

# Relationship Between Impaired Microvascular Function in the Non-Infarct-Related Area and Left Ventricular Remodeling in Patients With Myocardial Infarction

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**Relationship Between Impaired Microvascular Function in the  
Non-Infarct-Related Area and Left Ventricular Remodeling in Patients  
With Myocardial Infarction**

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**Abbreviations:** ACE-I, angiotensin-converting enzyme inhibitor;  
ARB, angiotensin II receptor blocker;  
ATP, adenosine triphosphate;  
CK, creatinine kinase;  
%DS, percent diameter stenosis;  
IRA, infarct-related area;  
K\*, influx rate constants;  
LVEDVI, left-ventricular end-diastolic volume index;  
MBF, myocardial blood flow;  
MFR, myocardial flow reserve;  
MI, myocardial infarction;  
MLD, minimum lumen diameter;  
NIRA, non-infarct-related area;  
PCI, percutaneous coronary intervention;  
PET, positron emission tomography;  
SD/Chord, standard deviation (from normal) per chord;  
TIMI, thrombolysis in myocardial infarction

## Structured abstract

**Background.** Myocardial flow reserve (MFR) in the non-infarct-related area (NIRA) has been reported to be impaired after the onset of myocardial infarction (MI). The aim of this study was to determine whether microvascular dysfunction in the NIRA is related to left-ventricular remodeling after MI.

**Methods.** We prospectively studied 17 patients who suffered their first single-vessel MI, and who underwent successful revascularization. The MFR in the NIRA was assessed quantitatively using  $^{13}\text{N}$ -ammonia positron emission tomography within 2 weeks after the onset. Peak creatinine kinase and the defect score on  $^{99\text{m}}\text{Tc}$ -tetrofosmin myocardial perfusion imaging were used as an index of the severity of MI. The left-ventricular end-diastolic volume index (LVEDVI) was calculated using left ventriculography at 1 month and 6 months after the onset.

**Results.** Patients with severely impaired MFR ( $< 2.09$ ) had higher peak creatinine kinase values ( $6,000 \pm 5,485$  IU/L vs.  $2,250 \pm 1,950$  IU/L,  $p = 0.0081$ ), defect scores ( $16.3 \pm 5.9$  vs.  $7.9 \pm 6.5$ ,  $p = 0.0404$ ), and LVEDVI at 1 month ( $125.6 \pm 34.4$  mL/m<sup>2</sup> vs.  $82.8 \pm 17.7$  mL/m<sup>2</sup>,  $p = 0.0036$ ) than those with mildly impaired MFR ( $\geq 2.09$ ). Moreover, the differences of LVEDVI between the 2 groups persisted over 6 months ( $133.3 \pm 43.6$  mL/m<sup>2</sup> vs.  $89.5 \pm 17.3$  mL/m<sup>2</sup>,  $p = 0.0078$ ). The MFR in the NIRA correlated inversely with the LVEDVI at 1 month and 6 months ( $r = -0.590$ ,  $p = 0.0127$  and  $r = -0.729$ ,  $p = 0.0031$ , respectively).

**Conclusions.** These data indicate that microvascular impairment in the NIRA might have contributed to left-ventricular remodeling after MI.

## Introduction

When the myocardium is exposed to ischemia for a long period in patients with acute myocardial infarction (acute MI), dysfunction of the microcirculatory system consisting of arterioles, capillaries, and venules can hinder the restoration of adequate myocardial tissue perfusion even if the infarct-related coronary artery is sufficiently dilated. It is well known that microvascular dysfunction in the infarcted myocardium is closely related to the recovery of left-ventricular function and to left-ventricular remodeling during the chronic phase, as well as to the complications and outcome of MI [1][2][3]. Consequently, it is considered clinically important to improve microvascular function in the infarcted myocardium, as well as to achieve angiographic reperfusion by percutaneous coronary intervention (PCI).

In addition to the infarcted region, microvascular function has also been reported to be impaired after acute MI even in the non-infarcted myocardium, which is not directly supplied by the infarct-related coronary artery. Although this decrease is gradually resolved over time, there have been cases in which the response was not normalized even after 6 months [4]. Using a rat model of myocardial infarction with cardioselective overexpression of the angiotensin II type 1 receptor, de Boer, *et al.* have demonstrated that MI causes a decrease in microvessel density in regions of the non-infarcted myocardium [5]. Thus, microvascular dysfunction secondary to acute MI involves not only the infarcted myocardium, but also the non-infarcted myocardium.

