

Impact of endothelial dysfunction on left ventricular remodeling after successful primary coronary angioplasty for acute myocardial infarction —Analysis by quantitative ECG-gated SPECT—

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Background: We hypothesized that endothelial cell integrity in the risk area would influence left ventricular remodeling after acute myocardial infarction. **Patients and Methods:** Twenty patients (61 ± 8 y.o.) with acute myocardial infarction underwent ^{99m}Tc -tetrofosmin imaging in the sub-acute phase and three months after successful primary angioplasty due to myocardial infarction. All patients were administered angiotensin-converting enzyme inhibitor after revascularization. Cardiac scintigraphies with quantitative gated SPECT were performed at the sub-acute stage and again 3 months after revascularization to evaluate left ventricular (LV) remodeling. The left ventricular ejection fraction (EF) and end-systolic and end-diastolic volume (ESV, EDV) were determined using a quantitative gated SPECT (QGS) program. Three months after myocardial infarction, all patients underwent cardiac catheterization examination with coronary endothelial function testing. Bradykinin (BK) ($0.2, 0.6, 2.0 \mu\text{g}/\text{min}$) was administered via the left coronary artery in a stepwise manner. Coronary blood flow was evaluated by Doppler flow velocity measurement. Patients were divided into two groups by BK-response: a preserved endothelial function group ($n = 10$) and endothelial dysfunction group ($n = 10$). **Results:** At baseline, both global function and LV systolic and diastolic volumes were similar in both groups. However, LV ejection fraction was significantly improved in the preserved-endothelial function group, compared with that in the endothelial dysfunction group ($42 \pm 10\%$ to $48 \pm 9\%$, versus $41 \pm 4\%$ to $42 \pm 13\%$, $p < 0.05$). LV volumes progressively increased in the endothelial dysfunction group compared to the preserved-endothelial function group (123 ± 45 ml to 128 ± 43 ml, versus 111 ± 47 ml to 109 ± 49 ml, $p < 0.05$). **Conclusion:** In re-perfused acute myocardial infarction, endothelial function within the risk area plays an important role with left ventricular remodeling after myocardial infarction.

Key words: endothelial function, myocardial infarction, SPECT, ventricular remodeling, coronary flow reserve

INTRODUCTION

LEFT VENTRICULAR (LV) remodeling after myocardial infarction is a predictor of the development of overt heart failure and an important factor determining mortality.¹ Multiple factors may contribute to LV remodeling at different stages, from the time of coronary occlusion to the development of left ventricular dilatation and dys-

function.¹ Infarct size, anterior location, transmural extent of necrosis, the perfusional status of infarct-related artery, and heart failure on admission have been identified as significant predictors of LV dilatation after myocardial infarction.

In part, the endothelium appears to be a key player determining the physiological and pathological responses of the vessel wall.^{2–7} Recently, endothelial dysfunction in coronary and peripheral arteries has been shown to predict the prognosis of patients with coronary artery disease.^{2–7} However, the importance of coronary endothelial function after myocardial infarction as a predictor of early remodeling has not yet been investigated.

This study tested the hypothesis that endothelial cell

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integrity in the risk area would influence left ventricular remodeling after acute myocardial infarction.

METHODS

The study population consisted of 20 patients with first anterior acute myocardial infarction referred to our catheterization laboratory for emergency primary percutaneous coronary intervention and presented with thrombosis in myocardial infarction (TIMI) grade 0 or 1 flow at initial coronary angiography. Admission criteria included prolonged chest pain (>30 minutes), an electrocardiographic ST segment elevation >2 mV in 2 or more adjacent precordial leads, successful reperfusion therapy within 24 hours of the onset, and >3-fold increase in serum creatine phosphokinase levels. Patients were excluded for the following reasons: age >80 years, cardiogenic shock or hypotension. All patients gave informed consent, and the study was approved by the Committee on Human Investigation at our institutions.

All patients underwent cardiac catheterization and percutaneous coronary intervention with standard techniques. All patients obtained revascularization (patency \geq 70% and TIMI 3 flow) and hemodynamic stability. Patients who could not obtain <70% patency or TIMI 3 flow were excluded from the study. If required, oral nitrates, calcium antagonists, beta-blockers, or diuretics were added and continued. Aspirin and angiotensin-converting enzyme (ACE) inhibitor (Enalapril) were administered to all patients. Patients with worsening renal failure (creatinine >2.0 mg/dl) or hyperkalemia (serum potassium >5.5 mEq/dl) were excluded from the study.

