the plasma adenosine concentrations between the controls and that on day 0 after AMI. The plasma adenosine concentration did not significantly increase on day 1 or 7 after AMI compared with that on day 0. The plasma adenosine concentration, however, significantly increased on day 14 compared with that on days 0, 1 and 7 after AMI (Figure 1). This means that MI in the acute phase does not necessarily increase the plasma adenosine concentration. Because the plasma adenosine concentration did not increase within 7 days after AMI, the reason why it increased on day 14 after AMI may involve factors other than solely myocardial ischemia. We recently reported that the plasma adenosine concentration increased in cardiac patients with LV dilation or LV dysfunction (reduced EF), suggesting that an elevated plasma adenosine concentration might counteract LV dilation or LV dysfunction. As a matter of fact, adenosine agonists have been reported to attenuate LV remodeling and improve LV function in animal models of MI and advanced HF. Although the precise mechanisms by which the plasma

Discussion
The present study demonstrated that: (1) the plasma adenosine concentration increases in the subacute phase after AMI, (2) Max adenosine was significantly higher in the negative ΔLVDd group than in the positive ΔLVDd group (Table 3). Concerning ΔEF, age was significantly higher in the positive ΔLVDd group than in the negative ΔLVDd group (Table 3). Therefore, among many factors, Max adenosine and Δadenosine were associated with attenuation of LV dilation.

Figure 4. Plasma adenosine concentration and left ventricular function. (A) Relationship between maximum (MAX) adenosine and ΔEF. (B) Relationship between Δadenosine and ΔEF. (C) Comparison of MAX adenosine between patients with positive ΔEF or negative ΔEF. (D) Comparison of Δadenosine between patients with positive ΔEF and those with negative ΔEF. Max adenosine, maximum plasma adenosine concentration; Δadenosine, maximum adenosine concentration – minimum plasma adenosine concentration; EF, ejection fraction.
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In the chronic phase 6 months after AMI. Concerning LV function, as shown in Figure 4, Max adenosine and ∆adenosine did not correlate with ∆EF. There was no significant difference in Max adenosine or ∆adenosine between patients with ∆EF <0 and those with ∆EF ≥0. These results suggested that endogenous adenosine released after AMI is not sufficient to improve LV function in the chronic phase. In order to improve LV function, it may be necessary to administer some adenosine agonists or adenosine-producing drugs. In human studies, it has been reported that an elevated plasma adenosine concentration caused by chronic treatment with dipyridamole improved LV function and remodeling and attenuated the severity of HF in patients with chronic HF.14,15

Measurements of the increase in the plasma adenosine concentration after AMI in the subacute phase might allow physicians to predict LV dilation in the chronic phase. In addition, because the clinical features that may affect Max adenosine and ∆adenosine would be factors that may cause ∆LVDd ≤0, the clinical feature that may influence higher Max adenosine and ∆adenosine was only younger age among the many factors as shown in Table 3.

In the present study, as shown in Figure 5, Max adenosine and ∆adenosine tended to inversely correlate with ∆LVDd. Max adenosine was significantly higher in patients with ∆LVDd <0 than in those with ∆LVDd ≥0. ∆adenosine was significantly higher in patients with ∆LVDd <0 than in those with ∆LVDd ≥0. These results suggested that an elevated plasma adenosine concentration in the subacute phase of AMI might contribute to attenuation of LV dilation in the chronic phase 6 months after AMI.

Concerning LV function, as shown in Figure 4, Max adenosine and ∆adenosine did not correlate with ∆EF. There was no significant difference in Max adenosine or ∆adenosine between patients with ∆EF <0 and those with ∆EF ≥0. These results suggested that endogenous adenosine released after AMI is not sufficient to improve LV function in the chronic phase. In order to improve LV function, it may be necessary to administer some adenosine agonists or adenosine-producing drugs. In human studies, it has been reported that an elevated plasma adenosine concentration caused by chronic treatment with dipyridamole improved LV function and remodeling and attenuated the severity of HF in patients with chronic HF.14,15

Measurements of the increase in the plasma adenosine concentration after AMI in the subacute phase might allow physicians to predict LV dilation in the chronic phase. Elevation of endogenous adenosine in the subacute phase may not be sufficient to facilitate robust recovery of LV function but may be sufficient to attenuate LV dilation in the chronic phase in patients with AMI.

As presented in Table 2 and Table 3, statistical analysis showed that, among many factors, the extent of endogenous adenosine favourably correlated with attenuation of LV dilation but not with improvement in LV function. It was suggested that older age negatively affected attenuation of
LV dilation despite the presence of endogenous adenosine (Table 3).

