学位論文　博士（医学）甲

Myocardial Production of Plasminogen Activator Inhibitor-1 is Associated with Coronary Endothelial and Ventricular Dysfunction after Acute Myocardial Infarction.

(心筋産生の Plasminogen Activator Inhibitor-1 は急性心筋梗塞後の冠内皮機能障害および心室機能障害と相関する)

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Original Article

Myocardial Production of Plasminogen Activator Inhibitor-1 is Associated with Coronary Endothelial and Ventricular Dysfunction after Acute Myocardial Infarction

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Aim: Although plasminogen activator inhibitor-1 (PAI-1) is abundantly expressed in infarcted myocardium, the pathogenic role of myocardial PAI-1 remains unknown. This study examined whether PAI-1 in the infarcted lesion contributes to coronary endothelial dysfunction and left ventricular (LV) dysfunction in patients with acute myocardial infarction (AMI).

Methods: Plasma levels of PAI-1 activity and tissue-plasminogen activator (tPA) antigen were measured 2 weeks and 6 months after MI by ELISA in plasma obtained from the aortic root (AO) and anterior interventricular vein (AIV) in 28 patients with a first AMI due to occlusion of the left anterior descending coronary artery (LAD). Coronary blood flow responses in LAD to intracoronary infusion of acetylcholine (ACh) and left ventriculography were measured at the same time points: 2 weeks and 6 months after MI.

Results: The trans-myocardial gradient of PAI-1 from AO to AIV, reflecting production/release of PAI-1 in the infarcted lesion, was inversely correlated with the coronary blood flow response to ACh 6 months after MI ($r=-0.43$, $p=0.02$) and with the percentage change in LV regional motion in the LAD territory from 2 weeks to 6 months after MI ($r=-0.38$, $p=0.04$). The trans-myocardial gradient of tPA level showed no significant correlations.

Conclusions: PAI-1 produced in the infarcted myocardium and released into the coronary circulation is associated with endothelial dysfunction in resistance vessels of the infarct-related coronary arteries and with progressive dysfunction of the infarcted region of the left ventricle in AMI survivors.

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Key words: Myocardial infarction, Plasminogen activator inhibitor-1, Coronary endothelial function, Ventricular remodeling

Introduction

The fibrinolytic system is impaired in patients with acute myocardial infarction (AMI)[1-3]. The net fibrinolytic activity in plasma is determined by the balance between plasminogen activator inhibitor-1 (PAI-1) and tissue-type plasminogen activator (tPA); PAI-1 activity is a major factor determining overall fibrinolytic activity[4-6]. The increase in PAI-1 concentration in plasma induces a prothrombotic and hypercoagulable state[7, 8]. Previous clinical studies have shown that the increased plasma PAI-1 concentration is a risk for recurrent coronary events in AMI survivors[9-11]. PAI-1 also inhibits the activities of matrix metalloproteinases (MMPs) and urokinase-type PA (uPA), which play important roles in tissue remodeling[7, 8, 12]. Experimental studies have shown that the increased expression of myocardial PAI-1 contributes

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to ventricular remodeling and fibrosis[13, 14]. Thus, PAI-1 plays an important role not only in fibrinolysis but also in tissue remodeling.

PAI-1 is expressed in several tissues, such as the vascular walls, adipose tissue, liver, spleen, and heart[15]. PAI-1 expression is up-regulated in injured coronary artery walls and the infarcted myocardium after MI[13, 16, 17]. Experimental studies have shown that the increased PAI-1 levels in coronary artery walls and infarcted myocardium may be the causal factors in recurrent coronary thrombosis and left ventricular (LV) adverse remodeling after MI[13, 14, 18]. Previous clinical reports have used PAI-1 concentration in the peripheral circulation for the analysis of its clinical significance[1-3, 9-11]. However, there have been few studies on the role of PAI-1 expressed locally in the infarcted heart in relation to post-MI coronary and ventricular functions.