^{99m}Tc-tetrofosmin single photon emission computed tomography

Resting ^{99m}Tc-tetrofosmin imaging was performed at the sub-acute phase and repeated 3 months after successful primary angioplasty for myocardial infarction in all patients. Under a resting condition, all patients received ^{99m}Tc-tetrofosmin at a dose of 240 MBq intravenously. A three-headed rotating gamma camera (GCA-9300 A/DI, Toshiba Medical) equipped with a low-energy, high resolution collimator and a medical image processor GMS-5500 A/DI (Toshiba Corporation, Tokyo) was employed for image processing.⁸ The gamma camera rotated, collecting 60 projections over 360°. The projection data were reconstructed into 64 × 64 matrix images using the filtered back projection method with a Butterworth filter (order 8, cut-off 0.25 cycles/pixel) and a ramp filter. For gating, 16 frames per cardiac cycle with a re-fixed RR interval and a 15% window were used.

In data analysis the QGS program, previously described and validated by Germano et al.,³ was applied to process short-axis tomograms to determine LVEF and end-systolic and end-diastolic volume (ESV, EDV).⁹ To assess the reproducibility of the technique, 20 studies

were selected and processed (including manual tomographic reconstruction and reorientation) by a second observer, who had no knowledge of the initial results. There was a good correlation between the first observer's and the second observer's calculations of LVEF (correlation coefficient $r = 0.996$, $p = 0.0001$), EDV ($r = 0.998$, $p = 0.0001$) and ESV ($r = 0.998$, $p = 0.0001$).

SPECT image interpretation

The left ventricle was divided into 13 segments (6 in basal short-axis view, 6 in mid-short axis view, and one apical segment on vertical long axis view). A 4-point scoring system by visual interpretation (3, normal; 2, mildly reduced; 1, severely reduced; 0, no activity).⁵ Summed perfusion score was defined as the sum of the score in each segment. All studies were evaluated by consensus between 2 experienced observers.

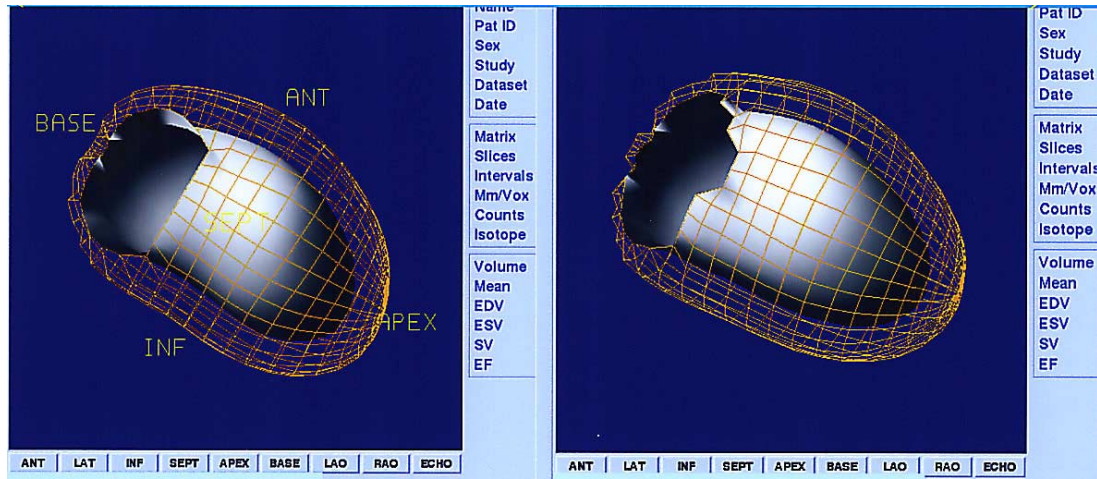
Coronary endothelial function

Three months after myocardial infarction, subjects without restenosis underwent coronary endothelial function testing. A 0.014-inch Doppler-tipped guidewire (FloWire, Cardiometrics Inc., Mountain View, California) was advanced to the proximal segment of the left anterior descending (LAD) coronary artery to measure the coronary diameter as previously reported.⁴ All drugs were infused directly into the left main coronary artery via the guide catheter at infusion rates ranging between 0.5 and 1 ml/min. Baseline coronary diameter measurement and coronary angiography were performed and were confirmed to be unchanged by a 2-min infusion of saline at 1 ml/min. Bradykinin (BK) was started at 0.2 mg/min then increased to 0.6 and 2.0 μ g/min for at 2-min intervals. During infusion of BK, coronary blood flow velocity reached a peak at about 60 seconds and maintained a plateau by 60 seconds. Subjects who developed restenosis at 3 months were excluded from the study.

