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Significance of Low-Dose Dobutamine Stress Echocardiography for the Prediction of the Long-Term Prognosis for Patients With Acute Myocardial Infarction

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Abstract

Objectives. Detection of stunned myocardium using low-dose dobutamine stress echocardiography is a good predictor of improvement of cardiac function in patients with acute myocardial infarction during short hospital stays. The present study evaluated the detection of stunned myocardium as a predictor of the long-term prognosis for patients with acute myocardial infarction.

Methods. One hundred and two patients (83 males, 19 females, mean age 61.5 years) with initial myocardial infarction underwent successful reperfusion therapy (direct percutaneous transluminal coronary angioplasty or stent) in the acute stage. Within 7 days, low-dose dobutamine was administered by intravenous drip and improvement of wall motion of the infarct area was evaluated by echocardiography. The patients were divided into two groups, the viable group that showed one grade or more improvement (61 patients), and the non-viable group that showed no improvement (41 patients). These groups were compared to determine the differences in clinical findings such as remodeling of the left ventricle measured by two-dimensional echocardiography, physical work capacity during serial multi-step exercise testing, and the prognosis.

Results. The viable group showed greater improvement in hemodynamics and wall motion of the infarct areas than the non-viable group. After discharge, the physical work capacity was significantly increased and there was no recognizable enlargement of the left ventricle in the viable group. No sudden cardiac death or heart failure occurred in the viable group, in contrast to incidences of 6% and 9%, respectively, in the non-viable group. Unstable angina and nonfatal re-infarction occurred more frequently in the viable group.

Conclusions. The presence of stunned myocardium is a predictor of the prognosis for patients with acute myocardial infarction.

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Key Words

■**Myocardium (stunned, viability)** ■**Stress echocardiography (low-dose dobutamine)**
■**Myocardial infarction, treatment (acute)** ■**Prognosis**

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INTRODUCTION

Selection of the optimum treatment in the acute and chronic stages of myocardial infarction requires accurate assessment of the condition of individual patients and knowledge of the incidence of cardiac events such as sudden death, re-infarction, and heart failure. Low-dose dobutamine stress echocardiography (LDSE) is effective for identifying and evaluating hibernating myocardium in patients with acute myocardial infarction, and LDSE is an independent predictor of the prognosis[1–4]. However, most LDSE studies have only investigated the infarcted area in the acute and chronic stages after intra-coronary thrombolysis to assess the correlation between hibernating myocardium and the prognosis. Relief of ischemia is believed to result in the recovery of the hibernating myocardium and consequently improves the outcome[5–8]. We previously found that LDSE can identify stunned myocardium after successful reperfusion in the hyper-acute stage (within 6 hr) of acute myocardial infarction[9]. However, the relationship between the identification of stunned myocardium and the long-term prognosis following myocardial infarction remains unclear[10,11]. This study investigated the relationship between the detection of stunned myocardium by LDSE and the prognosis for patients with acute myocardial infarction.

SUBJECTS AND METHODS

This study included 102 patients, 83 males and 19 females (mean age 61.5 years) with initial myocardial infarction who successfully underwent reperfusion therapy in the acute stage. The infarct area was located in the anterior wall in 45 patients and in the infero-posterior wall in 47 patients. All patients showed sinus rhythm during dobutamine stress. No serious complications occurred early after infarction such as cardiogenic shock, ventricular septal perforation, or severe arrhythmias.

After obtaining informed consent, LDSE was performed within 7 hospital days (mean 4.2 days) in all patients. The patients were placed in the left lateral or semi-lateral position, and images of the left ventricle were recorded by setting the long and short axis in the parasternal and apical approach. Examination of wall motion evaluated the 16 areas included in the American Society of Echocardiography Standard[12] using five grades, from normokinesis to akinesis or dyskinesis. The blood pressure, heart rate, electrocardiography, and recording echocardiography were all monitored during dobutamine administration. Dobutamine was administered by intravenous drip at 5 μg/kg/min for 5 min and 10 μg/kg/min for 5 min, and improvement of the wall motion of the infarct area was evaluated. Two trained operators with 10 years or longer experience of echocardiography individually analyzed myocardial wall motion to determine myocardial viability. If their analyses did not agree, the analysis of another trained operator was taken into consideration. The patients were divided into two groups, the viable group (Group V) with one grade or more improvement of the wall motion, and the non-viable group (Group NV) with no improvement. Comparisons between these groups focused on the hemodynamics, remodeling of the left atrium and left ventricle, improvement of the physical work capacity, and outcome after discharge.