To summarize, the results suggested that higher plasma adenosine concentrations in patients with AMI may counteract LV remodeling but still be insufficient to improve LV function in the chronic phase.

In conclusion, the plasma adenosine concentration increased during the subacute phase in patients with AMI. Endogenous plasma adenosine may counteract LV dilation in the chronic phase in patients with AMI.

**Study Limitations**

There are several to note. Although the plasma adenosine concentration significantly increased 14 days after AMI, we did not measure the concentrations after 14 days. Therefore, the peak plasma adenosine concentration after AMI is still unclear.

Because echocardiographic data were not obtained in

| Table 2. Comparison of Factors Affecting $\Delta$EF |
|-----------------------------------------------|
| $\Delta$EF≤0 | 0≤$\Delta$EF |
| (n=7) | (n=31) |
| Age (years) | 63.3±3.8 | 68.3±11.9 |
| Sex (M/F) | 6/1 | 22/9 |
| HTN, n (%) | 5 (71.4) | 22 (71.0) |
| HL, n (%) | 7 (100) | 18 (58.1) |
| DM, n (%) | 4 (57.1) | 8 (25.8) |
| Smoking, n (%) | 5 (71.4) | 10 (32.3) |
| CKD, n (%) | 4 (57.1) | 16 (51.6) |
| CVD, n (%) | 0 (0) | 4 (16.0) |
| PAD, n (%) | 0 (0) | 1 (3.2) |
| TIMI grade | | |
| Pre TIMI=0 | 5 (71.4) | 22 (71.0) |
| Post TIMI=3 | 7 (100) | 31 (100) |
| Target lesion | | |
| RCA/LAD/LCX | 1/4/2 | 12/14/5 |
| Pre LVEF (%) | 52.6±14.2 | 50.7±9.6 |
| Peak CK (U/L) | 5,232±3,813.0 | 2,703±1,960.9 |
| Peak CK-MB (U/L) | 445±303.3 | 274±245.9 |
| $\Sigma$CK (U/L) | 106,736±74,161.5 | 66,153±41,742.0 |
| $\Sigma$CK-MB (U/L) | 9,033±5,852.0 | 5,455±4,087.6 |
| Door to balloon time (min) | 60±16.2 | 55±20.1 |
| MAX adenosine (nmol/L) | 474.8±194.9 | 394.1±199.1 |
| $\Delta$adenosine (nmol/L) | 313.8±108.6 | 263.7±182.2 |
| WBC (µL) | 12,421±3,606.4 | 11,099±5,192.2 |
| TC (mg/dL) | 208±22.3 | 186±31.9 |
| LDL-C (mg/dL) | 142±28.8 | 110±23.9 |
| HDL-C (mg/dL) | 34±4.7 | 46±11.2 |
| TG (mg/dL) | 181±79.0 | 140±122.7 |
| HbA1c (%) | 6.4 (6.2–8.1) | 6.0 (5.8–6.2) |
| CRE (mg/dL) | 1.07±0.22 | 0.90±0.31 |
| BNP (pg/mL) | 22.8 (17.2–124.9) | 43.3 (18.4–143.7) |
| CRP (mg/dL) | 0.24 (0.07–0.71) | 0.08 (0.04–0.19) |
| Drugs (6 months’ later) | | |
| ACEI, n (%) | 3 (42.9) | 8 (25.8) |
| ARB, n (%) | 2 (28.6) | 13 (41.9) |
| CCB, n (%) | 1 (14.3) | 8 (25.8) |
| BB, n (%) | 6 (85.7) | 18 (58.1) |
| Diuretics, n (%) | 0 (0) | 22 (29.0) |
| MRA, n (%) | 4 (57.1) | 14 (45.2) |
| Statin, n (%) | 7 (100) | 26 (83.9) |
| EPA, n (%) | 0 (0) | 0 (0) |
| Aspirin, n (%) | 7 (100) | 30 (96.8) |
| Clopidogrel, n (%) | 6 (85.7) | 27 (87.1) |
| Insulin, n (%) | 1 (14.3) | 1 (3.2) |
| DPP-4 inhibitors, n (%) | 3 (42.9) | 3 (9.7) |

Abbreviations as in Table 1.
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their home towns. The number of AMI patients with 6 months' follow-up was relatively small, so a clinical study with a larger number of AMI patients is warranted.

It is difficult to clarify the mechanism by which a higher plasma adenosine concentration contributed to the attenuation of LV dilation in patients with AMI in a clinical setting.