Quantitative coronary angiography and measurement of coronary blood flow

Coronary cineangiograms were recorded using a Philips cineangiographic system (Philips Medical Systems, Tokyo, Japan). Change in diameter of the left anterior descending coronary artery was measured in a vessel segment 5 mm beyond the tip of the Doppler wire. Coronary angiograms were analyzed by quantitative coronary angiography using the Cardiovascular Measurement System (CMS-MEDICS Medical Imaging Systems, Leiden, Netherlands). Peak coronary blood flow velocity was continuously monitored using a fast Fourier transform-based spectral analyzer (FloMap, Cardiometrics Inc.). Coronary blood flow was derived from coronary blood flow velocity and diameter measurements by the formula: $0.125\pi \times \text{averaged peak coronary blood flow velocity} \times (\text{arterial diameter})^2$.⁴ We calculated % coronary blood flow (CBF), as defined by $100 \times \text{CBF}/\text{basal CBF}$.

Case 72-year-old male
(an endothelium functional disorder)



14 days after MI

90 days after MI

Fig. 1 QGS images of a 72-year-old male with myocardial infarction. LV image 14 days after myocardial infarction (MI) on the left, 90 days after MI on the right. The patient demonstrated severe endothelial dysfunction.

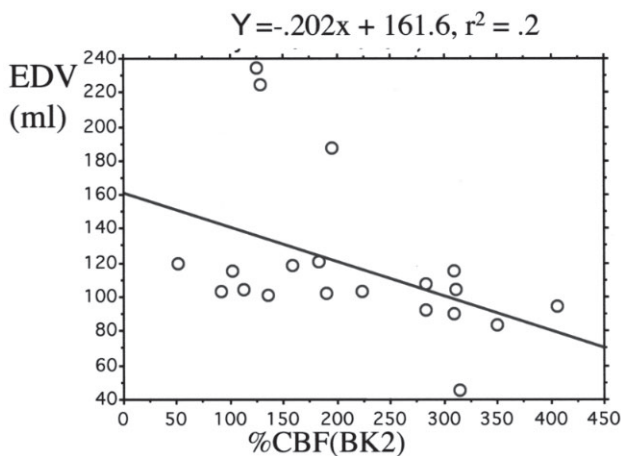


Fig. 2 Correlation between coronary blood flow increase by bradykinin and end-diastolic volume (EDV).

Statistical analysis

All values are presented as mean values \pm standard deviation. Scheffé's F test for multiple comparisons was applied to detect significant differences as defined by ANOVA. Linear regression analysis was used to determine the correlation between LVEF by QGS and LVEF by LVG. Using the unpaired t-test, variables were compared between patients with or without cardiac events (cardiac death and hospitalization due to angina pectoris or severe arrhythmia). Categorical data were compared using the chi-squared test. Student's t-test was used for comparison of paired data and p values less than 0.05 were considered significant.

Table 1 Baseline clinical characteristics of the study population

	Preserved Endothelial Function n = 10	Endothelial Dysfunction n = 10	p
Age	63 \pm 10	59 \pm 8	NS
Males	9	8	NS
Diabetes	3	4	NS
Hypertension	4	6	NS
Hyperlipidemia	4	6	NS
Smoker	4	7	NS
Symptom-to-balloon time	199 \pm 61	278 \pm 71	NS
Peak CK, IU//l	3314 \pm 1044	3623 \pm 1433	NS
ACEIs at discharge	10	10	NS
Oral nitrate	7	7	NS
Diuretics	3	4	NS
Ca ²⁺ antagonist	3	2	NS
β blockers	4	4	NS
Collateral (grade \geq 2)	2	1	NS
Multivessel CAD	4	5	NS
LVEF (%)	42 \pm 10	41 \pm 4	NS
EDV (ml)	111 \pm 47	123 \pm 45	NS
ESV (ml)	66 \pm 34	72 \pm 44	NS

CK; creatine phosphokinase, ACEI; angiotensin-converting enzyme inhibitor, CAD; coronary artery disease, NS; no significance. LVEF; left ventricular ejection fraction, EDV; end-diastolic volume, ESV; end-systolic volume.

