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Dynamics and Source of Endothelin-1 and Interleukin-6 Following Coronary Reperfusion in Patients with Acute Myocardial Infarction

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Abstract

Objectives: The goals of this study were to determine the source of circulating endothelin-1 (ET-1) and interleukin-6 (IL-6) in acute myocardial infarction (MI) and to study the effects of coronary reperfusion (CR) on plasma levels of ET-1 and IL-6.

Methods: We serially measured plasma concentrations of ET-1 and IL-6 at different sampling sites before and after CR in patients with acute MI. A femoral vein (FV) catheter, a Swan-Ganz catheter, and a femoral artery (FA) catheter were placed in 25 patients with acute MI who were admitted within 12 hours after onset . For the measurement of ET-1 and IL-6 concentrations, blood samples from the FV, right atrium (RA), pulmonary artery (PA), and FA were collected before and 1 hour, 8 hours, and 24 hours after CR therapy. In 5 of the 25 patients, blood samples were collected through a coronary sinus (CS) catheter. We also assessed the gradient across 3 vascular beds (systemic, pulmonary, and coronary) as indices of the net release of ET-1 and IL-6 from those vascular beds. The maximal serum creatine kinase (CK) levels were assessed as an index of myocardial necrosis.

Results: ET-1 levels were higher in the FV than in the RA, PA, or FA. On CR, ET-1 levels peaked after 1 hour and returned to baseline by 24 hours. Calculated net release of ET-1 from the systemic vascular bed (ET-1 at FV−ET-1 at FA) was the highest among the 3 vascular beds. Plasma ET-1 levels correlated with hemodynamic parameters. Plasma IL-6 levels were similar among different sampling sites, whereas calculated net release of IL-6 from the coronary vascular bed was the highest among the 3 vascular beds. IL-6 levels increased throughout 24 hours after coronary reperfusion and closely correlated with maximal CK levels.

Conclusions: The present study suggests that, in acute MI, the major source of ET-1 maintaining baseline plasma levels is the systemic vascular bed and that the ET-1 levels presumably reflect the congestion. ET-1 levels peaked 1 hour after CR. IL-6 increased for 24 hours after CR. The major source of IL-6 is the coronary vascular bed. Only a slight correlation was observed between plasma ET-1 and IL-6 levels.

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Key words: acute myocardial infarction, coronary reperfusion, endothelin-1, interleukin-6, hemodynamics

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Introduction

Endothelin-1 (ET-1), a 21-amino acid peptide, was isolated from cultured porcine aortic endothelial cells by Yanagisawa et al. in 1988[1]. Because of the potent vasoconstrictive effect of ET-1 among physiological compounds, dynamics, site of the production and the pathophysiologic role have been intensively investigated in various clinical settings, such as myocardial ischemia[2–13], heart failure[14–18], pulmonary hypertension[19–22], and essential hypertension[23]. In addition to the role as a vasoactive peptide, recent studies have demonstrated that ET-1 plays a pivotal role in the evolution and progression of coronary atherosclerosis in humans[24,25]. These findings facilitated the study of ET-1, interleukin (IL)-6, and C-reactive protein (CRP), in the context of local inflammation before the onset of acute coronary syndrome[26]. Moreover, a recent study has demonstrated involvement of ET-1 in the process of ventricular remodeling[27]. Thus, possible deleterious effects of ET-1 in myocardial infarction are threefold: facilitation of coronary plaque rupture before the onset of acute coronary syndrome, deterioration of the hemodynamic state by constricting peripheral and coronary vasculatures in acute phase, and a poor prognosis by promoting ventricular remodeling in the chronic phase. In the acute phase of myocardial infarction, however, because of complex dynamics neither the mechanism responsible for the elevation nor the major site of circulating ET-1 has been confirmed. Coincidence of production and clearance of ET-1 in a vascular bed makes it difficult to interpret plasma ET-1 levels. In heart failure, pulmonary release and coronary and peripheral consumption of ET-1 have been reported[2,18], whereas other investigators have reported conflicting results[28]. In myocardial ischemia, the pathophysiological role of ET-1 is even more complicated than in heart failure, since the ET-1 produced by myocardial ischemia overlaps with the ET-1 produced by the resulting heart failure. In one study[4], plasma ET-1 levels were elevated fivefold or more within a few hours after the onset of myocardial infarction, the origin of the ET-1 is, however, obscure. Few studies of human myocardial ischemia have focused on this point. Moreover, studies of plasma ET-1 level changes during coronary angioplasty have yielded conflicting results[9–12]. One study has found that the plasma ET-1 levels increase in the coronary sinus 2 to 5 minutes after coronary angioplasty of the left descending coronary artery[9], whereas other studies have not found significant changes in plasma ET-1 levels in the great cardiac vein or femoral artery[12]. Recently, Tsutamoto et al. reported that the myocardium extracts ET-1 during infarction and that the extent of ET-1 extraction across the coronary vascular bed correlates with left ventricular remodeling represented by changes in left ventricular endodiastolic volume index[27]. Moreover, several recent studies have demonstrated the relationship between circulating ET-1 levels and prognosis in patients with acute myocardial infarction who underwent percutaneous coronary intervention[29,30]. Bearing these findings in mind, studies are of critical importance to confirm the dynamics and the major sites of ET-1 production during myocardial infarction and reperfusion, since the results of such studies might contribute to the development of novel therapeutic strategies that improve patients' prognosis through modification of ET-1 activity. In addition, interest has also been focused on factors stimulating ET-1 production in myocardial ischemia and heart failure. The candidates are angiotensin II, arginine vasopressin, thrombin, transforming growth factor β, and cytokines, including tumor necrotizing factor (TNF)-α, IL-1β, and IL-6, as well as mechanical stretch[34–36]. In fact, IL-6 has been reported to be increased in acute myocardial infarction and heart failure[23,35–37].

Accordingly, the goals of this study were to determine whether the plasma levels of ET-1 rise following coronary reperfusion therapy and to determine the origin of the plasma ET-1 in patients with acute myocardial infarction. The third goal was to determine the relation between ET-1 and IL-6. To achieve these goals, we measured plasma levels of ET-1 and IL-6 in femoral vein, right atrium, pulmonary artery, and femoral artery before and 1 hour, 8 hours, and 24 hours after coronary

reperfusion therapy in 25 patients with acute myocardial infarction who were admitted to our hospital within 12 hours of onset. In 5 of the 25 patients, plasma ET-1 and IL-6 levels in coronary sinus were also measured.

Patients and Methods

Patient Population

Twenty-five patients with acute myocardial infarction who were admitted to the intensive and coronary care unit at Nippon Medical School from November 1992 through September 1997 and underwent coronary reperfusion therapy within 12 hours after onset were enrolled. Acute myocardial infarction was diagnosed by typical precordial pain and/or oppression, electrocardiographic changes, and the elevation of the serum creatine kinase (CK) levels to at least twice the normal upper limit. Coronary reperfusion was confirmed by direct coronary angiography in 20 patients and/or emergence of reperfusion arrhythmias, including accelerated idioventricular rhythm, ventricular premature contractions, and sinus bradycardia, within 2 hours after reperfusion therapy. Clinical backgrounds of the patients are shown in **Table 1**. No patients died during hospitalization. Before the study informed consent was obtained from all patients.

Table 1 Clinical background of the patients

Age (years)	60 ± 10
Sex (M/F)	18/7
Site of infarction (cases)	
Anterior	15
Inferior	10
Time to reperfusion therapy (hours)	7.3 ± 3.0
Reperfusion therapy (cases)	
Intravenous thrombolysis	5
Rescue PTCA	14
Direct stent	6
Peak CK level (IU/L)	3,797 ± 2,666

PTCA: percutaneous transluminal coronary angioplasty.

Measurement of Hemodynamics

Hemodynamics were assessed with standard techniques. Arterial blood pressure (AP) was monitored by radial artery catheter connected via heparinized-saline-filled polyethylene catheter with a pressure manometer. Central venous pressure (CVP), pulmonary artery pressure (PAP), and pulmonary capillary wedge pressure (PCWP) were monitored through a Swan-Ganz catheter. Cardiac output was monitored with the thermodilution method. The cardiac index (CI), total systemic resistance (TSR), and total pulmonary resistance (TPR) were calculated with the measured variables.

Measurement of Plasma ET-1 Levels

To assess plasma levels of ET-1, blood samples were obtained from 4 points: the femoral vein through the femoral vein catheter, the right atrium and pulmonary artery through the Swan-Ganz catheter, and the femoral artery through the femoral arterial catheter, before and 1 hour, 8 hours, and 24 hours after coronary reperfusion therapy. Besides these routinely placed catheters, 5-F coronary sinus catheters (Goodtec, Goodman, Inc, Nagoya, Aichi, Japan) were placed at the coronary sinus in 5 patients, and blood samples were collected in the same manner and schedule as at the other 4 sampling sites. The samples were decanted into tubes containing 13.5 mg of ethylenediaminetetraacetic acid (EDTA)-2Na and 9,000 units of aprotinin, centrifuged at 3,000 rpm for 15 minutes, and were stored at −20℃ until the measurement of ET-1. Plasma ET-1 levels were determined with the RIA using rabbit anti-ET-1 antibody (Peninsula Laboratories Inc., San Carlos, CA, USA). The mean plasma ET-1 level in 7 healthy volunteers was 1.30 ± 0.16 pg/ml[5].