This study examined the relation of PAI-1 produced in the infarcted lesion to coronary and ventricular functions in patients with MI. We measured the concentrations of PAI-1 activity and total tPA antigen in plasma collected from the aortic root (AO) and anterior interventricular vein (AIV) in patients with AMI due to occlusion of a proximal segment of the left anterior descending coronary artery (LAD)[19-21]. We calculated the AIV−AO gradients of the plasma concentrations of PAI-1 activity and tPA antigen, reflecting their release from the region of myocardium supplied by LAD. The trans-myocardial increases in the concentrations of PAI-1 activity and tPA antigen from AO to AIV were then considered to reflect their production rates in the infarcted myocardial region.

Methods

Study Patients

This prospective study included 70 consecutive patients with a first AMI due to occlusion of a proximal segment of LAD who were admitted to Yamanashi University Hospital between January 2007 and December 2014. All patients received emergency coronary angiography and successful reperfusion therapy within 12 h of the onset of symptoms by primary percutaneous coronary intervention (PCI) using stent. Diagnosis of MI was based on the presence of each of the following criteria[22]: typical chest pain persisting for ≥30 min, ST-segment elevation of ≥0.2 mV in two or more contiguous leads on a standard 12-lead electrocardiogram (ECG), and creatine kinase-MB ≥ two-fold the upper limit of normal or troponin T >0.1 ng/mL. The exclusion criteria were as follows: 1) residual organic stenosis ≥30% in LAD, 2) previous PCI in LAD, 3) previous coronary artery bypass surgery, 4) presence of collaterals to LAD with Rentrop grade ≥2, 5) congestive heart failure at 1 week after AMI, 6) persistent atrial fibrillation and pacing rhythm, 7) age >80 years, and 8) valvular heart disease, secondary hypertension, stroke, renal dysfunction (serum creatinine >2.0 mg/dL), or other serious disease. After applying these criteria, the study finally included 32 patients. Written informed consent was obtained from all patients before the study. The study was approved by the ethics committee of Yamanashi University Hospital.

Study Protocol and Blood Sampling

After the emergency coronary angiography on admission, cardiac catheterization was repeated twice, 2 weeks and 6 months after AMI, in all patients. Blood sampling from the anterior interventricular vein (AIV), the aortic root (AO), and an antecubital vein (peripheral vein; PV) was also performed at the cardiac catheterizations before systemic heparinization, as described in our previous reports[19-21]. In addition, coronary angiography and left ventriculography were repeated twice, 2 weeks and 6 months after AMI. The initial volumes of each blood sample, including those forcibly drawn, were discarded. Blood samples were immediately centrifuged at 3,000 rpm for 10 min at 4℃, and the serum and EDTA plasma were aliquoted and stored at −80℃ until analyzed. The same medications prescribed 2 weeks after MI were kept throughout 6 months after MI in each patient.

Measurement of Coronary Blood Flow Response to Acetylcholine (ACh) and Sodium Nitroprusside (SNP)

After blood sampling, quantitative coronary angiography was performed in all patients as described in our previous reports[19, 20]. After baseline angiography, ACh (10 and 50 μg/min) were infused directly into the left coronary artery through the Judkins catheter. After 15 min, intracoronary SNP (10 μg/min) was infused in the same manner as ACh. After another 15 min, intracoronary isosorbide dinitrate (1 mg) was administered. Coronary angiography was repeated before and during each infusion.

The luminal diameter in a segment 15−25 mm distal to the stent edge in LAD was measured quantitatively (QAngio XA, Medis Medical Imaging Systems, The Netherlands). Blood flow velocity was measured using a 0.014-inch wire equipped with a Doppler crystal at its tip (Flo Wire, Volcano, San Diego, USA). The wire was positioned carefully in a segment of LAD 5−15 mm from the distal edge of the stent[19, 20].