RESULTS

Twenty consecutive patients who met entry criteria were enrolled. The patients were divided by the median value

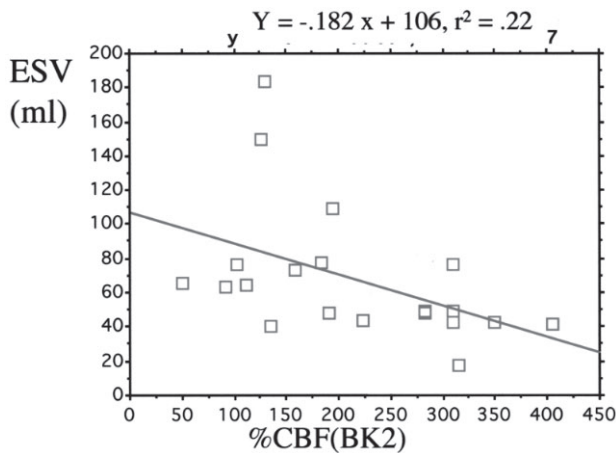


Fig. 3 Correlation between coronary blood flow increase by bradykinin and end-systolic volume (ESV).

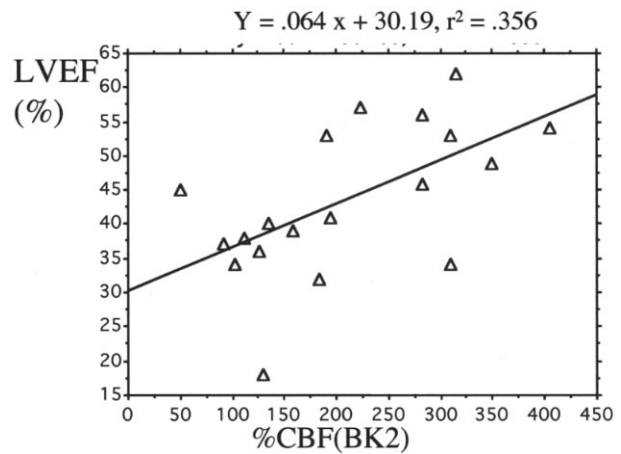


Fig. 4 Correlation between coronary blood flow increase by bradykinin and ejection fraction of the left ventricle (LVEF).

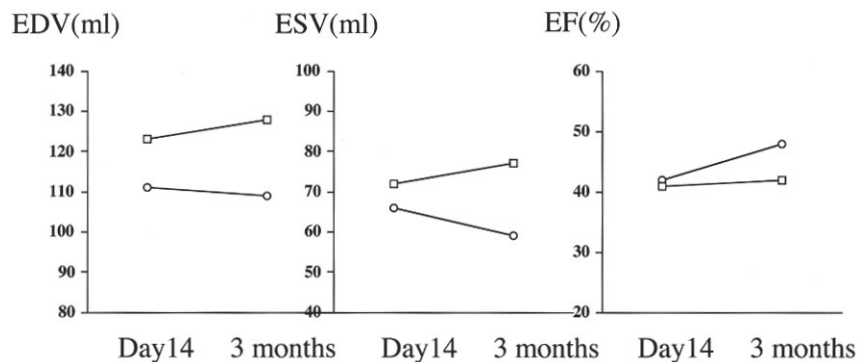


Fig. 5 Consecutive changes in left ventricular function after myocardial infarction. Open square indicates mean value of endothelial dysfunction group. Open circle indicates mean value of preserved endothelial group. A significant improvement in LV ejection fraction was observed in the preserved endothelial group on comparison of baseline findings with those on 3-month follow-up ($p < 0.05$).

of the CBF response by BK (mean value; $209 \pm 23\%$) into two groups: Endothelial dysfunction group (ED group) and Preserved endothelial function group (PE group). Baseline clinical characteristics of the two groups are shown in Table 1. There was no difference in acute to subacute therapy between the two groups, including ACE inhibitors and β blockers. A representative patient with endothelial dysfunction who had myocardial infarction is shown in Figure 1.

No major complications occurred during the procedure or during the hospital period in any patient.

Correlation with Left Ventricular Function

On overall analysis of 20 patients who underwent left ventriculography, the resting LVEF on technetium-gated SPECT showed a good linear correlation with LVEF on ventriculography, with coefficients of $r = 0.67$ ($p < 0.01$). A good correlation was obtained between EDV measured by QGS and EDV measured by LVG ($r = 0.88$, $p < 0.01$).

There was a good correlation between ESV by QGS and ESV by LVG ($r = 0.85$, $p < 0.01$).

Myocardial Perfusion and Baseline Characteristics

Twenty patients who met entry criteria were enrolled. There were no significant differences between ED group and PE group in terms of gender distribution or coronary risk factors. At the baseline, both global function and LV systolic and diastolic volumes were similar in both groups (Table 1). There was no significant difference in the summed perfusion score between ED group and PE group (29 ± 1 vs. 29 ± 1 , $p = \text{NS}$).