However, the clinical significance of microvascular dysfunction in the non-infarcted myocardium has not been fully examined. We hypothesized that microvascular dysfunction in the non-infarcted myocardium, as well as the infarcted myocardium, might have adverse effects on cardiac function after MI. Thus, we

investigated, using adenosine triphosphate (ATP) -loaded  $^{13}\text{N}$  ammonia positron emission tomography (PET), the relationship between microvascular dysfunction in the non-infarcted myocardium and left-ventricular remodeling after MI in patients whose epicardial coronary arteries had been successfully revascularized.

## **Materials and Methods**

### **Subjects and protocol**

This study included 17 consecutive patients (12 men and 5 women with a mean age of  $66.4 \pm 11.3$  years; range: 48 to 89 years) who suffered acute MI and were successfully treated by PCI within 12 hours after the onset of symptoms, and 6 normal subjects (4 men and 2 women with a mean age of  $62.3 \pm 8.2$  years; range: 48 to 74 years) who had no clinical or echocardiographic evidence of cardiac disease. The inclusion criteria were as follows: 1) first acute MI, 2) single-vessel disease, and 3) successful recanalization by PCI (defined as  $< 25\%$  residual stenosis and thrombolysis in myocardial infarction (TIMI) flow grade 3) within 12 hours after the onset of symptoms. Myocardial infarction was confirmed by the presence of chest pain for at least 30 min, ST segment elevation of more than 0.2 mV in at least two contiguous leads, and elevation of the serum creatinine kinase level to more than three times the upper limit of normal. We excluded patients who had another cardiac event during follow-up, and those who were hemodynamically unstable at the time of the PET study.

All patients received an intravenous bolus injection of 5,000 U of heparin before angioplasty. Intracoronary isosorbide dinitrate (2 mg) was given before coronary angiography, which was performed via the femoral approach using the Judkins technique. After an additional intravenous or intra-arterial bolus injection of 5,000 U of heparin, coronary angioplasty (including rescue stenting) was performed. An angiographic criterion of  $< 25\%$  residual stenosis was used to determine the end point of the angioplasty procedure. Serum creatinine kinase (CK) was measured serially every 3 hours after recanalization, until the peak value was obtained. Patients with coronary stenting received antiplatelet treatment with ticlopidine and aspirin (both at 100 mg

twice a day). Angiotensin-converting enzyme inhibitors (ACE-I) or angiotensin II receptor blockers (ARB) were routinely administered, if not contraindicated and if well tolerated. All patients underwent follow-up angiography to examine any restenosis of the infarct-related artery and the left-ventricular volume at 1 month and 6 months after the onset. The study protocol was approved by the institutional Ethical Committee, and all patients gave their informed consent.

### **Analysis of coronary angiography and left ventriculography**

Coronary angiography and biplane left ventriculography were performed at the onset, 1 month and 6 months thereafter. Coronary stenosis (percent diameter stenosis; %DS) was measured by experienced cardiologists using a quantitative cardiovascular angiographic software program (Automated Coronary Analysis D.C.I., Phillips, Best, Netherlands). Significant stenosis was defined as luminal narrowing of > 50%. Retrograde collateral vessels were graded on a four-point scale according to the system of Cohen and Rentrop [6]. The left-ventricular silhouette was divided into seven segments according to the recommendations of the American Heart Association [7]. In order to quantify regional LV wall motion, we used the centerline method [8]. The results were expressed as the standard deviation (from normal) per chord (SD/Chord) for each segment, and the infarct-related area (IRA) was defined as the segments showing hypokinesia ( $< -1$  SD) at the onset [9], while the non-infarct-related area (NIRA) was defined as the remaining segments without wall motion abnormalities. In order to assess the extent of post-infarct left-ventricular remodeling, the left-ventricular end-diastolic volume index (LVEDVI) and the change in LVEDVI ( $\Delta$ LVEDVI) were measured with the area length method [10].



## **PET studies**

$^{13}\text{N}$ -ammonia PET scanning was performed using a whole-body PET scanner (Advance; General Electric Medical Systems, Milwaukee, WI) within 14 days after the onset, which allows simultaneous acquisition of 35 image slices with an inter-slice spacing of 4.25 mm. Patients were hemodynamically stable by the time of the PET study. Drugs that were considered to influence coronary microcirculation were withdrawn for 24 hours. A 10-min transmission scan was acquired using  $^{68}\text{Ge}/^{68}\text{Ga}$  before the emission study for attenuation correction, followed by the administration of 555-MBq (15-mCi)  $^{13}\text{N}$ -ammonia in 10 mL of saline as a slow bolus over 30 sec through an antecubital vein. A 5-min dynamic scan acquisition was started at the time of tracer administration, with frame durations of  $12 \times 10$  s,  $2 \times 30$  s, and  $2 \times 60$  s. After an interval of 50 min from the baseline scan, intravenous infusion of ATP was started at 0.16 mg/kg/min over 5 min, using an infusion pump to increase myocardial blood flow (MBF). Three minutes after the commencement of ATP infusion, the second PET scan was started with another  $^{13}\text{N}$ -ammonia injection. The PET scan protocol was identical to that of the baseline study.