To demonstrate the organ responsible for the circulating ET-1 levels, net release of ET-1 was assessed in 5 patients with coronary sinus sampling by calculating the transorganic gradient of ET-1 levels: net release of ET-1 from systemic vascular bed=(ET-1 level at femoral vein) − (ET-1 level at femoral artery); net release of ET-1 from coronary vascular bed=(ET-1 level at coronary sinus) − (ET-1 level at femoral artery); and net release of ET-1 from pulmonary vascular bed=(ET-1 level at femoral artery) − (ET-1 level at pulmonary artery).

Table 2 Hemodynamic variables and serum CK levels

	Before CR	1 hour after CR	8 hours after CR	24 hours after CR
Arterial blood pressure (mmHg)	99.0 ± 21.6	90.3 ± 15.2	85.3 ± 11.0	81.9 ± 13.9
Heart rate (beats/minute)	79.9 ± 19.7	90.4 ± 19.5	92.0 ± 18.1	94.5 ± 20.5
Mean PAP (mmHg)	22.9 ± 10.2	23.5 ± 9.1	19.3 ± 7.9	17.8 ± 6.5
PCWP (mmHg)	15.5 ± 8.0	16.7 ± 6.9	13.4 ± 5.7	10.5 ± 4.3*
CI (*l*/minute/m^2)	3.3 ± 0.7	3.5 ± 0.9	3.6 ± 0.7	3.8 ± 0.8*
CVP (cm H_2O)	10.1 ± 6.0	12.4 ± 3.7	8.8 ± 4.2	8.2 ± 2.9
Serum CK level (IU/L)	1,770 ± 2,554	3,660 ± 3,273	3,714 ± 3,273	2,244 ± 1,673

CR: coronary reperfusion; PAP: pulmonary artery pressure; PCWP: pulmonary capillary wedge pressure; CI: cardiac index; CVP: central venous pressure; CK: creatine kinase. *P<0.05 as compared with that before CR

Measurement of Plasma IL-6 Levels

Blood samples for the measurement of IL-6 were collected in the same manner as for measurement of ET-1. The samples were decanted in tubes containing EDTA-2Na and centrifuged immediately at 4℃. Plasma was separated and stored at −20℃ until the assay. The plasma concentration of IL-6 was determined with a chemiluminescent enzyme immunoassay (Human IL-6 CLEIA, Fujirebio Inc, Tokyo, Japan). The IL-6 levels in 7 normal subjects were less than 4 pg/ml[35].

To demonstrate the organ responsible for the circulating IL-6 levels, net release of IL-6 was assessed in 5 patients with coronary sinus sampling by calculating the transorganic gradient of IL-6 levels: net release of IL-6 from systemic vascular bed=(IL-6 level at femoral vein) − (IL-6 level at femoral artery); net release of IL-6 from coronary vascular bed=(IL-6 level at coronary sinus) − (IL-6 level at femoral artery); and net release of IL-6 from pulmonary vascular bed=(IL-6 level at femoral artery) − (IL-6 level at pulmonary artery).

Measurement of CK Levels

Blood samples were collected from the femoral vein every 2 hours on the first day, every 4 hours on the second day, and every 6 to 12 hours until the 5th day. Samples were centrifuged, and separated serum was decanted into a tube and stored at −20℃. The CK levels were determined by ultraviolet spectroscopic analysis[38]. The CK-MB band was determined with the immunoinhibition method[39]. Peak CK levels were considered maximal levels.

Measurement of Serum CRP

Blood samples were collected from a peripheral vein on admission and on the second and third hospital days. Serum CRP levels were measured with enzyme-linked immunosorbent assay.

Statistical Analysis

All the numerical data are expressed as means ± standard deviation. An error probability of P<0.05 was regarded as significant. For the time-related comparison of plasma ET-1 and IL-6 levels among sampling sites, linear mixed-model analysis was applied[40]. Multiple comparisons were adjusted with a Bonferroni correction as appropriate. Correlations were assessed by simple linear regression analysis. The analyses were performed with a commercially available statistical package (SPSS Ver. 12, SPSS, Inc., Chicago, IL, USA).

Results

Hemodynamics and Creatine Kinase Levels

Hemodynamic parameters, and serum levels of CK are shown in **Table 2**. The PCWP decreased and the CI increased significantly at 24 hours after coronary reperfusion.

Plasma Levels of ET-1

The time course of plasma ET-1 levels in 25 cases at each of 4 sampling sites, the femoral vein, right atrium, pulmonary artery, and femoral artery, are shown in **Figure 1** (top panel). The ET-1 concentration at the femoral vein was the highest

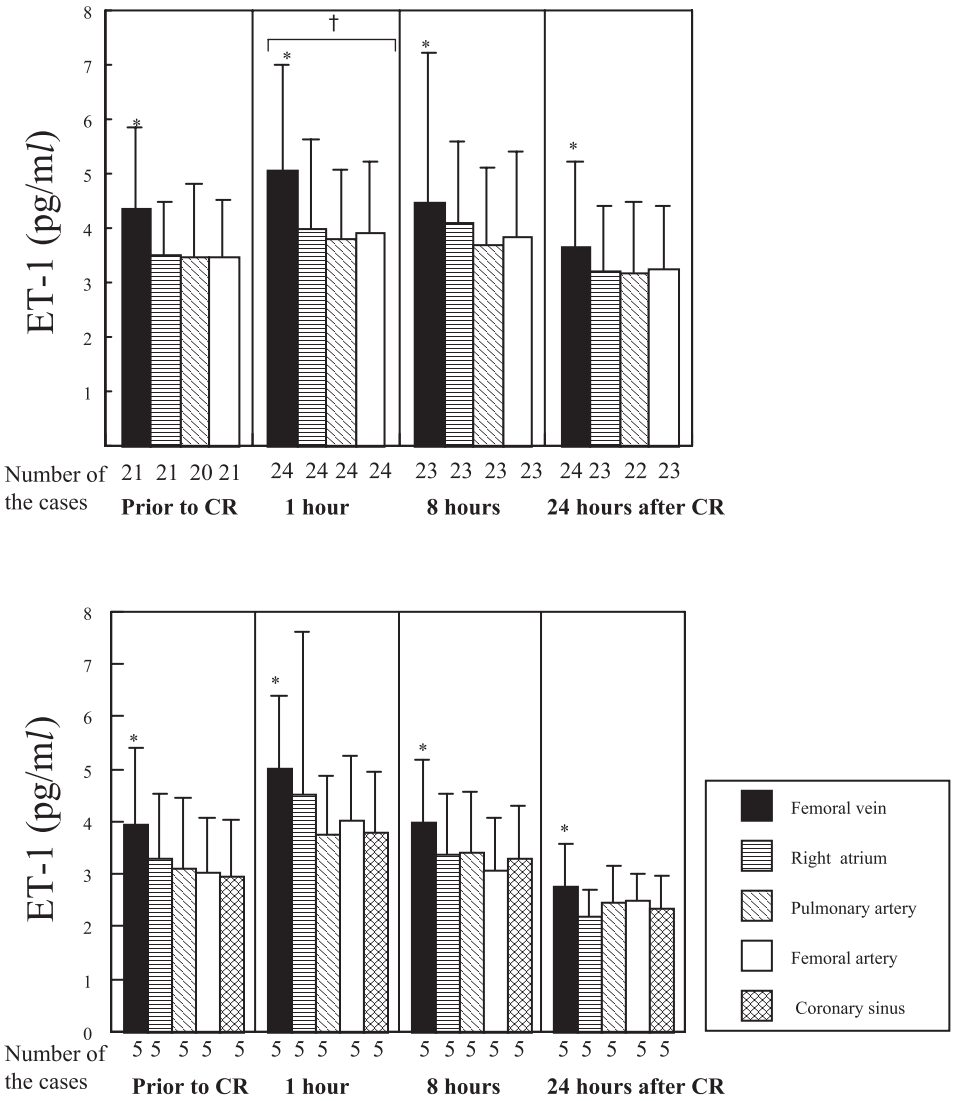

Fig. 1 Time course of plasma endothelin-1 levels on coronary reperfusion
Plasma levels of ET-1 in 25 patients prior to, 1 hour, 8 hours, and 24 hours after the coronary reperfusion (CR) are shown in the top panel. Levels of ET-1 at the femoral vein were higher than in the right atrium, pulmonary artery, or femoral artery ($P < 0.05$). No differences were observed among levels of ET-1 in the other 3 sampling sites. ET-1 levels peaked after 1 hour and returned to baseline levels by 24 hours after CR. The ET-1 level was highest 1 hour after CR ($P<0.05$). Levels of ET-1 in 5 patients with coronary sinus sampling before and 1 hour, 8 hours, and 24 hours after CR are shown in the bottom panel. Again, levels of ET-1 at the femoral vein were higher than those in the right atrium, pulmonary artery, femoral artery, or coronary sinus ($P<0.05$). *$P<0.05$ vs. right atrium, pulmonary artery, femoral artery, or coronary sinus. † $P<0.05$ vs. before, 8 hours after, or 24 hours after CR.

among the 4 sampling sites throughout the study period. No differences were observed among levels at the other 3 sampling sites. The overall ET-1 level peaked at 1 hour and returned to the baseline level at 24 hours after coronary reperfusion therapy. ET-1 levels in 5 patients with coronary sinus sampling are also shown in **Figure 1** (bottom panel). In this group also, ET-1 levels at the femoral vein were the highest among the 4 sampling sites.

The time course of the calculated net release of ET-1 in 5 patients with coronary sinus sampling is shown in **Figure 2**. Again, the net release of ET-1 from the systemic vascular bed was higher than that from the coronary or pulmonary vascular bed.