Serial multi-step exercise testing (Bruce's protocol) was carried out before discharge (mean 28 hospital days) and after discharge (mean 2 years). The target heart rate, ischemic changes by electrocardiography, and the appearance of severe arrhythmias and chest symptoms were employed as the discontinuation criteria. Patients with restenosis underwent further revascularization before discharge. Follow-up data were obtained from hospital records, personal communication with the patient's physician and follow-up examination such as echocardiography, coronary angiography and perfusion scintigraphy with exercise testing. After discharge, patients with suspected recurrent myocardial infarction or angina pectoris underwent myocardial perfusion scintigraphy and exercise testing for the detection of ischemia. Coronary angiography followed by revascularization was performed as required. Wall motion of the area in hospitalized and discharged patients was assessed by only echocardiography unless ischemia (hibernating myocardium) due to restenosis was identified. Changes in the wall motion of the area 1 year after discharge were assessed by echocardiography. The end-point of this study was the occurrence of cardiac events such as cardiac sudden death, angina pectoris or congestive heart failure during the long-term clinical progression after discharge. The incidence of cardiac events was assessed (mean 2.8 years follow-up).

Table 1 Clinical characteristics of the patients

	Group V	Group NV	*t*-test
Number of patients	61	41	NS
Age (yr)	61.2	62.0	NS
Sex (male/female)	48/13	35/6	NS
Infarct area (anterior, lateral/inferior, posterior)	22/39	19/22	NS
Reperfusion time (hr)	5.0	4.6	NS
Peak creatine kinase (IU/*l*)	2,133±1,452	2,955±1,732	$p<0.05$

There were no significant differences in age, sex, infarct area or reperfusion time, but there was a significant difference in peak creatine kinase between the two groups.
Group V (viable group) : Group with one grade or more improvement of the wall motion. Group NV (non-viable group) : Group with no improvement of the wall motion.

Table 2 Coronary risk factors

	Hypertension	Diabetes mellitus	Hyperlipidemia	Smoking	χ^2 test
Group V	26 (43%)	15 (26%)	31 (51%)	22 (36%)	NS
Group NV	21 (51%)	13 (32%)	24 (59%)	17 (41%)	NS

There were no significant differences in coronary risk factors such as hypertension, diabetes mellitus, hyperlipidemia or smoking between the two groups.
Explanation of the groups as in Table 1.

The unpaired *t*-test, the χ^2 test, and the Kaplan-Meier curve (Logrank, Breslow-Gehan-Wilcoxon) were used for statistical analysis. A p level of less than 0.05 was regarded as significant.

RESULTS

Clinical characteristics

The profiles of the 61 patients in Group V and the 41 patients in Group NV are shown in **Table 1**. There were no significant differences between the two groups in age, sex, infarct area or mean time until reperfusion. The peak creatine kinase in Group V was significantly lower than that in Group NV ($2,133 \pm 1,452$ vs $2,955 \pm 1,732$ IU/*l*, $p < 0.05$). Coronary risk factors are shown in **Table 2**. There were no significant differences regarding hypertension, hyperlipidemia, diabetes mellitus or smoking. All patients received angiotensin converting enzyme inhibitor, antiplatelet agent and nicolandil. Seven patients in Group V and four patients in Group NV required calcium antagonist and four patients and three patients, respectively, required β blocking agent during LDSE, with no significant difference.

Hemodynamics during dobutamine stress

The systolic blood pressure (118 vs 122 mmHg) and heart rate (62 vs 65 beats/min) in the resting state showed no significant difference between Group V and Group NV. The blood pressure and heart rate were increased to 134 and 130 mmHg, and 96 and 97 beats/min during LDSE, respectively, showing no significant differences. Palpitation and slight shortness of breath were observed during LDSE, but chest pain was not recognized. Electrocardiography detected no ischemic changes in ST requiring discontinuation. Supraventricular or ventricular extra-systole was observed in 32% and 20% of the patients in Groups V and NV, respectively, but no patients in either group developed severe arrhythmia requiring discontinuation of dobutamine stress.