The MBF images at baseline and during the ATP infusion were calculated using the Patlak plot method [11] [12]. The regions of interest were drawn in the cavity of the left ventricle using a couple of slice levels to obtain a time-activity curve for the arterial blood which was used as the arterial input function. Time frames of 30 sec to 2.5 min were generally used to calculate the influx rate constants ( $K^*$ ) in a pixel-by-pixel manner based on the dynamic data. The table-lookup method was then applied to convert  $K^*$  values into MBF. A constant recovery coefficient of 0.75 was used for the calculation of  $K^*$  with the graphical plotting method [11] [12]. On the resulting polar

maps, a seven-segment model was used to generate mean values for statistical analysis [13], in order to permit regional comparison with the corresponding left-ventriculography findings (Fig. 1). The MBF and myocardial flow reserve (MFR) in the IRA and NIRA were calculated. MFR was defined as the ratio of baseline MBF to MBF during ATP infusion.

### **<sup>99m</sup>Tc-tetrofosmin myocardial scintigraphy**

In order to examine the extent and severity of MI, <sup>99m</sup>Tc-tetrofosmin myocardial scintigraphy was performed at the same time as the PET study. We defined two nuclear variables using a 20-segment, 5-point scoring model [14]. Each segment was given the consensus score of two experienced observers using a 5-point scoring system (0 = normal, 1 = equivocal, 2 = moderate, 3 = severe reduction of tracer uptake, and 4 = absence of detectable tracer uptake). A defect score (representing the severity of MI) was obtained by adding the scores of the 20 segments on the tetrofosmin images, and an extent score (representing the extent of MI) was obtained from the total number of segments with abnormal tracer uptake.

### **Statistical analysis**

Continuous variables were expressed as means  $\pm$  standard deviation and analyzed with Student's *t*-test or the Mann-Whitney U test. Categorical variables were compared with the chi-square test or Fisher's exact test. The relationships between the continuous variables were examined by simple linear regression analysis. *P* values  $< 0.05$  were considered statistically significant. Statistical analysis was performed with StatView Ver. 5.0 software (SAS Institute, Cary, North Carolina).

## **Results**

### **Baseline characteristics**

All patients had been receiving nicorandil and at least one of two drugs (ACE-I or ARB) that were considered to exert an effect on coronary microcirculation and remodeling [15][16]. The infarct-related coronary artery was the LAD in 8 patients (47%), LCX in 3 (18%), and RCA in 6 (35%). Myocardial blood supply was restored 404 min (average) after infarction, indicating that reperfusion occurred relatively early in many patients. The mean peak CK value was  $3,353 \pm 3,638$  IU/L. After PCI, reperfusion was poor in one patient, resulting in a transient slow-flow phenomenon with recurrence of ST-segment elevation, decrease in blood pressure, and the onset of ventricular arrhythmia. Eventually, PCI restored satisfactory TIMI grade 3 coronary flow in every patient. Stenting was performed in 13 (76%) of the 17 patients. After PCI, the %DS was  $11.6 \pm 13.5\%$  and the minimum lumen diameter (MLD) was  $2.59 \pm 0.67$  mm, suggesting that the infarct-related arteries were adequately dilated. At the follow-up angiography 24 days after PCI, no progression of coronary stenosis was noted in any patient; the %DS was  $14.3 \pm 15.3\%$  and MLD was  $2.49 \pm 0.66$  mm (Tables 1 and 2).

### **Comparison of MBF and MFR between IRA and NIRA**

In the 17 patients, a total of 119 myocardial segments (47 infarcted and 72 non-infarcted) were studied.

In the IRA, the mean resting MBF was  $0.62 \pm 0.25$  mL/min/g, and that during ATP infusion was  $1.19 \pm 0.63$  mL/min/g. These two values were significantly lower than the corresponding values of the NIRA, which were  $0.73 \pm 0.26$  and  $1.56 \pm 0.75$  mL/min/g,

respectively ( $p = 0.0017$  and  $0.0004$ ) (Fig. 2). The mean MFR of the IRA was also significantly lower than that of the NIRA ( $1.73 \pm 0.40$  vs.  $2.01 \pm 0.53$ ,  $p = 0.0006$ ; Fig. 3), which was lower than that of the normal subjects ( $2.01 \pm 0.53$  vs.  $3.03 \pm 0.63$ ,  $p = 0.027$ ; Fig. 3).