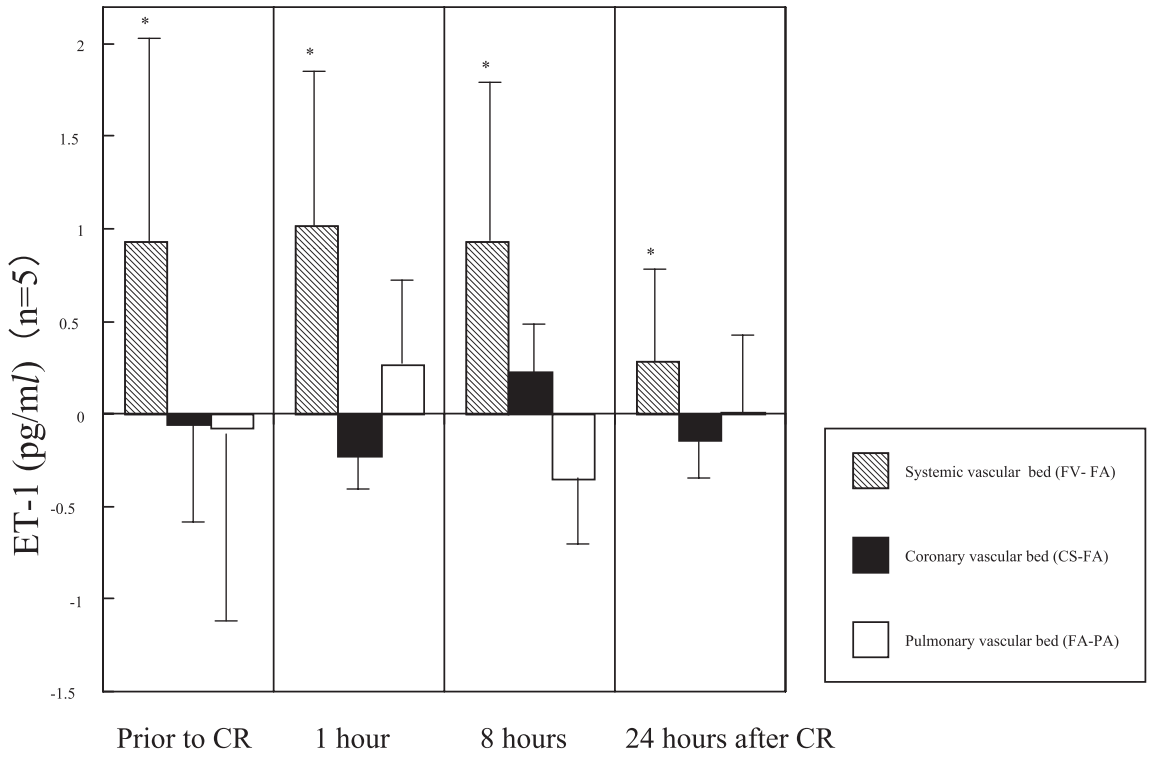

Fig. 2 Time course of the calculated net release of ET-1 on coronary reperfusion

Net release of endothelin-1 (ET-1) was calculated in 5 patients with coronary sinus sampling. Calculated net release of ET-1 from the systemic vascular bed was higher than from the coronary or pulmonary vascular bed ($P<0.05$), indicating that the major source of ET-1 is the systemic vascular bed. No differences in the calculated net releases of ET-1 were observed among the 4 sampling times.

*$P<0.05$ vs. coronary vascular bed or pulmonary vascular bed. CR: coronary reperfusion, FV: femoral vein, FA: femoral artery, CS: coronary sinus, PA: pulmonary artery.

Plasma Levels of IL-6

Plasma levels of IL-6 are shown in **Figure 3**. An increasing tendency was observed throughout the 24 hours in all 25 patients (top panel) and in 5 patients with coronary sinus blood sampling (bottom panel). There were no differences in IL-6 levels among the different sampling sites.

The time course of the calculated net release of the IL-6 in 5 patients with coronary sinus sampling is shown in **Figure 4**. The net release of IL-6 from the coronary vascular bed was higher than that from pulmonary vascular bed, and tended to be higher than that from the systemic vascular bed (P= 0.051) **(Fig. 4)**, possibly suggesting that coronary vascular bed is the major releasing site of IL-6 during acute myocardial infarction with reperfusion.

Correlations between ET-1 and Hemodynamics

Correlations between plasma ET-1 levels at the femoral artery, femoral vein, right atrium, and pulmonary artery, and hemodynamic variables including mean AP, mean PAP, PCWP, CI, CVP, heart rate, TSR, and TPR are shown in **Table 3–6** Plasma ET-1 levels at femoral vein correlated with CVP 1 hour after coronary reperfusion therapy, and with mean AP, and TSR 8 hours after coronary reperfusion therapy **(Table 3** and **Fig. 5)**. Plasma ET-1 levels in the right atrium correlated with CI, TSR, and TPR 8 hours after coronary reperfusion therapy **(Table 4)**. Plasma ET-1 levels at the pulmonary artery correlated with CVP before and 1 hour after coronary reperfusion therapy and with mean AP and PCWP 8 hours after coronary reperfusion therapy **(Table 5)**. Plasma ET-1 levels at the femoral artery correlated with mean AP pressure, TSR, and TPR 8 hours after coronary reperfusion therapy **(Table 6)**. Plasma ET-1 levels at the coronary sinus did not correlate significantly

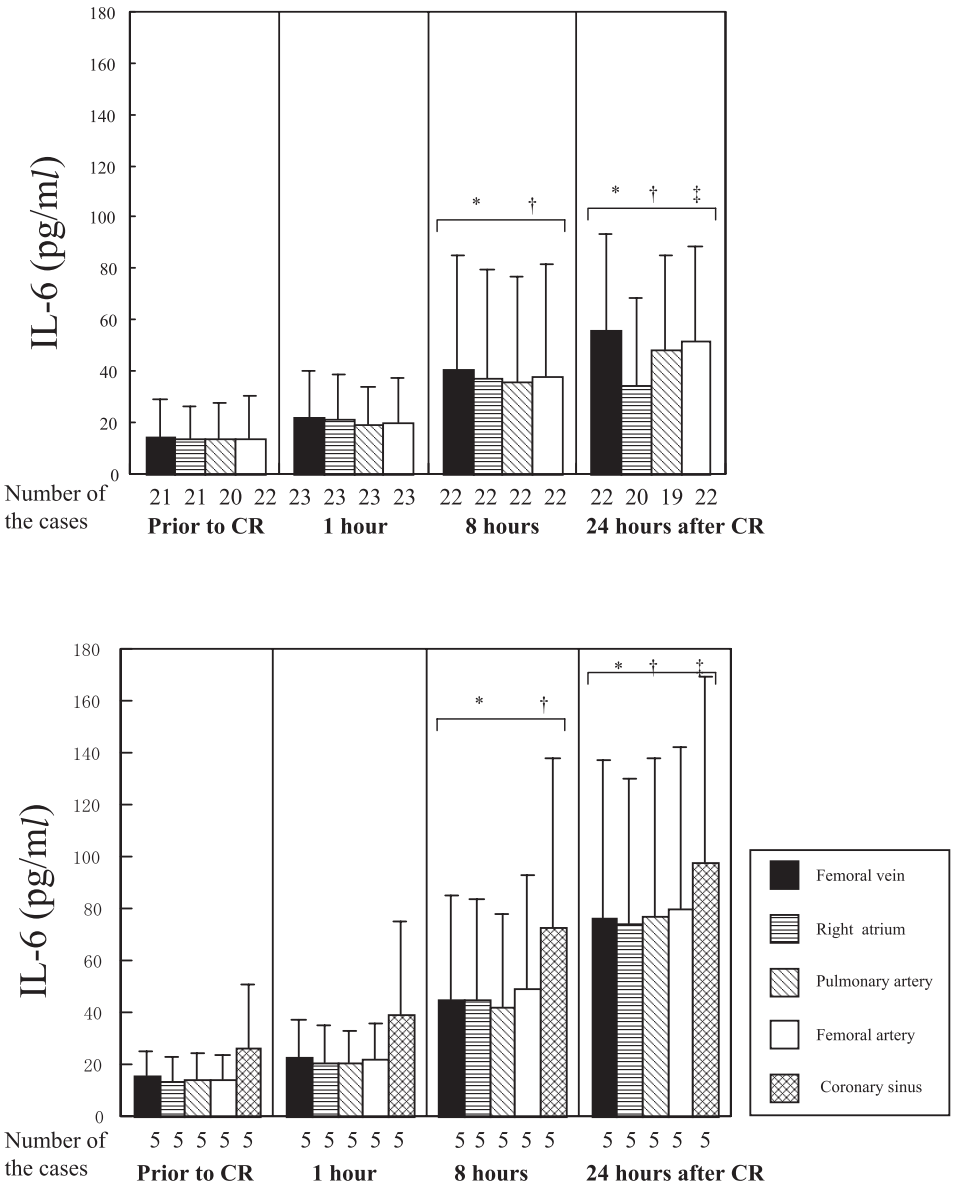

Fig. 3 Time course of plasma IL-6 levels on coronary reperfusion

Plasma levels of IL-6 in 23 patients before and 1 hour, 8 hours, and 24 hours after coronary reperfusion (CR) are shown in the top panel. Overall levels of plasma ET-1 are elevated 8 hours and 24 hours after CR (P<0.001). No differences were observed among plasma levels of IL-6 at the 4 sampling sites: the femoral vein, right atrium, pulmonary artery, and femoral artery. Levels of IL-6 in 5 patients with coronary sinus sampling before and 1 hour, 8 hours, and 24 hours after CR are shown in the bottom panel. Again, overall levels of plasma ET-1 were elevated 8 hours and 24 hours after CR (P<0.001). There were no differences in ET-1 levels among 5 sampling sites: the femoral vein, right atrium, pulmonary artery, femoral artery, and coronary sinus.