Relation of Endothelial Dysfunction to LV Functional Parameters at 3-Month

A significant inverse correlation was found between the LV end-diastolic volume and response by bradykinin ($r^2 = 0.2$, $p = 0.048$) (Fig. 2). Similarly, there was a direct relation between 3-month LV systolic volumes and coro-

nary blood flow response to bradykinin ($r^2 = 0.22$, $p = 0.038$) (Fig. 3). There was a significant correlation between the LV ejection fraction and response by bradykinin ($r^2 = 0.356$, $p = 0.0055$) (Fig. 4).

Time Course Changes in Global Ventricular Function and LV Volumes

Serial scintigraphic examination from baseline to 3 months were examined in all subjects, as shown in Figure 5. A significant improvement in LV ejection fraction was observed in PE group on comparison of baseline findings with those on 3-month follow-up (from $42 \pm 10\%$ to $48 \pm 9\%$, $p < 0.05$), whereas there was no significant improvement found in ED group ($41 \pm 4\%$ to $42 \pm 13\%$). Systolic and diastolic LV volumes progressively increased in ED group patients from baseline to 3 months (from 123 ± 45 ml to 128 ± 43 ml, $p = 0.012$, from 72 ± 44 ml to 77 ± 43 ml, $p = 0.012$). In PE group patients, systolic and diastolic volumes did not change significantly (from 111 ± 47 ml to 109 ± 49 ml, $p = 0.37$, from 66 ± 34 ml to 59 ± 35 ml, $p = 0.051$).

DISCUSSION

This study demonstrates that impaired endothelial function is related to the degree of LV remodeling after successful revascularization in patients with first acute myocardial infarction.

QGS for measurement of LV function

Germano et al. developed an automatic algorithm for ECG-gated SPECT to assess left ventricular function.⁹ The addition of gating to routine myocardial perfusion SPECT provides accurate and reproducible information on left ventricular function at rest and after exercise. ^{99m}Tc gated SPECT may provide regional and global functional parameters including EDV and ESV as well as LVEF without extra cost.¹⁰

Mechanisms of LV remodeling

The possible mechanisms that underlie dysfunction in the infarcted and peri-infarcted region include changes in mechanical load that lead to cellular hypertrophy and dysfunction, reduced coronary reserve and increased systolic wall stress and oxidative stress and inflammation.^{11–14} Furthermore, statin treatment may exert beneficial effects after myocardial infarction in an eNOS-dependent way.¹⁵ The endothelium appears to be a key player in determining the physiological and pathological responses of the vessel wall.^{4–7} The coronary vasodilator response to BK can also be measured in the catheterization laboratory, and this procedure is now an accepted method of assessing endothelium-dependent vasomotor function.^{4,7} Bradykinin is a vasoactive polypeptide that regulates the resting tone and flow-mediated vasodilatation of the coronary artery. It is known that BK causes

endothelium-dependent vasodilation through the production of nitric oxide (NO), prostacyclin and endothelium-derived hyperpolarizing factor (EDHF) through the BK2 receptor in the human coronary artery.^{4,7} It was reported that endothelium-derived NO regulates coronary vasomotor tone and myocardial perfusion abnormalities in failing ventricles.⁷ Angiotensin-converting enzyme (ACE) inhibitors improve endothelial function through an increase in NO bioavailability, by an increase in NO production and a decrease in NO inactivation.¹⁶ ACE inhibitors have a favorable effect on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction.^{16,17} The results of this study suggest that the preservation of endothelial function is a principal mechanism mediating the clinical outcome after myocardial infarction, and represents an important therapeutic target.

A limitation of the automated quantification algorithm in tracking myocardial edges might contribute to underestimation of LVEF. This study included only a few patients with akinetic or dyskinetic wall motion abnormalities. QGS software allows automatic edge contouring even in the absence of perfusion using smoothness, the isocontours of the coordinate system and the geometry of the defect boundaries as constraints. However, care must be taken in evaluating such lesions as a limitation of this study. LV remodeling was shown to be regulated by multiple factors, including symptom-balloon time, therapeutic factors and coronary risk factors. Further study is needed to elucidate the determinants of LV remodeling in a large number of subjects.

In reperfused acute myocardial infarction, endothelial function within the risk area may play an important role in left ventricular remodeling after myocardial infarction. Based on these observations, restoration of the functional integrity of the coronary microvasculature may represent the ultimate therapeutic goal in patients with acute myocardial infarction.

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