### **The relationship between MFR in the NIRA and the severity of infarction**

When we defined 2.09 as normal lower limit of MFR in the NIRA (the mean MFR minus 1.5 standard deviation of the normal subjects), the patients were divided into 2 groups: Group-S consisted of patients with severe microvascular dysfunction in the NIRA ( $MFR < 2.09$ ;  $n = 5$ ), and Group-M consisted of patients with mild microvascular dysfunction in the NIRA ( $MFR \geq 2.09$ ;  $n = 12$ ). The 2 groups of patients did not differ from each other in terms of treatment with statins and  $\beta$ -blockers, time of reperfusion after MI, frequency of left anterior descending artery disease, values of left-ventricular end-diastolic pressure or prevalence of risk factors (Table 3). Group-S had a significantly higher LVEDVI at 1 month ( $125.6 \pm 34.4$  vs.  $82.8 \pm 17.7$  mL/m<sup>2</sup>,  $p = 0.0036$ ),  $\Delta$ LVEDVI ( $19.6 \pm 12.7$  vs.  $-9.9 \pm 7.9$  mL/m<sup>2</sup>,  $p = 0.0003$ ), peak CK ( $6,000 \pm 5,485$  vs.  $2,250 \pm 1,950$  IU/L,  $p = 0.0081$ ), and defect score on tetrofosmin myocardial scintigraphy ( $16.3 \pm 5.9$  vs.  $7.9 \pm 6.5$ ,  $p = 0.0404$ ) compared with Group-M, and the ejection fraction of Group-S tended to be lower than that of Group-M ( $48.8 \pm 11.9$  vs.  $60.6 \pm 12.8\%$ ,  $p = 0.099$ ) (Table 3).

### **The relationship between MFR in the NIRA and left-ventricular remodeling**

At the follow-up, there was a significant negative correlation between MFR in the NIRA and LVEDVI at 1 month ( $r = -0.590$ ,  $p = 0.0127$ ; Fig. 4) and 6 months ( $r = -0.729$ ,

$p = 0.0031$ ), as well as between MFR in the IRA and LVEDVI at 1 month ( $r = -0.627$ ,  $p = 0.0070$ ; Fig. 4). In addition, immediately after PCI, the two groups showed no difference in LVEDVI. In the Group-S patients, however, the LVEDVI at 1 month was significantly increased compared with that immediately after PCI ( $125.6 \pm 34.4 \text{ ml/m}^2$  vs.  $102.3 \pm 26.4 \text{ ml/m}^2$ ,  $p = 0.0189$ ), and was significantly higher than in the Group-M patients ( $125.6 \pm 34.4 \text{ ml/m}^2$  vs.  $82.8 \pm 17.7 \text{ ml/m}^2$ ,  $p = 0.0036$ ). Moreover, the differences of LVEDVI between the 2 groups persisted over 6 months ( $133.3 \pm 43.6 \text{ ml/m}^2$  vs.  $89.5 \pm 17.3 \text{ ml/m}^2$ ,  $p = 0.0078$ ; Fig. 5).

## **Discussion**

All of the patients in this study attained reperfusion relatively early after the onset of single-vessel MI, and had excellent TIMI grade 3 coronary flow following PCI. About 1 month after PCI, however, the increase in LVEDVI was significantly greater in the Group-S patients compared with the Group-M patients. Thus, the extent of the decrease in the vasodilator response in the non-infarcted region was significantly related to the left-ventricular volume during the chronic phase. It is quite reasonable to speculate that the decreased vasodilator response of microvessels, not only in the infarcted myocardium but also in the non-infarcted myocardium, is one of the factors responsible for left-ventricular remodeling. In the Group-S patients, parameters that reflect the severity of the infarction, including the defect score on tetrofosmin myocardial scintigraphy and the peak CK value, were significantly increased and left-ventricular remodeling was advanced in the chronic phase.

### **Microvascular dysfunction in the non-infarcted myocardium in patients with acute MI**

There have been several reports on the hemodynamics of the microcirculation in the non-infarcted myocardium of acute MI patients. Uren, *et al.* have performed an O-15 water PET study [4] and found that the coronary vasodilator response was decreased even in the non-infarcted myocardium, with the decrease being persistent and not normalized even after 6 months. According to the coronary angiography study conducted by Gibson, *et al.* [17], after the stenotic coronary artery was successfully dilated by PCI, the corrected TIMI frame count of the non-infarct-related coronary artery was comparable to that of the infarct-related artery, and the coronary blood flow