Wall motion in the infarct area

Fig. 1 shows the improvement of wall motion in the infarct area. Wall motion was improved in 53 of 61 patients (87%) in Group V after 1 month, and in 58 of 61 patients (95%) after 1 year. In contrast, wall motion was improved in only 9 of 41 patients (22%) in Group NV after 1 month and 1 year. Thus, LDSE had a sensitivity of 95% and specifici-

ty of 78% for evaluating the improvement of wall motion after 1 year.

Cardiac hemodynamics

Fig. 2 compares the cardiac hemodynamics on admission and after 1 month. The mean pulmonary arterial pressure and the pulmonary capillary wedge pressure on the first hospital day in Groups V and NV were not significantly different (20.9 vs 20.6 mmHg and 15.4 vs 15.3 mmHg, respectively).

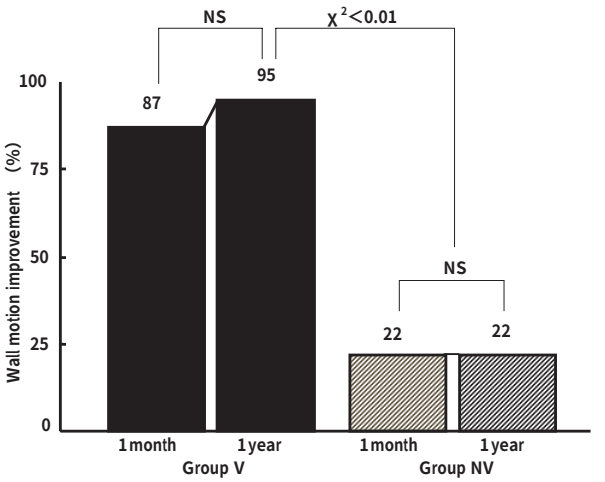

Fig. 1 Wall motion improvement in the infarct area during low-dose dobutamine stress echocardiography
Wall motion was improved significantly in Group V compared to Group NV after 1 year (95% vs 22%).
Explanation of the groups as in Table 1.

However, 1 month later, both values were significantly improved in Group V (15.3 vs 19.8 mmHg and 9.2 vs 14.2 mmHg, respectively, $p < 0.05$).

Changes in the left atrial and left ventricular diameters

Fig. 3 shows intra-group comparisons of the time-course changes in the left atrial and left ventricular diameters measured by M-mode echocardiography. The mean left atrial diameters on the first hospital day were 3.4 cm and 3.6 cm in Groups V and NV, respectively, showing no significant difference. The mean diameters were 3.7 cm and 4.2 cm after 1 month and 3.6 cm and 4.4 cm after 6 months, respectively. The mean left atrial diameter was significantly increased in Group NV ($p < 0.01$).

The mean left ventricular diameters on the first hospital day were 4.7 cm and 5.0 cm in Groups V and NV, respectively, showing no significant difference. The mean diameters were 4.9 cm and 5.9 cm after 1 month and were 4.8 cm and 5.9 cm after 6 months, respectively. The mean left ventricular diameter was also significantly increased in Group NV ($p < 0.01$).

Physical work capacity

Fig. 4 compares the physical work capacity. The physical work capacity 1 month after onset was 5.2 ± 2.0 METs and 5.1 ± 2.4 METs in Groups V and NV, respectively (NS). The physical work