Coronary blood flow (mL/min) was estimated from the coronary blood flow velocity and luminal diameters, as described previously[19, 20]. Responses of the coronary blood flow to infusions of ACh and SNP were expressed as percentage changes from baseline values taken immediately before each infusion. These measurements were performed by two independent observers (Y. W. and K. W.) blinded to the study protocol and the patients' clinical characteristics. Measurements of percentage changes in coronary blood flow in response to ACh (10 μg/min) relative to the respective baseline values by the observers were very reproducible ($r=0.97$, mean difference: 2.6% ± 0.3%).

Analysis of Left Ventriculogram

LV ejection fraction (EF) was determined with left ventriculograms by area−length methods, using computer-assisted analysis (QAngio XA, Medis Medical Imaging Systems, The Netherlands). The centerline method was used for the quantification of regional wall motion (QAngio XA, Medis Medical Imaging Systems, The Netherlands)[19]. The severity of the regional wall motion abnormality was expressed as the average standard deviation from the mean wall motion of normal subjects per chord (SD/Chord) within the LAD territory, using digitized left ventriculography in the 30-degree right anterior oblique projection[19]. The reduction of regional wall motion in the infarct-related area yielded approximately 1−4 SD/Chord[19]. These measurements were performed by two independent observers (T. N. and J. O.) blinded to the study protocol and the patients' clinical characteristics. Measurements of SD/Chord by the observers were highly reproducible ($r=0.97$, mean difference: 3.7% ± 0.5%).

Assays

Plasma concentrations of PAI-1 activity and total tPA antigen were measured using ELISA (Innovation Research, Greenwich CT, USA and Sekisui Diagnostics, Stamford CT, USA, respectively). The intra- and inter-assay coefficient of variation of PAI-1 assay was 4.7% and 7.4%, respectively. The intra- and inter-assay coefficient of variation of tPA assay was 4.9% and 7.8%, respectively. The minimal detection limits of the assays of PAI-1 and tPA were 0.15 ng/mL and 1.0 ng/mL, respectively. C-reactive protein (CRP) levels in the serum were assayed by rate nephelometry (Dade Behring, Tokyo, Japan). Plasma levels of the brain natriuretic peptide (BNP) were measured using an immunoradiometric assay (Shionogi Pharmaceutical LTD., Osaka, Japan).

Table 1. Baseline clinical characteristics of patients

	AMI ($n=28$)
Age (yrs)	61.5 (50.8−68.8)
Male, n (%)	26 (92.9)
Current smoker, n (%)	14 (50.0)
Hypertension, n (%)	17 (60.7)
Diabetes mellitus, n (%)	10 (35.7)
BMI (kg/m^2)	24.6 ± 2.8
LDL-C (mg/dL)	141 ± 31
Triglyceride (mg/dL)	149 (107−196)
BNP (pg/mL)	94 (31−178)
eGFR (mL/min/1.73 m^2)	65.5 ± 13.0
CRP (mg/L)	2.2 (1.0−5.3)
PRA (ng/mL/h)	4.1 (1.7−7.2)
LVEF (%)	52.9 ± 12.3
Number of diseased vessels	1.4 ± 0.6
Peak CK (IU/L)	3687 (874−6205)
DES implantation, n (%)	18 (64.3)
Medications used	
Aspirin, n (%)	28 (100)
Clopidogrel, n (%)	28 (100)
ARBs, n (%)	16 (57.1)
CCBs, n (%)	18 (64.3)
β-blockers, n (%)	8 (28.6)
Statins, n (%)	24 (87.7)

Data are expressed as either the mean ± SD, median and interquartile range (25th and 75th percentages) or number (%) of patients. Variables were obtained at two weeks after MI.
AMI indicates acute myocardial infarction; BMI, body mass index; LDL-C, low-density lipoprotein cholesterol; BNP, brain natriuretic peptide; eGFR, estimated glomerular filtration rate; CRP, C-reactive protein; PRA, plasma rennin activity; LVEF, left ventricular ejection fraction; CK, creatine kinase; DES, drug-eluting stent; ARB, angiotensin II type I receptor blocker; CCB, calcium channel blocker.