*P<0.001 vs. prior to CR, † P<0.001 vs. 1 hour after CR, ‡ P<0.05 vs. 8 hours after CR

with any hemodynamic variable at any time point after coronary reperfusion therapy.

Correlations between IL-6 and Hemodynamics

Correlations between plasma IL-6 levels and hemodynamic variables are shown in **Table 7–11**. Plasma levels of IL-6 at the femoral vein correlated with heart rate 1 hour after coronary reperfusion therapy **(Table 7)**. Plasma levels of IL-6 at the right atrium correlated with heart rate 1 hour and 8 hours after coronary reperfusion therapy **(Table 8)**. Plasma levels of IL-6 at the pulmonary artery

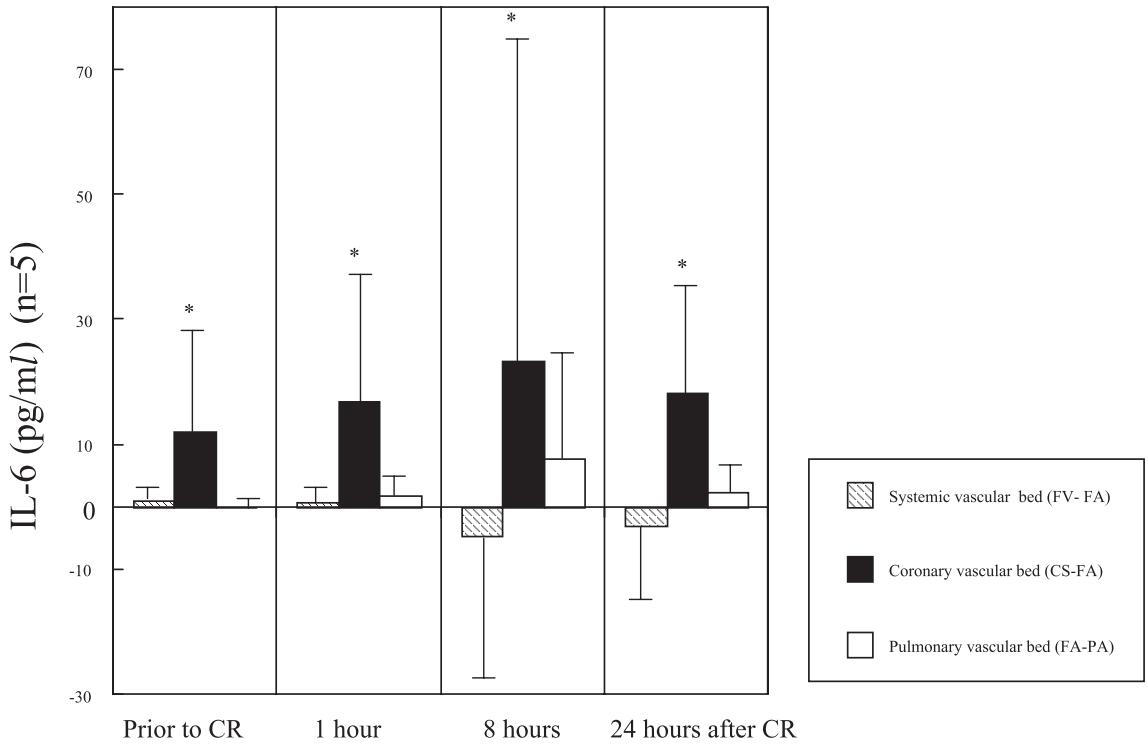

Fig. 4 Time course of calculated net release of plasma IL-6 on coronary reperfusion
Calculated net release of IL-6 from the systemic vascular bed, coronary vascular bed, and pulmonary vascular bed is shown. Net release of IL-6 from the systemic vascular bed=(IL-6 level at femoral vein) − ET-1 level at femoral artery), net release of ET-1 from the coronary vascular bed=(IL-6 level at coronary sinus) − (IL-6 level at femoral artery), net release of IL-6 from the pulmonary vascular bed=(IL-6 level at femoral artery) − (IL-6 level at pulmonary artery). Net release of IL-6 from the coronary vascular bed was higher than that from the pulmonary vascular bed and tended to be higher than that from the systemic vascular bed (P=0.051), possibly suggesting that coronary vascular bed is the major releasing site of IL-6 during acute myocardial infarction with reperfusion.
CR: coronary reperfusion, FV: femoral vein, FA: femoral artery, CS: coronary sinus, PA: pulmonary artery.

correlated with heart rate 1 hour and 8 hours after coronary reperfusion therapy (**Table 9**). Plasma levels of IL-6 at the femoral artery correlated with heart rate 1 hour and 8 hours after coronary reperfusion therapy (**Table 10**). Plasma levels of IL-6 at the coronary sinus correlated with mean PAP, CVP, and TPR before coronary reperfusion therapy, with mean AP 1 hour after coronary reperfusion therapy, and with mean PAP, PCWP, CVP, and TSR 8 hours after coronary reperfusion therapy (**Table 11**).

Correlations between ET-1 and Peak CK

Correlations between plasma ET-1 levels and peak CK are shown in **Table 3−6**. Significant correlation was observed only between the plasma ET-1 levels at the right atrium and peak CK 1 hour after coronary reperfusion therapy (**Table 4**).

Correlations between IL-6 and Peak CK

Correlations between plasma IL-6 levels and peak CK are shown in **Table 7−11**. Plasma IL-6 levels at the femoral artery correlated with peak CK levels and peak CK-MB levels 1 hour and 8 hours after coronary reperfusion therapy (**Table 10**). Plasma IL-6 levels at the femoral vein correlated with peak CK levels and peak CK-MB levels 8 hours after coronary reperfusion therapy (**Table 7**). Plasma IL-6 levels at the pulmonary artery correlated with peak CK levels before and 8 hours after coronary reperfusion therapy (**Table 9**). Plasma IL-6 levels at the pulmonary artery correlated with peak CK-MB levels 8 hours after coronary reperfusion therapy (**Table 9**, and **Fig. 6**, top panel). Plasma IL-6 levels

Table 3 Relationship between plasma ET-1 levels at femoral vein, and hemodynamics, serum CK, CK-MB, and plasma IL-6 levels

ET-1 vs.	Before CR		1 hour after CR		8 hours after CR		24 hours after CR	
	R	*P*	*R*	*P*	*R*	*P*	*R*	*P*
Mean AP	0.039	0.8651	0.005	0.9833	0.441	0.0354*	0.070	0.7438
Mean PAP	0.261	0.2540	0.110	0.7212	0.285	0.1874	0.242	0.2650
PCWP	0.273	0.2313	0.176	0.5641	0.367	0.0853	0.192	0.3829
CI	0.099	0.6684	0.020	0.9482	0.233	0.2970	0.129	0.5571
CVP	0.376	0.0932	0.586	0.0354*	0.262	0.2280	0.066	0.7661
Heart rate	0.064	0.7840	0.125	0.5798	0.309	0.1514	0.187	0.3829
TSR	0.022	0.9528	0.126	0.6816	0.424	0.0490*	0.146	0.5068
TPR	0.306	0.1769	0.064	0.8365	0.364	0.0961	0.111	0.6134
Peak CK	0.087	0.7063	0.210	0.3244	0.333	0.1208	0.210	0.3109
Peak CK-MB	0.064	0.7819	0.171	0.4230	0.294	0.1727	0.275	0.1937
IL-6	0.200	0.3985	0.357	0.0943	0.520	0.0130*	0.142	0.5290

ET-1: endothelin-1; CK: creatine kinase; CK-MB: creatine kinase MB band fraction; IL-6: interleukin-6; CR: coronary reperfusion; AP: arterial pressure; PAP: pulmonary arterial pressure; PCWP: pulmonary apillary wedge pressure; CI: cardiac index; CVP: central venous pressure; TSR: total systemic resistance; TPR: total pulmonary resistance. *P<0.05

Table 4 Correlations between plasma ET-1 levels at right atrium, and hemodynamics, serum CK, CK-MB, and plasma IL-6 levels

ET-1 vs.	Before CR		1 hour after CR		8 hours after CR		24 hours after CR	
	R	*P*	*R*	*P*	*R*	*P*	*R*	*P*
Mean AP	0.099	0.9867	0.161	0.4749	0.400	0.0583	0.095	0.6661
Mean PAP	0.234	0.3680	0.283	0.3484	0.268	0.2158	0.075	0.7352
PCWP	0.310	0.1718	0.320	0.2872	0.347	0.1047	0.141	0.5217
CI	0.169	0.4632	0.163	0.5945	0.499	0.0181*	0.183	0.4030
CVP	0.404	0.0693	0.373	0.2093	0.260	0.2305	0.069	0.7561
Heart rate	0.165	0.4735	0.329	0.1351	0.012	0.9575	0.212	0.3305
TSR	0.059	0.8011	0.312	0.3000	0.618	0.0022*	0.201	0.3579
TPR	0.334	0.1394	0.108	0.7256	0.504	0.0167*	0.045	0.8391
Peak CK	0.073	0.7520	0.412	0.0453*	0.273	0.2081	0.217	0.3191
Peak CK-MB	0.036	0.8770	0.349	0.0944	0.337	0.1158	0.302	0.1613
IL-6	0.077	0.7482	0.359	0.0930	0.323	0.1432	0.270	0.2498

ET-1: endothelin-1; CK: creatine kinase; CK-MB: creatine kinase MB band fraction; IL-6: interleukin-6; CR: coronary reperfusion; AP: arterial pressure; PAP: pulmonary arterial pressure; PCWP: pulmonary capillary wedge pressure; CI: cardiac index; CVP: central venous pressure; TSR: total systemic resistance; TPR: total pulmonary resistance. *P<0.05

at the right atrium correlated with peak CK levels and plasma CK-MB levels 1 hour and 8 hours after coronary reperfusion therapy (**Table 8**). Plasma IL-6 levels at the coronary sinus correlated with peak CK levels 8 hours after coronary reperfusion therapy and with CK-MB levels before and 1 hour and 8 hours after coronary reperfusion therapy (**Table 11**, and **Fig. 6**, bottom panel).