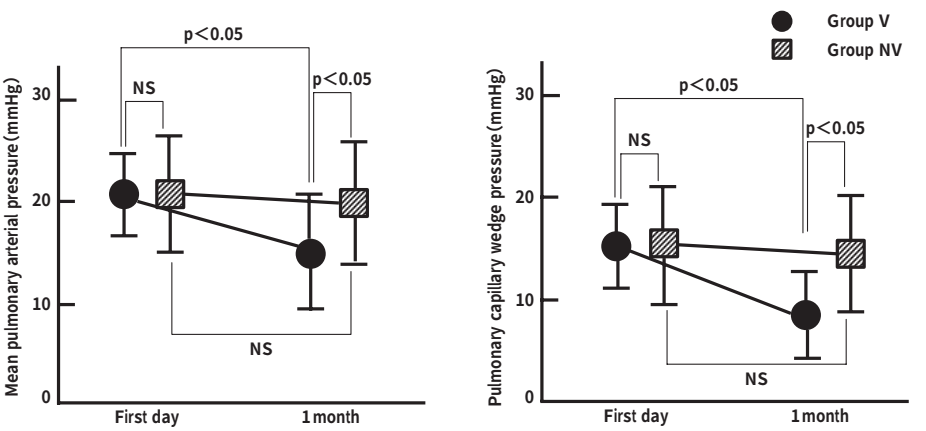

Fig. 2 Mean pulmonary arterial pressure (*left*) and pulmonary capillary wedge pressure (*right*) on the first hospital day and 1 month later
The mean pulmonary arterial pressure and the pulmonary capillary wedge pressure on the first hospital day were not significantly different between the two groups, but these values were significantly improved in Group V 1 month later (15.3 vs 19.8 mmHg and 9.2 vs 14.2 mmHg), respectively ($p < 0.05$).
Explanation of the groups as in Table 1.

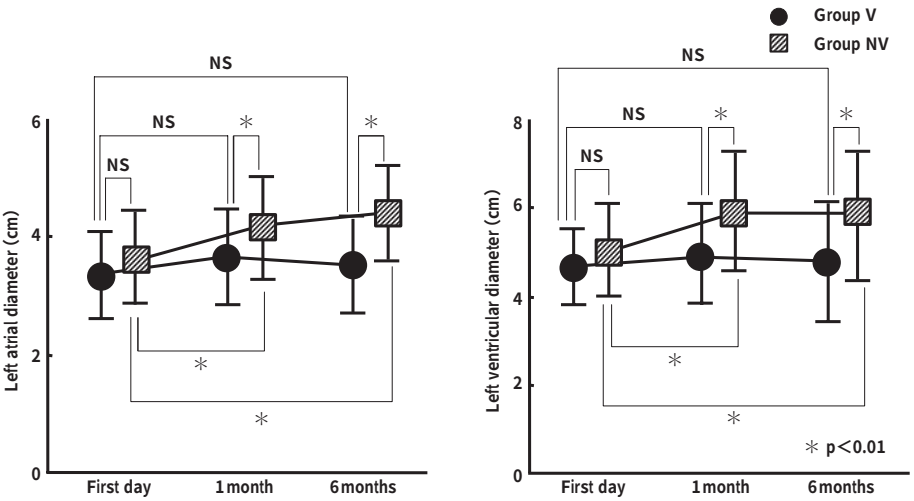

Fig. 3 Left atrial (*left*) and left ventricular (*right*) diameters on the first day, 1 month later, and 6 months later

The left atrial diameter and left ventricular diameter on the first hospital day were not significantly different between the two groups. Both left atrial and left ventricular diameters were significantly increased in Group NV after 1 month and 6 months later ($p < 0.01$).

Explanation of the groups as in Table 1.

capacity after about 2 years had significantly improved to 6.3 ± 1.9 METs in Group V, but showed significantly less improvement to 5.5 ± 2.2 METs in Group NV ($p < 0.05$).

Outcome

Narrowed coronary arteries (> 75% restenosis) were detected after revascularization in eight hospitalized patients in Group V and six patients in Group NV, showing no significant difference. **Figs. 5** and **6** compare the incidence of cardiac events over about 2.8 years in 83 patients who could be followed up. None of the 50 patients in Group V experienced sudden cardiac death or congestive heart failure. Two of the 33 patients in Group NV suffered sudden cardiac death and three experienced congestive heart failure. No patient in either group suffered non-cardiac death during the follow-up period. The difference between the two groups was significant ($\chi^2 < 0.02$). Unstable angina and nonfatal re-infarction were both observed in 13 patients (26%) in Group V. In contrast, unstable angina was observed in only two patients in Group NV. The Kaplan-Meier method found a significant difference between the incidences of ischemic events in the two groups ($p < 0.02$).