Statistical Analysis

Data were expressed as either mean ± SD, median and interquartile range (IQR, 25th and 75th percentiles), or frequency (%). Continuous variables were compared using Student's paired or unpaired t test, as appropriate. The Shapiro−Wilk test showed that age, triglyceride, BNP, CRP, plasma renin activity (PRA), and creatinine kinase (CK) were not distributed normally. Therefore, these variables were expressed as median and interquartile range and compared using the Mann−Whitney U test. The relations of PAI-1 and tPA concentrations to the clinical parameters were examined by linear regression analysis. Dichotomous variables were coded as 1 or 0 for the presence or absence of a factor, respectively. Statistical significance was defined as $p<0.05$. Analyses were performed using STATA version 10.0 (Stata Corp, College Sta-

Table 2. Changes in coronary vasomotor function, LV function, PAI-1 activity and total tPA antigen level from 2 weeks to 6 months after AMI

	2 weeks	6 months	*p*-value
CBF response to ACh (50 μg/min) (%)	88.0±107.5	167.1±71.2	<0.01
CBF response to SNP (%)	161.9±117.8	177.4±96.3	0.54
Global LVEF (%)	52.9±12.3	55.5±12.9	0.04
LV regional motion (SD/Chord)	−1.02±0.52	−0.85±0.47	<0.01
PAI-1 activity (ng/mL)			
PV	4.9±2.6	4.7±3.7	0.77
AIV	4.9±2.4	3.8±2.6	0.04
AO	4.5±2.4	3.8±2.5	0.22
AIV-AO	0.48±1.02	−0.02±0.64	0.03
tPA antigen (ng/mL)			
PV	7.2±4.6	7.0±2.9	0.81
AIV	8.2±4.3	7.1±3.1	0.16
AO	7.5±4.4	8.4±3.5	0.27
AIV-AO	0.70±2.30	−1.25±2.02	<0.01

Data are expressed as the mean ± SD. LV indicates left ventricular; PAI-1, plasminogen activator inhibitor-1; tPA, tissue plasminogen activator; AMI, acute myocardial infarction; CBF, coronary blood flow; ACh, acetylcholine; SNP, sodium nitroprusside; LVEF, left ventricular ejection fraction; PV, peripheral vein; AIV, anterior interventricular vein; AO, aortic root.
CBF responses to infusions of ACh or SNP were expressed as percentage changes from baseline values taken immediately before each infusion.

tion, TX).

Results

Changes in Coronary Vasomotor Function, LV Function, PAI-1 Activity, and Total tPA Antigen Concentrations from 2 Weeks to 6 Months after AMI

Four patients were withdrawn because they were lost after 1st session of a cardiac catheterization and blood sampling. The remaining 28 patients were analyzed. Clinical characteristics of the patients are shown in **Table 1**. An increment in PAI-1 activity and tPA antigen concentration from AO to AIV, reflecting their release from the infarcted myocardium, was observed in 20 and 21 patients (71% and 75% of total patients, respectively) at 2 weeks after MI and 16 and 7 patients (57% and 25% of total patients, respectively) at 6 months after MI. Coronary blood flow responses to ACh, global LVEF, and LV regional wall motion improved from 2 weeks to 6 months after MI (**Table 2**). Coronary blood flow response to SNP did not change significantly (**Table 2**). The trans-myocardial gradients of PAI-1 activity and total tPA antigen concentrations from AO to AIV (AIV-AO) were significantly reduced, whereas their concentrations in PV did not change significantly (**Table 2**).