Correlations between Plasma Levels of ET-1 and IL-6

Correlations between plasma ET-1 and IL-6 levels are shown in **Table 3–6**. Plasma ET-1 and IL-6 levels correlated only at the femoral vein 8 hours after coronary reperfusion therapy (**Table 3**).

Correlations between Net Release of ET-1 and Hemodynamics or Creatine Kinase

No significant correlations were observed between calculated net releases of ET-1 from the systemic, coronary, or pulmonary vascular beds, and hemodynamics or serum CK levels.

Table 5 Correlations between plasma ET-1 levels at pulmonary artery, and hemodynamics, serum CK, CK-MB, and plasma IL-6 levels

ET-1 vs.	Before CR		1 hour after CR		8 hours after CR		24 hours after CR	
	R	*P*	*R*	*P*	*R*	*P*	*R*	*P*
Mean AP	0.146	0.5386	0.076	0.7355	0.547	0.0069*	0.025	0.9104
Mean PAP	0.301	0.1967	0.286	0.3443	0.342	0.1101	0.223	0.3184
PCWP	0.164	0.4891	0.404	0.1708	0.431	0.0402*	0.140	0.5338
CI	0.187	0.4300	0.282	0.3500	0.179	0.4253	0.067	0.7685
CVP	0.490	0.0282*	0.531	0.0617	0.378	0.0749	0.106	0.6403
Heart rate	0.195	0.4095	0.102	0.6522	0.091	0.6799	0.204	0.3013
TSR	0.065	0.7852	0.453	0.1203	0.406	0.0607	0.019	0.9339
TPR	0.367	0.1119	0.070	0.8208	0.389	0.0782	0.141	0.5306
Peak CK	0.084	0.7241	0.048	0.8246	0.237	0.2762	0.183	0.4145
Peak CK-MB	0.085	0.7205	0.022	0.9191	0.201	0.3586	0.260	0.2435
IL-6	1.144	0.9996	0.196	0.3690	0.336	0.1267	0.160	0.5130

ET-1: endothelin-1; CK: creatine kinase; CK-MB: creatine kinase MB band fraction; IL-6: interleukin-6; CR: coronary reperfusion; AP: arterial pressure; PAP: pulmonary arterial pressure; PCWP: pulmonary capillary wedge pressure; CI: cardiac index; CVP: central venous pressure; TSR: total systemic resistance; TPR: total pulmonary resistance. *P<0.05

Table 6 Correlations between plasma ET-1 levels at femoral artery, and hemodynamics, serum CK, CK-MB, and plasma IL-6 levels

ET-1 vs.	Before CR		1 hour after CR		8 hours after CR		24 hours after CR	
	R	*P*	*R*	*P*	*R*	*P*	*R*	*P*
Mean AP	0.182	0.4299	0.115	0.6103	0.419	0.0465*	0.070	0.7438
Mean PAP	0.103	0.6572	0.229	0.4524	0.323	0.1329	0.278	0.1985
PCWP	0.224	0.3283	0.224	0.4619	0.369	0.0835	0.298	0.1672
CI	0.136	0.5568	0.099	0.7647	0.371	0.0894	0.096	0.6639
CVP	0.216	0.3461	0.388	0.1907	0.231	0.2894	0.050	0.8190
Heart rate	0.173	0.4536	0.041	0.8549	0.069	0.7561	0.095	0.6663
TSR	0.081	0.7287	0.017	0.9551	0.501	0.0177*	0.099	0.6529
TPR	0.138	0.5513	0.152	0.6210	0.457	0.0327*	0.167	0.4450
Peak CK	0.045	0.8640	0.219	0.3045	0.233	0.2846	0.117	0.5941
Peak CK-MB	0.086	0.7123	0.147	0.4930	0.247	0.2556	0.189	0.3880
IL-6	0.003	0.9894	0.280	0.1950	0.158	0.4836	0.187	0.4160

ET-1: endothelin-1; CK: creatine kinase, CK-MB: creatine kinase MB band fraction; IL-6: interleukin-6; CR: coronary reperfusion; AP: arterial pressure; PAP: pulmonary arterial pressure; PCWP: pulmonary capillary wedge pressure; CI: cardiac index; CVP: central venous pressure; TSR: total systemic resistance; TPR: total pulmonary resistance. *P<0.05

Correlations between Net Release of IL-6 and Hemodynamics or CK

Correlations between calculated net releases of IL-6 from the systemic, coronary, and pulmonary vascular beds, and hemodynamics and serum CK levels are shown in **Table 12**. Net release of IL-6 from the coronary vascular bed correlated with peak CK levels 8 and 24 hours after coronary reperfusion therapy, and with peak CK-MB levels 1 and 24 hours after coronary reperfusion therapy.

Correlations between Serum CRP Levels and ET-1 or IL-6

Serum CRP levels were 0.40 ± 0.54 mg/d*l* on admission, 3.21 ± 4.17 mg/d*l* on the second hospital day, and 10.01 ± 6.58 mg/d*l* on the third hospital day. At no sampling time point was there a correlation between CRP levels and ET-1 levels at the femoral vein. Close correlations were observed between serum CRP levels on the second and the third hospital days and plasma IL-6 levels at the femoral vein (**Table 13**).

Discussion

Source and Plasma Levels of ET-1

A major finding of the present study is that the overall concentration of ET-1 was the higher at the femoral vein than at the right atrium, pulmonary artery, or femoral artery throughout the observation period of 24 hours, suggesting that the major source of circulating ET-1 at baseline is the systemic vascular bed in patients with acute myocardial infarction with coronary reperfusion. At the onset of myocardial infarction, some of ET-1 is supposed to be released from the coronary vascular bed[41]. Shortly, it is followed by congestion, even at a subclinical level, resulting in pulmonary and systemic vascular stretch that will stimulate ET-1 release from the endothelium of those vascular beds. An analysis of transvascular-bed gradient of ET-1 in terms of calculated net release of ET-1 confirmed this. The systemic arteriovenous gradient of plasma ET-1 levels was constantly positive and was maintained at the highest level among those from the 3 vascular beds throughout the 24 hours after coronary reperfusion. These scenarios do not rule out ET-1 release from the pulmonary vascular bed. Indeed, the transpulmonary gradient of the ET-1 level was positive 1 hour after coronary reperfusion, indicating the possibility of release of ET-1 from the pulmonary vascular bed, although the net release was transient and the amount was less and had a trivial effect on systemic plasma levels of ET-1. The systemic vascular bed is 20-fold larger than the coronary vascular bed and 5-fold larger than the pulmonary vascular bed. Tsutamoto et al.[18] have reported that the main source of circulating ET-1 in chronic heart failure is the pulmonary vascular bed and not the peripheral vascular bed. Conflicting results may explained by the presence or absence of acute myocardial infarction.

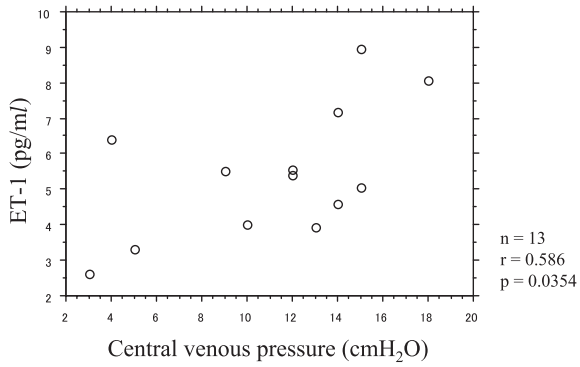

Fig. 5 Correlation between plasma ET-1 levels at the femoral vein and CVP 1 hour after coronary reperfusion.
There was a significant correlation between plasma ET-1 levels at the femoral vein and CVP 1 hour after coronary reperfusion.