Acknowledgment

We thank Miss Akiko Tsujimoto for technical assistance.

Table 3. Comparison of Factors Affecting DLVDd

|                  | ΔLVDd≤0 (n=24) | 0<ΔLVDd (n=14) | P value |
|------------------|----------------|----------------|---------|
| Age (years)      | 64.3±10.3      | 72.6±10.2      | 0.026   |
| Sex (M/F)        | 20/4           | 8/6            | 0.17    |
| HTN, n (%)       | 16 (66.7)      | 11 (78.6)      | 0.46    |
| HL, n (%)        | 16 (66.7)      | 9 (64.3)       | 0.72    |
| DM, n (%)        | 9 (37.5)       | 3 (21.4)       | 0.47    |
| Smoking, n (%)   | 12 (50.0)      | 7 (50.0)       | 0.74    |
| CKD, n (%)       | 12 (50.0)      | 8 (57.1)       | 0.74    |
| CVD, n (%)       | 3 (13.6)       | 1 (7.1)        | 0.56    |
| PAD, n (%)       | 0 (0)          | 1 (7.1)        | 0.29    |
| TIMI grade       |                |                |         |
| Pre TIMI=0       | 19 (79.2)      | 8 (57.1)       | 0.27    |
| Post TIMI=3      | 24 (100)       | 14 (100)       | >0.99   |
| Target lesion    |                |                |         |
| RCA/LAD/LCX      | 8/11/5         | 5/7/2          | 0.89    |
| Pre LVEF (%)     | 52.1±7.2       | 49.3±14.6      | 0.52    |
| Peak CK (U/L)    | 3,135±2,323.2  | 3,226±3,022.5  | 0.93    |
| Peak CK-MB (IU/L)| 299±238.1      | 317±307.4      | 0.86    |
| ΔCK (U/L)        | 75,855±51,259.0| 69,812±52,465.2| 0.74    |
| ΔCK-MB (IU/L)    | 6,086±4,638.6  | 6,164±4,378.3  | 0.96    |
| Door to balloon time (min) | 54±17.2 | 60±22.3 | 0.42 |
| MAX adenosine (nmol/L) | 458.0±208.1 | 324.7±154.7 | 0.038 |
| Δadenosine (nmol/L) | 317.4±174.0 | 196.7±139.0 | 0.038 |
| WBC (/μL)        | 10,990 (7,963–14,335) | 9,270 (7,625–10,743) | 0.21 |
| TC (mg/dL)       | 193±28.7       | 187±34.9       | 0.63    |
| LDL-C (mg/dL)    | 120±25.6       | 109±25.6       | 0.30    |
| HDL-C (mg/dL)    | 45±12.5        | 43±9.4         | 0.57    |
| TG (mg/dL)       | 165±135.9      | 116±63.0       | 0.15    |
| HbA1c (%)        | 6.4±0.98       | 6.0±0.65       | 0.106   |
| CRE (mg/dL)      | 0.96±0.28      | 0.89±0.33      | 0.50    |
| BNP (pg/mL)      | 22.8 (14.1–72.8) | 79.8 (21.8–251.8) | 0.051 |
| CRP (mg/dL)      | 0.10 (0.04–0.26) | 0.10 (0.05–0.34) | 0.91 |
| Drugs (6 months’ later) |         |                |         |
| ACEI, n (%)      | 6 (25.0)       | 5 (35.7)       | 0.74    |
| ARB, n (%)       | 12 (50.0)      | 3 (21.4)       | 0.16    |
| CCB, n (%)       | 8 (33.3)       | 1 (7.1)        | 0.15    |
| BB, n (%)        | 15 (62.5)      | 9 (64.3)       | 0.81    |
| Diuretics, n (%) | 3 (12.5)       | 6 (42.9)       | 0.084   |
| MRA, n (%)       | 14 (58.3)      | 4 (28.6)       | 0.15    |
| Statin, n (%)    | 23 (95.8)      | 10 (71.4)      | 0.099   |
| EPA, n (%)       | 0 (0)          | 0 (0)          | >0.99   |
| Aspirin, n (%)   | 23 (95.8)      | 14 (100)       | 0.78    |
| Clopidogrel, n (%) | 20 (83.3) | 13 (92.9) | 0.73 |
| Insulin, n (%)   | 2 (8.3)        | 0 (0)          | 0.72    |
| DPP-4 inhibitors, n (%) | 5 (20.8) | 1 (7.1) | 0.51 |

Abbreviations as in Table 1.
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