Association of PAI-1 and tPA Concentrations with Coronary Blood Flow Response and LV Function

The trans-myocardial gradient of PAI-1 from AO to AIV (AIV-AO) 6 months after MI had a significant inverse correlation with the coronary blood flow response to ACh at 6 months, but not at 2 weeks, after MI (**Table 3, Fig. 1A**). The trans-myocardial gradient of PAI-1 6 months after MI had no significant correlation with coronary blood flow response to SNP (**Table 3**). The trans-myocardial gradient of PAI-1 had no significant correlation with global LVEF and LV regional wall motion (**Table 3**). As post-MI LV functions are largely influenced by the extent of infarction, we tested percentage changes in LV function from 2 weeks to 6 months after MI to assess the relation of post-MI LV function to the concentrations of PAI-1 and tPA. As shown in **Table 3** and **Fig. 1B**, the trans-myocardial gradient of PAI-1 6 months after MI had a significant inverse correlation with the percentage change in LV regional motion in the LAD territory from 2 weeks to 6 months after MI. The trans-myocardial gradient of PAI-1 had no significant correlation with the percentage change in global LVEF (**Table 3**). PAI-1 concentration in PV had no significant correlation with LV functions or with the coronary blood flow response to either ACh or SNP (**Table 3**). The tPA concentrations either 2 weeks or 6 months after MI had no significant correlation with

Table 3. Univariate linear regression analysis for correlation of PAI-1 and tPA level with coronary blood flow response and LV function

	PAI-1				tPA			
	2 weeks		6 months		2 weeks		6 months	
	AIV-AO	PV	AIV-AO	PV	AIV-AO	PV	AIV-AO	PV
CBF response								
ACh 10 (μg/min)								
2 weeks	0.18	−0.17	0.06	0.09	0.14	0.26	0.37	0.26
6 months	−0.07	−0.12	−0.39*	−0.25	0.29	0.03	0.25	−0.06
ACh 50 (μg/min)								
2 weeks	−0.10	−0.04	0.11	0.01	0.04	0.24	0.34	0.06
6 months	−0.11	−0.02	−0.43*	−0.31	−0.05	0.13	0.14	−0.20
SNP 10 (μg/min)								
2 weeks	−0.18	−0.29	0.01	−0.15	0.03	0.01	0.32	0.09
6 months	−0.17	0.01	0.05	0.14	0.03	0.08	0.01	0.24
Global LVEF								
2 weeks	−0.28	−0.08	0.07	0.15	−0.17	−0.34	0.11	−0.01
6 months	−0.01	−0.05	−0.10	−0.22	0.01	−0.29	0.11	0.06
LV regional motion								
2 weeks	−0.08	0.06	0.15	−0.03	−0.13	−0.36	0.12	−0.29
6 months	0.11	0.13	−0.16	−0.21	−0.03	−0.20	0.32	−0.20
% change in global LVEF	0.33	−0.33	−0.01	−0.29	0.34	0.01	0.10	0.05
% change in LV regional motion	0.32	−0.05	−0.38*	−0.22	0.06	0.10	0.18	−0.18

Data are expressed as regression coefficient. *$p<0.05$. % change in global LVEF and LV regional motion indicates % change in them from 2 weeks to 6 months after AMI. Abbreviations are as in Tables 1 and 2.

the coronary blood flow response or LV function (**Table 3**). These results indicate that a trans-myocardial increment in PAI-1 in the chronic phase of MI (6 months after MI), but not in the early phase (2 weeks after MI), was related to coronary vasomotor dysfunction and progressive dysfunction of LV regional motion in the territory of the culprit coronary artery. Treatment with angiotensin II type I receptor blocker (ARB), but not other medications, had a significant correlation with coronary vasomotor response to ACh (50 μg/min) ($r=0.45$, $p=0.02$) and with percentage change in LV regional motion ($r=0.40$, $p=0.04$) (**Supplemental Table 1**).

Factors Related to the Trans-myocardial Gradient of PAI-1 6 Months after MI

We examined clinical factors that may be related to the trans-myocardial gradient of PAI-1 6 months after MI. Among the clinical factors listed as variables in **Table 1**, use of ARB and current smoking had significant correlations with the trans-myocardial gradient of PAI-1 6 months after MI by univariate linear regression analysis (**Table 4**). In agreement with this result, patients taking ARB had significantly lower trans-myocardial gradients of PAI-1 6 months after MI than those who were not taking ARB (**Fig. 2**). There was no significant difference in the trans-myocardial gradient of PAI-1 among types and doses of ARBs (Olmesartan in nine patients, Telmisartan in four, and Candesartan in three) (data not shown). Other medications had no relation with the trans-myocardial gradient of PAI-1 (**Table 4**). In this study, no patient was treated with angiotensin-converting enzyme inhibitors (ACE-I).