In addition, it is noteworthy that ET-1 levels were higher at the femoral vein than those of right atrium, in part, possibly because ET-1 was catabolized in the bloodstream, and in part because the ET-1-rich blood was diluted by the bloodstream

Table 7 Correlations between plasma IL-6 levels at femoral vein, and hemodynamics, serum CK, and CK-MB levels

IL-6 vs.	Before CR		1 hour after CR		8 hours after CR		24 hours after CR	
	R	*P*	*R*	*P*	*R*	*P*	*R*	*P*
Mean AP	0.258	0.2595	0.274	0.2300	0.136	0.5459	0.118	0.6002
Mean PAP	0.229	0.3182	0.078	0.7997	0.387	0.0750	0.192	0.4047
PCWP	0.147	0.5248	0.080	0.7956	0.351	0.1090	0.214	0.3517
CI	0.006	0.9811	0.041	0.8940	0.079	0.7327	0.348	0.1223
CVP	0.407	0.6710	0.302	0.3152	0.371	0.0895	0.250	0.2749
Heart rate	0.053	0.8194	0.482	0.0268*	0.513	0.0146*	0.337	0.1252
TSR	0.273	0.2307	0.200	0.5133	0.133	0.5661	0.157	0.4957
TPR	0.220	0.3383	0.040	0.9889	0.439	0.0464*	0.258	0.2580
Peak CK	0.311	0.1707	0.406	0.0547	0.524	0.0123*	0.266	0.2308
Peak CK-MB	0.330	0.1439	0.393	0.0633	0.561	0.0066*	0.112	0.6193

IL-6: interleukin-6; CK: creatine kinase; CKMB: creatine kinase MB band fraction; CR: coronary reperfusion; AP: arterial pressure; PAP: pulmonary arterial pressure; PCWP: pulmonary capillary wedge pressure; CI: cardiac index; CVP: central venous pressure; TSR: total systemic resistance; TPR: total pulmonary resistance. *$P<0.05$

Table 8 Correlations between plasma IL-6 levels at right atrium, and hemodynamics, serum CK, and CK-MB levels

IL-6 vs.	Prior to CR		1 hour after CR		8 hours after CR		24 hours after CR	
	R	*P*	*R*	*P*	*R*	*P*	*R*	*P*
Mean AP	0.188	0.4137	0.338	0.1345	0.062	0.7853	0.051	0.8316
Mean PAP	0.190	0.4104	0.121	0.6935	0.346	0.1151	0.209	0.3774
PCWP	0.115	0.6191	0.103	0.7374	0.312	0.1577	0.322	0.1664
CI	0.005	0.9840	0.107	0.7269	0.056	0.8098	0.147	0.5361
CVP	0.375	0.0940	0.320	0.2866	0.302	0.1721	0.378	0.1000
Heart rate	0.106	0.6467	0.554	0.0091*	0.507	0.0160*	0.248	0.2924
TSR	0.222	0.3333	0.128	0.6777	0.082	0.7240	0.032	0.8929
TPR	0.177	0.4437	0.175	0.5680	0.391	0.0797	0.159	0.5033
Peak CK	0.324	0.1519	0.451	0.0307*	0.482	0.0232*	0.397	0.0834
Peak CK-MB	0.381	0.0888	0.473	0.0226*	0.528	0.0116*	0.272	0.2464

IL-6: interleukin-6; CK: creatine kinase; CK-MB: creatine kinase MB band fraction; CR: coronary reperfusion; AP: arterial pressure; PAP: pulmonary arterial pressure; PCWP: pulmonary capillary wedge pressure; CI: cardiac index; CVP: central venous pressure; TSR: total systemic resistance; TPR: total pulmonary resistance. *P<0.05

Table 9 Correlations between plasma IL-6 levels at pulmonary artery, and hemodynamics, serum CK, and CK-MB levels

IL-6 vs.	Before CR		1 hour after CR		8 hours after CR		24 hours after CR	
	R	*P*	*R*	*P*	*R*	*P*	*R*	*P*
Mean AP	0.276	0.2397	0.322	0.1551	0.089	0.6948	0.076	0.7578
Mean PAP	0.259	0.2709	0.137	0.6565	0.376	0.0845	0.148	0.5457
PCWP	0.156	0.5181	0.145	0.6356	0.328	0.1361	0.278	0.2490
CI	0.007	0.9597	0.088	0.7758	0.039	0.8672	0.137	0.5764
CVP	0.426	0.0611	0.394	0.1823	0.327	0.8044	0.400	0.0895
Heart rate	0.129	0.5872	0.453	0.0394*	0.467	0.0283*	0.318	0.1492
TSR	0.303	0.1940	0.269	0.3748	0.092	0.6921	0.147	0.5254
TPR	0.252	0.2848	0.043	0.8900	0.409	0.0653	0.095	0.6994
Peak CK	0.295	0.0260*	0.411	0.0513	0.501	0.0176*	0.329	0.1687
Peak CK-MB	0.326	0.1605	0.400	0.0584	0.546	0.0085*	0.183	0.4528

IL-6: interleukin-6; CK: creatine kinase; CK-MB: creatine kinase MB band fraction; CR: coronary reperfusion; AP: arterial pressure; PAP: pulmonary arterial pressure; PCWP: pulmonary capillary wedge pressure; CI: cardiac index; CVP: central venous pressure; TSR: total systemic resistance; TPR: total pulmonary resistance. *P<0.05

from the renal and hepatic vascular beds, indicating neither was a major source of circulating ET-1 in the present clinical settings, although the kidney and liver would play major roles in different clinical settings[42,43]. In the context of inflammation, the present study did not find significant correlations between plasma ET-1 levels and serum CRP levels, suggesting that ET-1 does not contribute to the systemic inflammatory response following coronary reperfusion in the acute phase of myocardial infarction. Because of the considerable correlation between plasma ET-1 levels and hemodynamic parameters, we assume that ET-1 was released in response to the mechanical stretch of the systemic vasculature[34] caused by congestion as a result of myocardial infarction. Once ET-1 was released into the systemic circulation, ET-1 contributes to vascular constriction, which causes heart failure to worsen by increasing vascular resistance and by exacerbating myocardial ischemia.

Effect of Coronary Reperfusion

Another important finding is that overall plasma ET-1 levels were elevated following coronary reperfusion therapy. Although the levels of ET-1 had already been elevated before coronary reperfusion therapy, the concentration was significantly higher 1 hour after reperfusion than baseline values before

coronary reperfusion. Analysis of the calculated net release of ET-1, however, did not find an increase in net secretion of ET-1 from the coronary vascular bed 1 hour after coronary reperfusion. Importantly, ET-1 levels at all 4 sampling sites were elevated 1 hour after reperfusion, potentially indicating that net secretion of ET-1 is elevated similarly at various vascular beds. This finding might be attributed to the change in hemodynamics or to unknown substances released from the coronary vascular bed on reperfusion. Net release of ET-1 from the coronary vascular bed 8 hours after reperfusion seems to have increased but did not affect the circulating ET-1 levels, presumably because of the relatively small amount. Previous studies with coronary ligation/reperfusion animal models have shown that plasma ET-1 levels are elevated 1 hour after reperfusion[44]. The difference between the present results and those of earlier studies might be explained by difference in the reperfusion process. In animal models, the reperfusion process develops abruptly because reperfusion is achieved by the release of ligation, whereas in clinical settings complete reperfusion is achieved gradually, especially with intravenous thrombolyic intervention. It is not clear whether the increased net release of ET-1 from the coronary vascular bed following reperfusion is due to the augmentation of ET-1 synthesis or to reduced clearance of the peptide. In connection with this, it has been reported that ET-1 levels at the coronary sinus were not higher than arterial ET-1 levels[27,44].

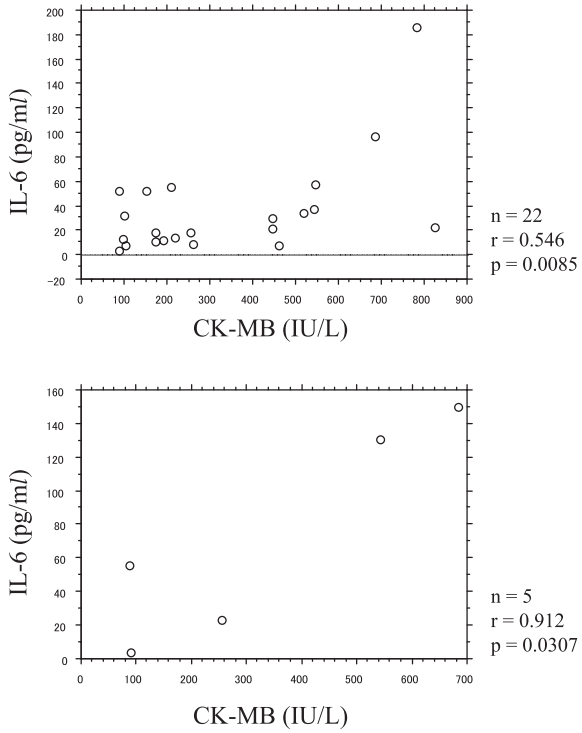

Fig. 6 Correlation between plasma IL-6 levels and serum CK-MB levels.
There were significant correlations between plasma IL-6 levels at the pulmonary artery or coronary sinus, and serum CK-MB levels 8 hours after coronary reperfusion in all 22 cases (top panel) and in 5 patients with coronary sinus sampling (bottom panel).