decreased by 45% from normal. Thus, microvascular dysfunction has been reported to occur globally in patients with acute MI, irrespective of whether the myocardium is infarcted or not. These reports agree with our findings demonstrating microvascular damage in the remote myocardium soon after MI, a phenomenon related to the severity of the infarction. In our patients, the MFR of the non-infarcted myocardium was only 2.02 on average, and lower than that determined by PET in normal subjects (3.03 on average), although the myocardium was normal and not supplied directly by the infarct-related coronary artery. In patients with diabetes, hyperlipidemia or smoking, microvascular function is impaired due to oxidative stress, so the blood flow reserve is decreased even in the absence of coronary disease [18][19][20][21]. It is possible that the vasodilator response was abnormal in the remote myocardium because our patients had had some risk factors before acute MI occurred. In the patients with lower MFR levels, however, myocardial infarction itself should have affected the microcirculation in the remote myocardium, because the peak CK and the defect score determined by tetrofosmin myocardial scintigraphy were significantly higher in the Group-S patients.

Several studies have demonstrated that  $\beta$ -blockers have anti-remodeling effects on the left ventricle in patients with chronic heart failure [22]. It has been reported that metoprolol is associated with a significant increase in coronary flow reserve (= increased supply) and the reduction in oxygen consumption (= decreased demand) in patients with coronary artery disease. This reduction in coronary vascular resistance can be explained by a diminution of extravascular compressive forces either due to a reduced filling pressure or a decrease in myocardial contractility with a reduction in vascular tone [23]. In our study, there were no significant differences between the 2 groups of patients in terms of treatment with  $\beta$ -blockers and the values of left-ventricular end-diastolic

pressure after PCI. On the other hand, experimental study has shown that the effects of  $\beta$ -blocker, bisoprolol on left ventricular remodeling after MI strongly depend on infarct size and timing of treatment [24]. Koepfli P, et al. has reported that  $\beta$ -blockers predominantly improve coronary flow reserve in stenosis-dependent rather than remote segments in coronary artery disease [25]. Thus, the effects of  $\beta$ -blockers on remote myocardium after MI still remain controversial.

### **Possible mechanism of microvascular dysfunction in the non-infarcted myocardium**

There are several reports explaining microvascular dysfunction in the non-infarcted myocardium. In a dog model of myocardial infarction (proximal occlusion of the left anterior descending coronary artery), focal necrosis (micro-infarcts) occurred in the remote myocardium [26][27]. It has been suggested that such infarction of the remote myocardium may occur as part of more extensive necrosis, because the microvascular system is shared between regions of infarcted and non-infarcted myocardium or as a result of vasoconstriction mediated by local neurohumoral reflexes. In a transgenic rat model of myocardial infarction with cardioselective overexpression of the angiotensin II type 1 receptor, the microvessel density decreased in the non-infarcted myocardium [5] independently of myocardial hypertrophy and expression of the vascular endothelial growth factor, suggesting that the activation of the renin-angiotensin system after infarction directly causes microvascular dysfunction in the remote myocardium. In patients undergoing PCI after acute MI, administration of an  $\alpha$ -blocker (phentolamine) improved flow through non-infarct-related arteries and fractional shortening of non-infarcted myocardium [28]. Experimental studies have



shown that acute coronary occlusion activates intercoronary reflexes that increase alpha-adrenergic activity to remote regions perfused by normal coronary arteries [29][30][31][32], and this phenomenon could represent an explanation for reduced MFR. These reports indicate that neural mechanisms might be involved in the suppression of microcirculatory blood flow in the remote myocardium and in left-ventricular dysfunction. Other studies suggest that focal myocardial damage may result in deranged glucose metabolism in remote myocardium [33][34]. The fact that metabolic abnormalities may be present in remote areas as a consequence of the greater compensatory contractility imposed on these regions is considered [35][36]. Such a phenomenon has been demonstrated in aerobic myocardium remote from the ischemic/necrotic area, both in experimental [37] and human models [38][39].

Although we could not clarify the mechanisms that caused microvascular dysfunction in the remote myocardium, the existence of a relationship between remote microvascular dysfunction and cardiac function after MI was demonstrated in this study. To the best of our knowledge, this is the first clinical study to demonstrate the existence of a relationship between microvascular dysfunction in the non-infarcted myocardium and the extent of left-ventricular remodeling in patients with acute MI. At present, the intravenous or intracoronary injection of adenosine or nicorandil [15][40][41] and the prevention of distal embolization using a distal protection device during PCI [42] are considered to lead to a better outcome through the improvement of microvascular dysfunction in the infarcted myocardium. Based on the present data, we speculate that a therapy achieving global improvement of myocardial microvascular dysfunction is necessary to enable better cardiac function after MI. Furthermore, the use of PET for non-invasive quantification of the severity of microvascular dysfunction in the infarcted

and the non-infarcted myocardium during the subacute phase after MI should allow the prediction of subsequent left-ventricular function and remodeling, thus providing us with additional information for designing therapies.