Discussion

This study showed that a high trans-myocardial gradient of PAI-1 from AO to AIV, reflecting the release of PAI-1 from the infarcted lesion, was associated with endothelial vasomotor dysfunction in the culprit coronary arteries and with progressive dysfunction of the regional motion of the infarcted myocardium. In contrast, the PAI-1 level in PV had no significant association with coronary endothelial dysfunction or LV dysfunction. Thus, PAI-1 produced in the infarcted lesion may have a pathogenic role in coronary endothelial dysfunction and LV regional motion

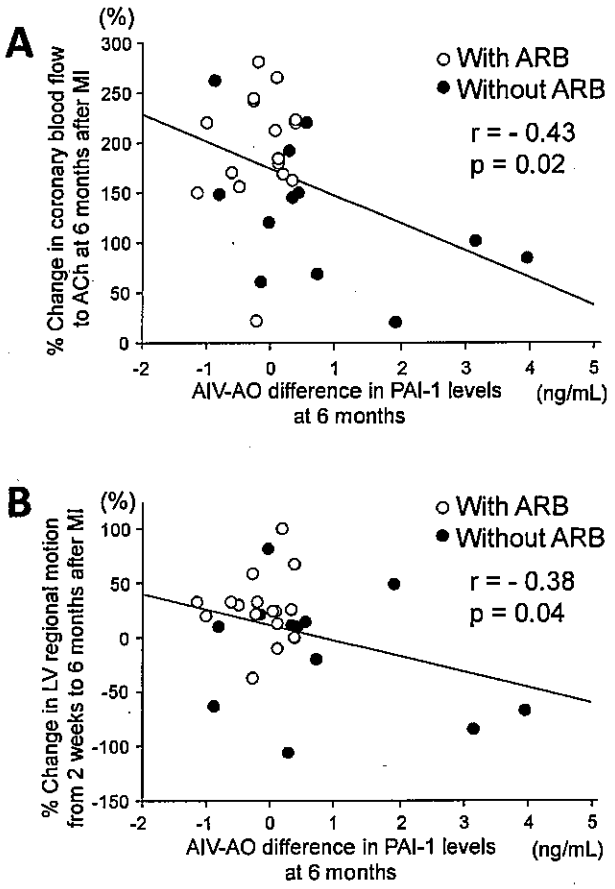

Fig. 1. Correlation of the trans-myocardial gradient of PAI-1 level from the aortic root (AO) to the anterior interventricular vein (AIV) (AIV−AO difference) with the percentage change in coronary blood flow response to acetylcholine (ACh, 50 μg/min) 6 months after MI (A), and with the percentage change in LV regional motion from 2 weeks to 6 months after MI (B). White circles represent patients taking an angiotensin II type I receptor blocker (ARB).

Table 4. Univariate linear regression analysis for correlation of trans-myocardial gradient of PAI-1 6 months after MI with various clinical parameters

	r	*p*-value
Age	−0.08	0.68
Male	−0.16	0.42
Current smoker	0.41	0.03
Hypertension	−0.22	0.26
Diabetes mellitus	−0.04	0.84
BMI	−0.07	0.71
LDL-C	−0.16	0.42
Triglyceride	0.03	0.87
BNP	−0.11	0.58
eGFR	−0.22	0.26
CRP	−0.19	0.34
PRA	−0.13	0.50
Number of diseased vessels	−0.04	0.83
Peak CK	0.03	0.89
DES implantation	−0.17	0.39
Medications used		
ARBs	−0.43	0.02
CCBs	0.18	0.37
β-blockers	−0.13	0.51
Statins	−0.34	0.07