Table 10 Correlations between plasma IL-6 levels at femoral artery, and hemodynamics, serum CK, and CK-MB levels

IL-6 vs.	Before CR		1 hour after CR		8 hours after CR		24 hours after CR	
	R	*P*	*R*	*P*	*R*	*P*	*R*	*P*
Mean AP	0.237	0.2873	0.309	0.1722	0.057	0.8023	0.019	0.9328
Mean PAP	0.209	0.3501	0.140	0.6475	0.312	0.1574	0.116	0.6164
PCWP	0.167	0.4588	0.140	0.6487	0.308	0.1635	0.259	0.2560
CI	0.009	0.9689	0.017	0.9554	0.072	0.7567	0.140	0.5464
CVP	0.389	0.0737	0.300	0.3189	0.294	0.1842	0.323	0.1530
Heart rate	0.117	0.6045	0.528	0.0139*	0.481	0.0233*	0.189	0.3996
TSR	0.268	0.2284	0.198	0.5176	0.089	0.7013	0.048	0.8366
TPR	0.191	0.3956	0.102	0.7414	0.364	0.1045	0.074	0.7487
Peak CK	0.297	0.1789	0.456	0.0287*	0.438	0.0417*	0.311	0.1594
Peak CK-MB	0.305	0.1674	0.465	0.0255*	0.471	0.0268*	0.167	0.4580

IL-6: interleukin-6; CK: creatine kinase; CK-MB: creatine kinase MB band fraction; CR: coronary reperfusion; AP: arterial pressure; PAP: pulmonary arterial pressure; PCWP: pulmonary capillary wedge pressure; CI: cardiac index; CVP: central venous pressure; TSR: total systemic resistance; TPR: total pulmonary resistance. *$P<0.05$

Table 11 Correlations between plasma IL-6 levels at coronary sinus, and hemodynamics, serum CK, and CK-MB levels

IL-6 vs.	Before CR		1 hour after CR		8 hours after CR		24 hours after CR	
	R	*P*	*R*	*P*	*R*	*P*	*R*	*P*
Mean AP	0.274	0.6557	0.962	0.0089*	0.242	0.6944	0.773	0.1256
Mean PAP	0.935	0.0195*	0.647	0.2378	0.911	0.0316*	0.499	0.3920
PCWP	0.867	0.0567	0.507	0.3837	0.992	0.0009*	0.647	0.2375
CI	0.533	0.3552	0.059	0.9247	0.751	0.1439	0.775	0.1238
CVP	0.976	0.0046*	0.649	0.2360	0.930	0.0219*	0.788	0.1133
Heart rate	0.413	0.4890	0.756	0.1393	0.011	0.9864	0.069	0.9128
TSR	0.326	0.5929	0.657	0.2280	0.889	0.0321*	0.316	0.6042
TPR	0.922	0.0260*	0.711	0.1778	0.852	0.0670	0.752	0.1426
Peak CK	0.779	0.1205	0.846	0.0707	0.935	0.0195*	0.511	0.3785
Peak CK-MB	0.903	0.0357*	0.939	0.0181*	0.912	0.0307*	0.511	0.3785

IL-6: interleukin-6; CK: creatine kinase; CK-MB: creatine kinase MB band fraction; CR: coronary reperfusion; AP: arterial pressure; PAP: pulmonary arterial pressure; PCWP: pulmonary capillary wedge pressure; CI: cardiac index; CVP: central venous pressure; TSR: total systemic resistance; TPR: total pulmonary resistance. *P<0.05

Table 12 Correlations between net release of plasma IL-6 from systemic, coronary, and pulmonary vascular beds, and hemodynamics, serum CK, and CK-MB levels

IL-6 vs.	Before CR		1 hour after CR		8 hours after CR		24 hours after CR	
	R	*P*	*R*	*P*	*R*	*P*	*R*	*P*
FV-FA (systemic vascular bed)								
CVP	0.170	0.7846	0.538	0.3947	0.161	0.7960	0.447	0.4499
TSR	0.434	0.4653	0.581	0.3044	0.681	0.2060	0.391	0.5151
CS-FA (coronary vascular bed)								
Peak CK	0.725	0.8290	0.829	0.0830	0.930	0.0221*	0.989	0.0015*
Peak CK-MB	0.852	0.0665	0.923	0.0255*	0.851	0.0674	0.953	0.0121*
A-PA (pulmonary vascular bed)								
PAP mean	0.003	0.9910	0.091	0.7615	0.170	0.4508	0.001	0.9970
PCWP	0.137	0.5749	0.068	0.8257	0.014	0.9495	0.262	0.2777
TPR	0.060	0.8066	0.204	0.5040	0.073	0.7535	0.011	0.9637

CK: creatine kinase; CK-MB: creatine kinase MB fraction band; CR: coronary reperfusion; FV: femoral vein; FA: femoral artery; CVP: central venous pressure; TSR: total systemic resistance; CS: coronary sinus, level; PA: pulmonary artery; PAP: pulmonary arterial pressure; PCWP: pulmonary capillary wedge pressure; TPR: total pulmonary resistance. *P<0.05

Table 13 Correlations between serum CRP levels and plasma IL-6 levels at femoral vein

CRP vs.	on admission		the second hospital day		the third hospital day	
	R	*P*	*R*	*P*	*R*	*P*
IL-6						
Before CR	0.182	0.4557	0.662	0.0028*	0.145	0.5661
1 hour after CR	0.189	0.4128	0.615	0.0039*	0.227	0.3355
8 hours after CR	0.247	0.2936	0.292	0.2256	0.759	0.0002*
24 hours after CR	0.010	0.9680	0.251	0.2862	0.650	0.0019*

CRP: C reactive protein; IL-6: interleukin-6; CR: coronary reperfusion. *P<0.05

Source and Plasma Levels of IL-6

In contrast to ET-1, IL-6 showed a tendency to increase throughout the 24 hours after coronary reperfusion. Analysis of the calculated net release of IL-6 clearly indicated that the major source of IL-6

was the coronary vascular bed, although overall plasma IL-6 levels tended to be higher in the coronary sinus than at the other 4 sampling sites, but the difference did not reach the level of significance. There was a strong correlation between plasma IL-6 levels and peak CK levels as an index of the amount of infarcted myocardium. These findings suggest that the release of IL-6 is directly induced by the myocardial injury caused by coronary occlusion itself or reperfusion. In addition to CK , IL-6 at coronary sinus was strongly correlated with hemodynamics; higher plasma IL-6 levels indicate a worse hemodynamic state, higher PAP, PCWP, CVP, and TSR. This findings confirm our previous study[32], which suggested that IL-6 causes myocardial stunning[45] with resultant hemodynamic deterioration.

The present study demonstrated a behavioral discrepancy between plasma levels of ET-1 and IL-6, suggesting little cause-and-effect relation between these two biological substances in spite of the significant correlations reported in previous studies [33,46]. Discrepancy between ET-1 and IL6 was observed again in relation to the serum CRP levels. Significant correlation was not observed between plasma ET-1 levels and serum CRP levels, whereas strong correlations were observed between plasma IL-6 levels and serum CRP levels.

Clinical Implication

To date, ET-1 antagonists have failed to demonstrate the clinical utility[47,48], despite the experimental data using animal models have shown the beneficial effects on heart failure[49,50]. To achieve a breakthrough, more information on the pathophysiologic mechanism of ET-1 production is necessary. Meanwhile, numerous studies have been conducted to elucidate the production and clearance of ET-1 and IL-6 in the ischemic or failed heart, but the results were still equivocal. Our study has provided data that potentially answer these questions, at least in part.

Study Limitations

There are several study limitations in the present study. First, no control group of patients with acute myocardial infarction who did not undergo coronary reperfusion therapy was included. With contrast to the group, the effect of reperfusion on plasma ET-1 levels should have been demonstrated with more clarity. Second, coronary reperfusion was not confirmed by angiography in all patients . Possibly, this impaired the precision of the reperfusion time. Third, sampling time points might not be frequent enough to detect the transient production of ET-1 from a vascular bed. After ET-1 was produced in a short time period and entered the circulating plasma, it would be difficult to detect changes in the production afterwards. Fifth, numerous medications, including cardiotonic agents and vasodilators, were administered to the patients, which might have had substantial effects on hemodynamics and on the production of ET-1 or IL-6, resulting in blunted correlations between hemodynamics and ET-1 or IL-6. Last, we did not assess the role of the hepatic or renal vascular beds, which have been previously reported. ET-1 production at the systemic vascular bed observed in the present study possibly reflects the production at those two vascular beds. Further investigation focusing on this point would be necessary to better define the role of ET-1.

Conclusions

The present study suggests that, in the acute phase of myocardial infarction, the major source of circulating ET-1 maintaining the baseline plasma levels is the systemic vascular bed and that ET-1 levels presumably reflect congestion. On coronary reperfusion, ET-1 levels increase after 1 hour through unknown mechanisms other than the increased production of ET-1 at the coronary vascular bed. Levels of IL-6 increased for 24 hours after coronary reperfusion. The major site of IL-6 production is the coronary vascular bed. Only a weak correlation was observed between plasma ET-1 and IL-6 levels.