### **Limitations**

The results of this study should be considered in light of their limitations. First, the number of patients enrolled in our study was small, so a study consisting of a larger number of patients is needed in the future. Second, we could not clarify whether microvascular dysfunction in the remote myocardium after MI was a cause or a result of cardiac dysfunction. It has been reported that the MFR improved with time after MI, although it remained subnormal during the chronic phase [4][43]. In order to determine whether microvascular dysfunction is the cause or result, <sup>13</sup>N-ammonia PET should be followed to clarify the changes in MFR over time in patients with and without left-ventricular remodeling. Third, we defined significant stenosis as luminal narrowing of >50%. Reduced coronary flow reserve in subjects with normal coronary arteries has been reported, and is dependent on the existence of coronary risk factors and the degree of endothelial dysfunction [18][19][20][21][44]. However, Gould KL, et al. has reported that maximal hyperemic coronary flow begins to decrease in coronary arteries with >50% luminal diameter stenosis [45].

## **Conclusions**

In patients with acute MI, microvascular dysfunction was noted not only in the infarcted myocardium but also in the non-infarcted myocardium after reperfusion. The extent of this dysfunction was dependent on the severity of the MI and might have contributed to left-ventricular remodeling after the MI.

## **Acknowledgements**

We are grateful to Mr. Katsuya Sugimoto and the rest of the cyclotron staff for their technical assistance. We also thank the technical and nursing staff of our cardiac catheterization laboratory and coronary care unit for their skillful assistance.

**Table 1.** Baseline Characteristics of Patients (n = 17)

<b>Characteristic</b>	
Age,y	66.4 ± 11.3
Male (%)	12 (71)
Risk factors (%)	
Hypertension	10 (59)
Diabetes mellitus	6 (35)
Hyperlipimедia	7 (41)
Smoking	11 (65)
Medications (%)	
Asprin	17 (100)
Nicorandil	17 (100)
ACE-I or ARB	17 (100)
Statins	5 (29)
Culprit lesions (%)	
Left anterior descending	8 (47)
Left circumflex	3 (18)
Right coronary artery	6 (35)
Elapsed time, min	404 ± 281
Peak CK, IU/L	3353 ± 3638

ACE-I, angiotensine converting enzyme inhibitor;

ARB, angiotensine II receptor blocker; CK, creatinine kinase

**Table 2.** Cardiac catheterization findings

	After PCI	Follow up (1 month)
Collateral flow (Rentrop grade < 1) (%)	1 (6)	17 (100)
TIMI flow grade (%)		
Grade 0	0 (0)	0 (0)
Grade 1	0 (0)	0 (0)
Grade 2	0 (0)	0 (0)
Grade 3	17 (100)	17 (100)
Rescue stenting (%)	13 (76)	1 (6)
Residual stenosis		
%DS, %	11.6 ± 13.5	14.3 ± 15.3
MLD, mm	2.59 ± 0.67	2.49 ± 0.66
ST re-elevation (%)	1 (6)	
Left ventricular ejection fraction, %	46.4 ± 11.8	57.1 ± 13.4 *
LVEDVI, ml/m <sup>2</sup>	94.3 ± 18.8	95.4 ± 30.2

TIMI, thrombolysis in myocardial infarction; %DS, %diameter stenosis;

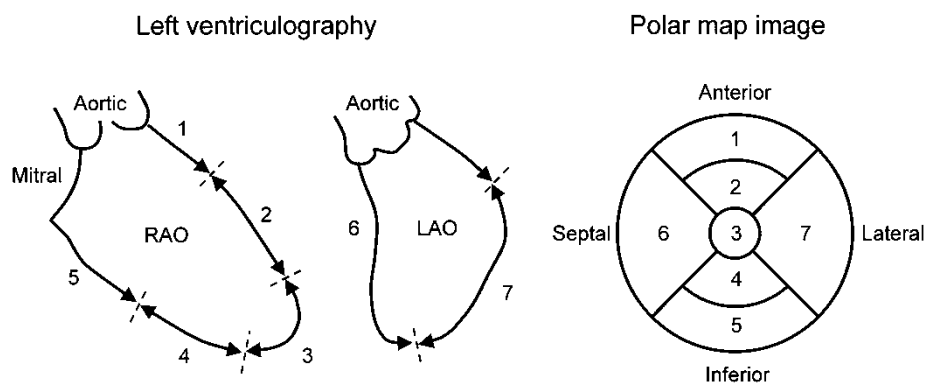
MLD, minimal lumen diameter; LVEDVI, left ventricular end-diastolic volume index;

\*p < 0.05 vs. After PCI.