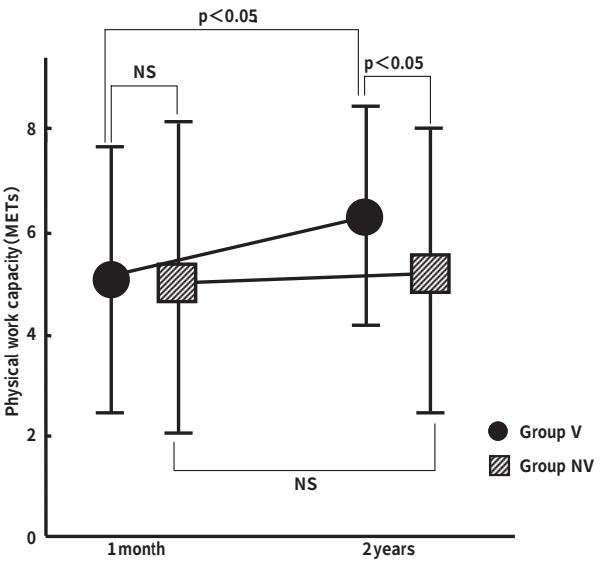

Fig. 4 Physical work capacity at 1 month and at 2 years after onset

One month after onset, the physical work capacity was not significantly different between the two groups. The physical work capacity in Group V significantly improved to 6.3 ± 1.9 METs, whereas physical work capacity in Group NV showed significantly less improvement (5.5 ± 2.2 METs, $p < 0.05$).

Explanation of the groups as in Table 1.

DISCUSSION

The present study showed that LDSE had a sen-

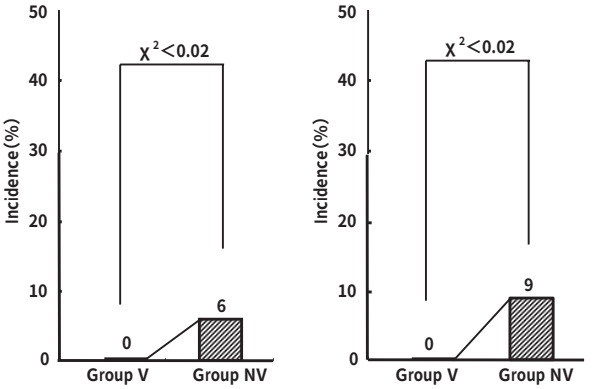

Fig. 5 Incidences of sudden death (*left*) and congestive heart failure (*right*) over the follow-up period of mean 2.8 years

None of the 50 patients followed up in Group V experienced sudden cardiac death or congestive heart failure. Two of the 33 patients in Group NV suffered sudden cardiac death and three experienced congestive heart failure. The difference between two groups was significant ($\chi^2 < 0.02$).

Explanation of the groups as in Table 1.

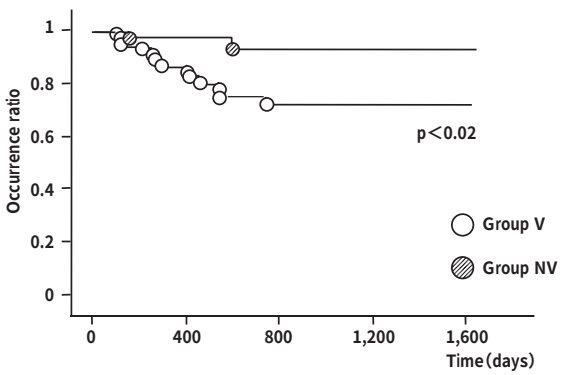

Fig. 6 Incidences of angina pectoris and re-infarction using the Kaplan-Meier method

Both unstable angina and nonfatal re-infarction were observed in 13 patients in Group V. In contrast, only unstable angina was observed in only two patients in Group NV. The Kaplan-Meier method found a significant difference between the incidences of ischemic cardiac events in the two groups ($p < 0.02$).

Explanation of the groups as in Table 1.

sitivity of 95% and specificity of 78% for detecting wall motion improvement in patients with stunned myocardium successfully treated by reperfusion therapy during the acute stage of acute myocardial infarction. LDSE has a sensitivity of 81−87% and specificity of 84−88% for detecting hibernating myocardium[11,13,14]. The period required for recovery from myocardial stunning varies from within 3 days[15] or 3−6 days[16] to longer periods of 7−10 days.