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References

1. Yanagisawa M, Kurihara H, Kimura S, et al.: A novel potent vasoconstrictor peptide produced by vascular endothelial cells. Nature 1988; 332: 411–415.
2. Miyauchi T, Yanagisawa M, Tomizawa T, et al.: Increased plasma concentrations of endothelin-1 in acute myocardial infarction. Lancet 1989; 2: 53–54.
3. Yasuda M, Kohno M, Tahara A, et al.: Circulating immunoreactive endothelin in ischemic heart disease. Am Heart J 1990; 119: 801–806.
4. Stewart DJ, Kubac G, Costello KB, Cernacek P: Increased plasma endothelin-1 in the early hours of acute myocardial infarction. J Am Coll Cardiol 1991; 18: 38–43.
5. Setsuta K, Seino Y, Tomita Y, Nejima J, Takano T, Hayakawa H: Origin and pathophysiological role of increased endothelin-1 in patients with acute myocardial infarction. Angiology 1995; 46: 557–565.
6. Battistelli S, Billi M, Manasse G, Vittoria A, Roviello F, Forconi S: Behavior of circulating endothelin-1 in a group of patients with acute myocardial infarction. Angiology 1999; 50: 629–638.
7. Toyo-oka T, Aizawa T, Suzuki N, et al.: Increased plasma level of endothelin-1 and coronary spasm induction in patients with vasospastic angina pectoris. Circulation 1991; 83: 476–483.
8. Salomone O, Elliot PM, Calvino R, Holt D, Kaski JC: Plasma immunoreactive endothelin concentration correlates with severity of coronary artery disease in patients with stable angina pectoris and normal ventricular function. J Am Coll Cardiol 1996; 28: 14–19.
9. Vojacek J, Lisy O, Simek S, et al.: Local changes in plasma endothelin level in the coronary artery immediately after percutaneous transluminal coronary angioplasty. Cardiology 1997; 88: 1–5.
10. Velasco CE, Turner M, Inagami T, et al.: Reperfusion enhances the local release of endothelin after regional myocardial ischemia. Am Heart J 1994; 128: 441–451.
11. Malatino LS, Grassi R, Stancanelli B, et al.: Release of immunoreactive endothelin from the heart during percutaneous transluminal coronary angioplasty. Am Heart J 1993; 126: 700–702.
12. Montalescot G, Viossat I, Chabrier PE, et al.: Endothelin-1 in patients with coronary heart disease undergoing cardiac catheterization. J Am Coll Cardiol 1994; 24: 1236–1241.
13. Miyauchi T, Doi T, Suzuki N, et al.: Plasma endothelin-1 concentrations in the coronary sinus in dogs with artificially induced myocardial infarction. Peptides 1992; 13: 1013–1015.
14. Takeda S, Takano T, Ogawa R: The effect of nasal continuous positive airway pressure on plasma endothelin-1 concentrations in patients with severe cardiogenic pulmonary edema. Anesth Analg 1997; 84: 1091–1096.
15. McMurray JJ, Ray SG, Abdullah I, Dargie HJ, Mortin JJ: Plasma endothelin in chronic heart failure. Circulation 1992; 85: 1374–1379.
16. Stangl K, Dshietzig T, Richter C, et al.: Pulmonary release and coronary and peripheral consumption of big endothelin and endothelin-1 in severe heart failure. Acute effect of vasodilator therapy. Circulation 2000; 102: 1132–1138.
17. Azevedo ER, Stewart DJ, Parker JD: Increased Extraction of endothelin-1 across the failing human heart. Am J Cardiol 2001; 88: 180–182.
18. Tsutamoto T, Wada A, Maeda Y, Adachi T, Kinoshita M: Relation between endothelin-1 spillover in the lungs and pulmonary vascular resistance in patients with chronic heart failure. J Am Coll Cardiol 1994; 23: 1427–1433.
19. Stewart DJ, Levy RD, Cernacek P, Langleben D: Increased plasma endothelin-1 in pulmonary hypertension: marker or mediator of disease? Ann Intern Med 1991; 114: 464–469.
20. Giaid A, Yanagisawa M, Langleben D, et al.: Expression of endothelin-1 in the lung of patients with pulmonary hypertension. N Engl J Med 1993; 328: 1732–1739.
21. Takeda S, Nakanishi K, Inoue T, Ogawa R: Delayed elevation of plasma endothelin-1 during unilateral alveolar hypoxia without systemic hypoxemia in humans. Acta Anaesth Scand 1997; 41: 274–280.
22. Dupuis J, Cernacek P, Tardif JC, et al.: Reduced pulmonary clearance of endothelin-1 in pulmonary hypertension. Am Heart J 1998; 135: 614–620.
23. Saito Y, Nakao K, Mukoyama M, Imura H: Increased plasma endothelin level in patients with essential hypertension. New Engl J Med 1990; 322: 205.
24. Zeiher AM, Goebel H, Schachinger V, Ihling C: Tissue endothelin-1 immunoreactivity in the active coronary atherosclerotic plaque: a clue to the mechanism of increased vasoactivity of the culprit lesion in unstable angina. Circulation 1995; 91: 941–947.
25. Lerman A, Edwards BS, Hallett JW, Heublein DM, Sandberg SM, Burnett JC Jr: Circulating and tissue endothelin immunoreactivity in advanced atherosclerosis. N Engl J Med 1991; 325: 997–1001.
26. Verma S, Li SH, Badiwala MV, et al.: Endothelin antagonism and interleukin-6 inhibition attenuate the proatherogenic effects of C-reactive protein. Circulation 2002; 105: 1890–1896.
27. Tsutamoto T, Wada A, Hayashi M, et al.: Relationship between transcardiac gradient of endothelin-1 and left ventricular remodeling inpatients with first anterior myocardial infarction. Eur Heart J 2003; 24: 346–355.
28. Sakai S, Miyauchi T, Sakurai T, et al.: Endogenous endothelin-1 participates in the maintenance of cardiac function in rats with congestive heart failure. Marked increase in endothelin-1 production in the failing heart. Circulation 1996; 93: 1214–1222.
29. Yip Y-K, Wu C-J, Chang H-W, et al.: Prognostic value of circulating levels of endothelin-1 in patients after acute myocardial infarction undergoing primary coronary angioplasty. Chest 2005; 127: 1491–1497.
30. Katayama T, Yano K, Nakashima H, et al.: Clinical significance of acute-phase endothelin-1 in acute myocardial infarction patients treated with direct coronary angioplasty. Circ J 2005; 69: 654–658.
31. Ito H, Hirata Y, Adachi S, et al.: Endothelin-1 is an autocrine/paracrine factor in the mechanism of angiotensin II-induced hypertrophy in cultured rat cardiomyocytes. J Clin Invest 1993; 92: 398–403.

32. Kurihara H, Yoshizumi M, Sugiyama T, et al.: Transforming growth factor-beta stimulates the expression of endothelin mRNA by vascular endothelial cells. Biochem Biophys Res Commun 1989; 159: 1435–1540.
33. Yamashita J, Ogawa M, Nomura K, et al.: Interleukin 6 stimulates the production of immunoreactive endothelin 1 in human breast cancer cells. Cancer Res 1993; 53: 464–467.
34. Yoshizumi M, Kurihara H, Sugiyama T, et al.: Hemodynamic shear stress stimulates endothelin production by cultured endothelial cells. Biochem Biophys Res Commun 1989; 161: 859–864.
35. Seino Y, Setsuta K, Tomita Y, Nejima J, Takano T, Hayakawa H: Increase plasma levels of interleukin-6 and myocardial stunning after coronary reperfusion therapy. Am J Cardiol 1995; 76: 718–720.
36. Ikeda U, Ohkawa F, Seino Y, et al.: Serum interleukin-6 levels become elevated in acute myocardial infarction. J Mol Cell Cardiol 1992; 24: 579–584.
37. Miyao Y, Yasue H, Ogawa H, et al.: Elevated plasma interleukin-6 levels in patients with acute myocardial infarction. Am Heart J 1993; 126: 1299–1304.
38. Gerhart W: Creatine kinase. In Methods of enzymatic analysis 3rd. (Bergmeyer HU, ed), 1983; pp 508–539, Verlag Chemie, Weinheim.
39. Wuerzburg U, Hennrich N, Orth HD, et al.: Quantitative determination of creatine kinase isoenzyme catalytic concentrations in serum using immunological methods. J Clin Chem Clin Biochem 1977; 15: 131–137.
40. Verbeke G, Molenberghs G: Lenear mixed models in practice. In A SAS-oriented Approach (Verbeke G, Molenberghs G, eds), 1997; Springer-Verlag, New York.
41. Watanabe T, Suzuki N, Shimamoto N, Fujino M, Imada A: Contribution of endogenous endothelin to the extension of myocardial infarct size in rats. Circ Res 1991; 69: 370–377.
42. Koyama H, Tabata Y, Nishizawa T, Inoue H, Morii H, Yamaji T: Plasma endothelin levels in patients with uremia. Lancet 1989; 1: 991–992.
43. Dupuis J, Schwab AJ, Simard A, et al.: Kinetics of endothelin-1 binding in the dog liver microcirculation in vivo. Am J Physiol 1999; 277 (Gastrointest Liver Physiol 40): G905–G914.
44. Saito M, Kabazawa N, Imura H: Endothelin in human disease I: essential hypertension, vasospastic angina, acute myocardial infarction and chronic renal failure. In Endothelin (Rubany GM, ed), 1992; pp 209–220, Oxford University Press, New York.
45. Finkel MS, Oddis CV, Jacob TD, Watkins SC, Hattler BG, Simmons RL: Negative inotropic effects of cytokines on the heart mediated by nitric oxide. Science 1992; 257: 387–389.
46. Takahashi A, Xin X, Cai Y, Sakai T, Matsumoto K: Stimulation of interleukin-6 production by endothelin in rat bonemarrow-derived stromal cells. Blood 1994; 84: 2231–2538.
47. Anand I, McMurray J, Cohn JN, et al.: Long-term effects of darusentan on left-ventricular remodeling and clinical outcomes in the endothelin A receptor antagonist trial in heart failure (EARTH): randomized, double-blind, placebo-controlled trial. Lancet 2004; 364: 347–354.
48. O'Connor CM, Gattis WA, Adams KF, et al.: Tezosentan in patients with acute heart failure and acute coronary syndromes. J Am Coll Cardiol 2003; 41: 1452–1457.
49. Mulder P, Richard V, Derumeaux G, et al.: Selective endothelin-A versus combined endothelin-A / endothelin-B receptor blockade in rat chronic heart failure. Circulation 1997; 96: 1976–1982.
50. Sakai S, Miyauchi T, Kobayashi M, et al.: Inhibition of myocardial endothelin pathway improves long-term survival in heart failure. Nature 1996; 384: 353–355.

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