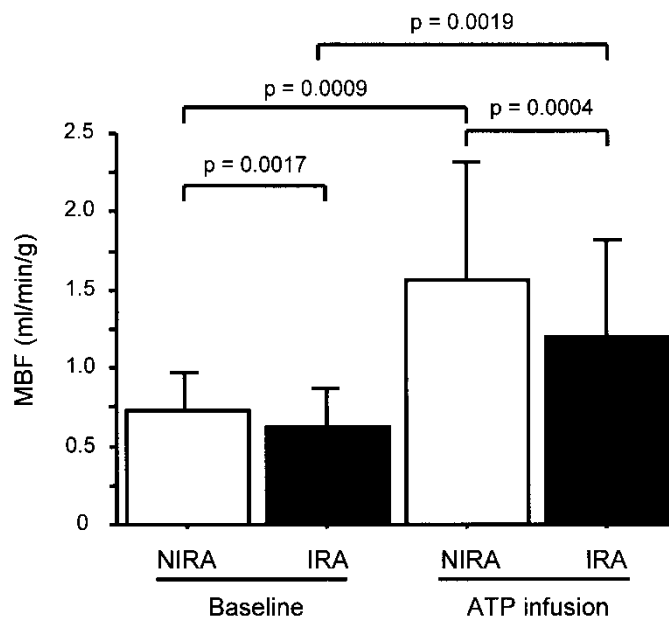
**Table 3.** Comparison of clinical variables (Cut-off MFR of 2.09 in the NIRA)

	Group S (MFR < 2.09)	Group M (MFR ≥ 2.09)	p value
Number of patients	5	12	
Elapsed time, min	383 ± 266	411 ± 299	0.8659
Culprit vessel (LAD)	3	5	0.6199
Diabetes mellitus	2	4	0.7933
Hyperlipidemia	4	3	0.1007
Smoking	4	4	0.1312
Peak CK, IU/l	6000 ± 5485	2250 ± 1950	0.0081
Rest MBF in IRA, l/min/g	0.499 ± 0.222	0.675 ± 0.223	0.158
SD/Chords in IRA at follow up, %	-2.70 ± 0.98	-1.62 ± 1.23	0.1014
LV ejection fraction at follow up, %	48.8 ± 11.9	60.6 ± 12.8	0.099
LV end-diastolic pressure, mmHg	17.0 ± 9.0	14.5 ± 4.9	0.5804
LVEDVI at follow up, ml/m <sup>2</sup>	125.6 ± 34.4	82.8 ± 17.7	0.0036
ΔLVEDVI, ml/m <sup>2</sup>	19.6 ± 12.7	-9.9 ± 7.9	0.0003
Tc-TF extent score	7.5 ± 2.4	4.3 ± 3.1	0.0786
Tc-TF defect score	16.3 ± 5.9	7.9 ± 6.5	0.0404

NIRA, non-infarct-related area; IRA, infarct-related area; MFR, myocardial flow reserve; LAD, left anterior descending artery; MBF, myocardial blood flow; CK, creatinine kinase; LVEDVI, left ventricular end-diastolic volume index; Tc-TF, technetium-tetrofosmin



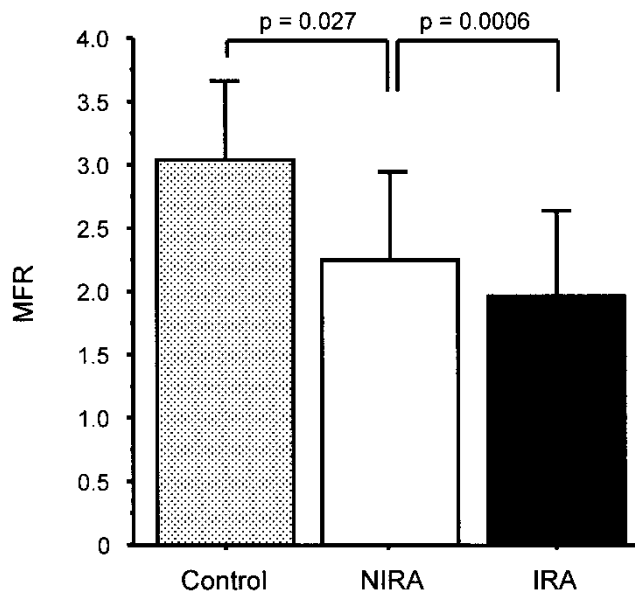
**Figure 1.** Schematic representation of the tomographic segments. On the resulting polar maps, a seven-segment model was used to generate mean values for statistical analysis, in order to permit regional comparison with the corresponding left-ventriculography findings.