In our study, recovery occurred after 1 month or later in 5 of the 58 patients (8.6%) in Group V. Such delayed improvement in wall motion until up to 30 days or later was also found in patients with severely decreased cardiac function who had undergone bypass surgery several times[17]. Our five patients who showed delayed improvement had the lowest and mean values of escaped myocardial enzyme (peak creatine kinase) of 2,638 IU/*l* and 3,328 IU/*l*, respectively, which were significantly higher than the overall mean values of the patients in Group V. Although it is generally considered that myocardium recovers from stunning in about 7 days, our results show that patients with seriously compromised cardiac function may show delayed recovery. Careful observation is essential in such patients.

The left atrial and left ventricular diameters were not increased in Group V but were significantly increased in Group NV ($p < 0.01$). Apparently, improvement of the intra-cardiac pressure was good in Group V and the clinical course involved no remodeling. In contrast, improvement was delayed in Group NV and the persistent cardiac load resulted in remodeling. Therefore, myocardial viability assessment is useful for the prediction of left atrial or left ventricular remodeling 6 months after discharge, and also for short-term changes in cardiac function following myocardial infarction. Patients with non-viable myocardium should be treated with angiotensin converting enzyme inhibitor early in the course of acute myocardial infarction because remodeling is likely to develop by 6 months after discharge. The physical work capacity showed significantly more improvement in Group V than in Group NV after 2 years. The maximal oxygen consumption rate is significantly improved during exercise in ischemic cardiomyopathic patients with hibernating myocardium[18]. Improvement of the wall motion in patients with hibernating myocardium through exercise therapy may be due to structural and functional changes in the microvascular vessels perfusing the myocardium rather than the main coronary artery[18]. The improvement in physical work capacity is generally believed to derive from improved cardiac pump function and adaptation to exercise of the peripheral tissues (muscle). Many studies on healthy adults conducted more than 20 years ago have confirmed that appropriate exercise therapy effectively

improves the cardiac function[19–21]. Similarly, our study found that cardiac function significantly improved in Group V with improved wall motion of the area compared to Group NV without improved wall motion and remodeling and no remodeling. Our study suggests that Group V had a greater circulating blood volume than Group NV, contributing to the significantly improved physical work capacity in Group V.

The incidence of re-infarction at the same site and unstable angina during the 2.8-year observation period was 26% in Group V, in contrast to only 6% in Group NV. Two patients in Group V experienced recurrence of acute myocardial infarction at the same site within 6 months after discharge. Eleven patients in Group V experienced unstable angina pectoris following acute myocardial infarction, seven patients within 1 year of discharge who all had restenosis at the same site, and four after 1 year of whom two had restenosis at the same site. Two patients in Group NV experienced unstable angina pectoris following acute myocardial infarction within 6 months of discharge, one had restenosis at the same site, whereas the other had restenosis at a different site. Such incidents may be due to ischemia caused by restenosis of the responsible blood vessel during the clinical course[1,22]. The incidence of re-infarction and unstable angina was 40% in patients with hibernating myocardium, in contrast to only 7.5% in patients without hibernating myocardium[22]. Patients with non-Q-myocardial infarction have smaller infarct size and better cardiac function than patients with Q-myocardial infarction, whereas patients with Q-myocardial infarction develop re-infarction and angina more readily because of the greater viability[23].

Heart failure occurred in 9% of Group NV compared to 0% in Group V. Patients in Group NV showed remodeling of the left atrium and left ventricle, so the cardiac function was reduced and heart failures were more likely to occur. Patients without hibernating myocardium had reduced left ventricular ejection fraction and the incidence of heart failure was 18%, compared to 10% in patients with hibernating myocardium[22]. In our study, the incidence of sudden death was 0% in Group V versus 6% in Group NV. Sudden death occurred in 4% and 2% of patients with and without hibernating myocardium, respectively, within a mean of 1.5 years due to new ischemia[1]. Our study found poor left ventricular function with increased infarction volume in two cases of sudden deaths in Group NV (peak creatine kinase = 6,225 IU/*l*, 7,003 IU/*l*, left ventricular end-diastolic dimension 6 months after discharge = 6.6 cm, 7.0 cm). Therefore, our study suggests that exacerbation of chronic heart failure or arrhythmia may contribute to sudden death, so follow-up examination must consider the possibility of ischemia in patients with stunned myocardium, and heart failure in patients without stunned myocardium.