Data are expressed as a regression coefficient (*r*). Independent variables were obtained 2 weeks after AMI. Abbreviations are as in Tables 1, 2.

abnormality after MI. In addition, the trans-myocardial gradient of PAI-1 in the chronic phase of MI (6 months after MI), rather than in the early phase (2 weeks after MI), was associated with coronary vasomotor dysfunction and progressive dysfunction of LV regional motion. Many confounders, such as inflammatory responses and ischemic stunning, may be involved in the mechanisms of coronary vasomotor and LV dysfunction in the early phase of MI. These may impede the relations of the trans-myocardial gradient of PAI-1 with coronary endothelial vasomotor and LV regional dysfunction in the early phase of MI. A major proportion of tPA antigen in plasma is inactive as a component of a tPA−PAI-1 complex[4-6]. Thus, the tPA antigen concentration does not necessarily correlate with the level of its active form in plasma, which may account for its lack of association with coronary endothelial vasomotor and LV dysfunction after MI.

Myocardial ischemia/reperfusion (I/R) induces endothelial injury in the vascular trees of the infarct-related coronary artery[19]. Endothelial damage incurred during the reperfusion injury may limit the restoration of blood flow to potentially viable ischemic myocardium, which importantly contributes to infarct extension and poor prognosis after AMI[23, 24]. The I/R-induced endothelial dysfunction can be reversible for several months after AMI[19]. Recent studies showed that thrombus remains within the culprit coronary arteries for several months after MI[25]. Microthrombus and vasoactive mediators derived from the thrombus have a causative role in endothelial vasomotor dysfunction after MI[26-28]. The increase in PAI-1 concentration in the coronary circulation may induce a high prothrombotic state in the culprit artery, leading to impairment of restoration resulting from I/

R-mediated coronary endothelial vasomotor dysfunction. In addition, PAI-1 may cause endothelial vasomotor dysfunction in the injured arteries via inhibition of re-endothelialization after MI[12, 29-31]. This inhibitory effect of PAI-1 may be mediated by reducing the plasmin-dependent matrix degradation required for angiogenesis and tissue neovascularization[32] and pro-apoptotic effects on endothelial cells[29]. In addition, PAI-1 reduces the migration of endothelial cells by inhibiting binding of the uPA/uPA receptor complex to integrins and blocks uPA–integrin-dependent cellular attachment, migration[30], and cell growth[31].

This is the first clinical study to show that a trans-myocardial gradient of PAI-1 concentration from AO to AIV, reflecting production of PAI-1 in the infarcted lesion, is associated with progressive dysfunction of the regional motion of the infarcted myocardium. This finding is supported by previous experimental studies showing that myocardial overexpression of PAI-1 induces LV adverse remodeling and dysfunction after MI due to the inhibition of uPA and MMP activities[8, 12-14]. Suppression of matrix degradation may also cause inhibition of tissue microvasculature growth, leading to LV adverse remodeling and dysfunction after MI[32]. The uPA/plasmin converts latent transforming growth factor-β (TGF-β) to active TGF-β in the repair process after MI[13]. TGF-β expression is upregulated in the infarcted myocardial lesion, and the active TGF-β has an important role in scar formation of the infarcted lesion through anti-inflammatory and pro-fibrotic effects[33]. Thus, PAI-1 may be possibly related to the dysfunction of the infarcted myocardial lesion in concert with TGF-β. Experimental studies have shown that PAI-1 expression is upregulated in the infarcted myocardial lesion[13, 16]. The increased PAI-1 expressed in the infarcted myocardium may have negative effects on the cardiac healing process after MI.