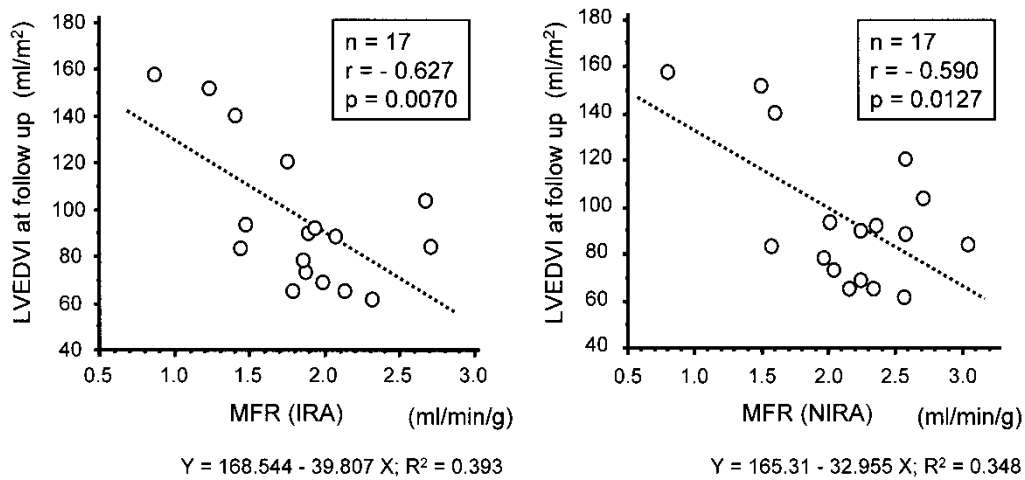
**Figure 2.** Comparison of myocardial blood flow in the IRA and NIRA. In the IRA, the mean resting MBF and that during ATP infusion were significantly lower than the



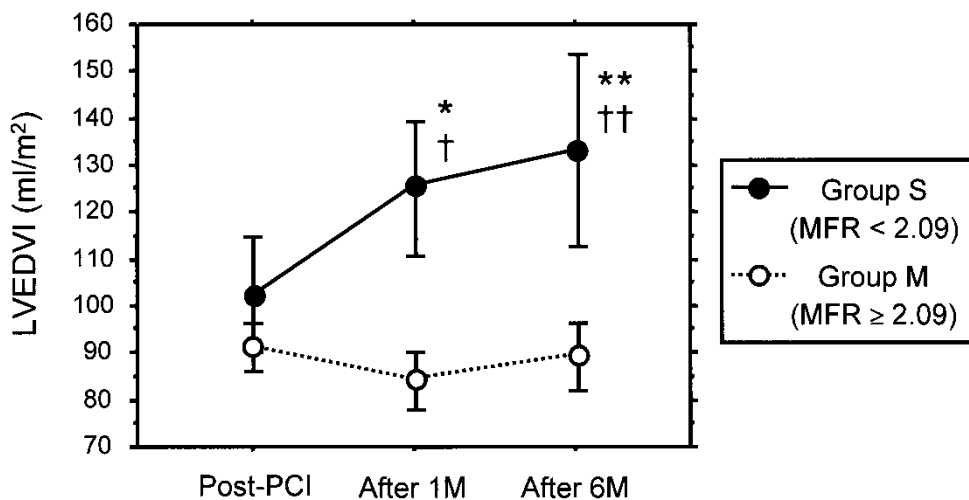
corresponding values for the NIRA.



**Figure 3.** Comparison of myocardial flow reserve in the IRA and NIRA. The mean MFR of the IRA was also significantly lower than that of the NIRA, which was lower than that of the normal subjects.



**Figure 4.** Correlation between MFR in the two areas and the follow-up LVEDVI (1 month). There was a significant negative correlation between LVEDVI and MFR in the NIRA ( $r = -0.590$ ,  $p = 0.0127$ ), as well as between LVEDVI and MFR in the IRA ( $r = -0.627$ ,  $p = 0.0070$ ).



**Figure 5.** Change in LVEDVI between post-PCI and follow-up in patients with severe microvascular dysfunction in the NIRA (Group S; MFR < 2.09, black circles), and with

mild microvascular dysfunction in the NIRA (Group M; MFR  $\geq$  2.09, white circles). In the Group-S patients, the LVEDVI at 1 month was significantly higher compared with that immediately after PCI and was significantly higher than in the Group-M patients. Moreover, the differences of LVEDVI between the 2 groups persisted over 6 months. Data were expressed as means  $\pm$  standard error.

\*  $p = 0.0189$  vs. post-PCI; \*\*  $p = 0.0326$  vs. post-PCI, †  $p = 0.0036$ , ††  $p = 0.0078$  between the two groups.

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