LDSE is generally considered to be a safe method. Ventricular extrasystole, paroxysmal atrial fibrillation and decreased blood pressure were observed during LDSE in 13–14%, 3%, and 3% of patients tested, respectively, but there were no ischemic changes or serious complications, and LDSE was discontinued in none of the patients. In our study, no serious arrhythmia or ischemic changes were observed during LDSE, and dobutamine stress could be applied at a rate up to 10 μg/kg/min. Therefore, we also concluded that LDSE is a safe test method. Therefore, LDSE is clinically useful to detect stunned myocardium and hibernating myocardium for predicting the long-term prognosis for patients with myocardial infarction.

Limitations

Coronary angiography was routinely performed twice, during the hyper-acute stage of myocardial infarction and before discharge, in nearly all patients. Patients underwent revascularization if significantly narrowed coronary arteries (75% restenosis) were observed. However, myocardial perfusion scintigraphy in conjunction with an exercise test was performed if ischemia was suspected in the patients at post-discharge follow-up examination. Patients with ischemia underwent coronary angiography followed by revascularization. The underlying disease may not have been detected, but ischemia was relieved if the area could be identified.

Left atrial and left ventricular remodeling was assessed by M-mode echocardiography which generates a one-dimensional view of the heart. Accurate assessment of remodeling requires shape analysis of remodeling with the modified Simpson method in the presence or absence of ventricular aneurysm using the left ventricular volume as an index.

No-reflow or slow-flow phenomenon identified

by coronary angiography in the hyper-acute stage was not examined. If the extent of no-reflow or slow-flow is assessed, more detailed information on the prediction of cardiac events can be obtained.

CONCLUSIONS

LDSE is a safe and useful method for detecting stunned myocardium in the infarct area of acute myocardial infarction, and the presence of stunned myocardium is a predictor of the prognosis for patients with myocardial infarction.

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要　　約

急性心筋梗塞の長期予後予測における低用量ドブタミン負荷心エコー図法の有用性

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目　的: 冬眠心筋は心筋梗塞患者の長期予後を推測するうえでの独立した規定因子であると報告されている．これまでに我々は，低用量ドブタミン負荷心エコー図法を用いて心筋梗塞急性期の気絶心筋を検出し，気絶心筋を有する例は入院後短期間における心機能の改善が良好であると報告してきた．本研究は気絶心筋が心筋梗塞の長期予後を推測するうえでの規定因子になりうるかを検討することである．

方　法: 対象は急性期再灌流療法(ダイレクト経皮的冠動脈形成術またはステント留置)に成功した初回心筋梗塞102例(男性83例，女性19例，平均年齢61.5歳)である．全例7病日以内に末梢静脈より低用量のドブタミンを点滴投与し，心エコー図法で梗塞部の壁運動改善を評価した．壁運動改善の違いから対象を1段階以上壁運動が改善したViable群(61例)と改善しなかったNon-viable群(41例)の2群に分けそれぞれ，心エコー図法から求めた左房と左室径の経時的変化，連続的多段階運動負荷試験から得られた運動耐容能の改善などや退院後の長期予後について比較検討した．

結　果: Viable群はNon-viable群に比べて入院後短期間における梗塞部の壁運動の改善が有意に大きかった．Viable群は退院後の運動耐容能の改善がNon-viable群に比べて有意に大きかった．Viable群では退院半年後の左房および左室拡大は認められなかったのに対して，Non-viable群では有意に拡大した．経過観察中，Viable群では突然死や心不全がまったく認められなかったのに対して，Non-viable群では突然死が6%，心不全が9%に認められた．不安定狭心症や非致死性の再梗塞が認められる率において，Viable群はNon-viable群に比べて有意に高かった．Viable群はNon-viable群に比べて心機能の改善が大きいため，突然死や心不全は認められないが，梗塞部がviableであるために新たな虚血が生じるものと考えられた．

結　語: 気絶心筋は急性心筋梗塞患者の予後を推測するうえでの規定因子になると考えられた．

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