The details of the regulatory mechanisms underlying the increase in myocardial production of PAI-1 after AMI are unclear. It has been reported that the PAI-1 concentration in the peripheral circulation increases early after AMI through the mechanism of the acute phase response[34] and returns to baseline within 1 month[3]. As the renin–angiotensin–aldosterone system is activated after AMI[35], angiotensin II-mediated upregulation of PAI-1 may also contribute to the increase in PAI-1 in the peripheral circulation[2, 36, 37]. In agreement with these previous reports[2, 36, 37], the present study showed that treatment with ARB was associated with a low trans-myocardial gradient of PAI-1 from AO to AIV, indicating that ARBs may suppress PAI-1 production in the infarcted myocardium. There have been numerous clinical studies showing that ARB treatment protects against post-MI adverse remodeling and dysfunction of the infarcted myocardium[38, 39]. The present study indicates that it may exert beneficial effects on post-MI LV function through suppression of PAI-1 expression in the infarcted myocardium. This mechanism may be an additional benefit of ARB therapy after MI. Although no patients were treated with ACE-I in the present study, it is expected that ACE-I may exert similar effects on the trans-myocardial gradient of PAI-1 after MI[40].

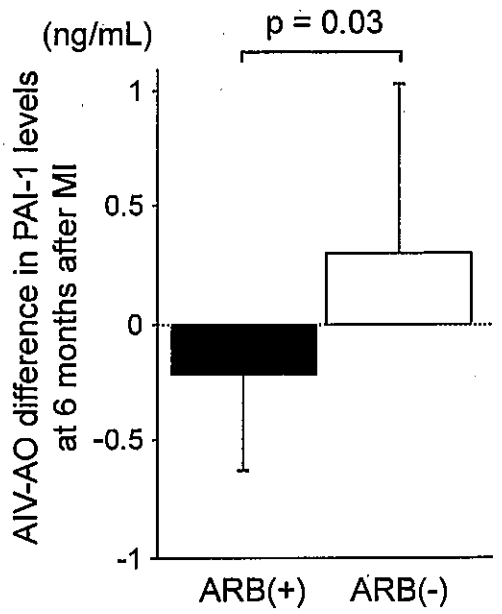

Fig. 2. Comparison of the trans-myocardial gradient of PAI-1 level from AO to AIV (AIV–AO difference) 6 months after MI between patients taking (n=16) and not taking (n=12) ARB. Data are expressed as a mean ± SD.

Our study has several limitations. First, it was observational, and it is possible that other mechanisms including cytokines expressed in the infarcted lesion also have participated in endothelial vasomotor dysfunction of the culprit coronary artery and dysfunction of the infarcted myocardium. Second, some patients with no increase in PAI-1 may nevertheless release PAI-1 from the infarcted lesion, as the trans-myocardial gradient is determined by the net balance between release and uptake in the coronary circulation.

Conclusions

PAI-1 produced in the infarcted myocardium

and released into the coronary circulation was associated with endothelial dysfunction in resistance vessels of the infarct-related coronary arteries and with progressive dysfunction of the infarcted region of the left ventricle in AMI survivors.

COI

We have no conflict of interest and no financial disclosure to declare in relation to the publication of this work.

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Supplemental Table 1.
Univariate linear regression analysis for correlation of each of medications used with coronary blood flow response and % changes in LV regional motion 6 months after MI

	CBF response to ACh (50 μg/min)		% change in LV regional motion	
	r	*p*-value	*r*	*p*-value
ARBs	0.45	0.02	0.40	0.04
CCBs	−0.15	0.45	−0.12	0.55
β-blockers	0.13	0.52	0.16	0.43
Statins	−0.04	0.84	0.07	0.73
Pioglitazone	−0.13	0.51	0.29	0.14
Sulfonylurea	0.01	0.96	−0.08	0.71
DPP-4 inhibitors	0.09	0.67	0.15	0.46
Antiuratics	−0.13	0.53	−0.19	0.35
Diuretics	−0.27	0.16	−0.04	0.81

Data are expressed as regression coefficient (*r*). % change in LV regional motion indicates % change in it from 2 weeks to 6 months after AMI. Independent variables were obtained 6 months after AMI. DPP indicates dipeptidyl peptidase. Other abbreviations are as in Tables 1 and 2.