Identification of asynergic but viable myocardium in patients with chronic coronary artery disease by gated blood pool scintigraphy during isosorbide dinitrate and low-dose dobutamine infusion: Comparison with thallium-201 scintigraphy with reinjection

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To evaluate the ability of low-dose dobutamine and isosorbite dinitrate (ISDN) gated blood pool scintigraphy (GBPS) and thallium SPECT with reinjection to identify viability in asynergic myocardium, both procedures were performed in 38 consecutive patients with chronic coronary artery disease and left ventricular dysfunction. Twenty-two of the 38 patients with successful revascularization were analyzed. GBPS was performed at the baseline and during continuous infusion of low dose dobutamine (5 μg/kg/min) and ISDN (2 μg/kg/min). Cine mode GBPS wall motion was scored from normal (0) to dyskinesis (4) semiquantitatively. Forty-seven of 110 segments with severe asynergy at the baseline were analyzed. Viability determined by GBPS was defined as wall motion score improvement by more than 1 grade. Thallium viability was defined as the segment with redistribution or fill in with severe initial perfusion defect. GBPS was 76.7% sensitive and 70.6% specific for predicting post vascularization wall motion improvement ($p < 0.005$). Of 47 segments with severe asynergy, concordance of judgement was obtained in 40 segments (85.1%), and reversibility was correctly diagnosed in 34 of 40 patients (85.0%), but thallium with reinjection correctly identified tissue viability in 6 of 7 segments with discordance between 2 studies.

These data suggest that most cases of reversible asynergy (hibernating myocardium) respond to ISDN and dobutamine, suggesting the possibility of predicting improvement by revascularization, although some underestimation of tissue viability remained to be resolved. Thallium with re-injection is superior to low-dose dobutamine + ISDN GBPS for the assessment of myocardial viability.

Key words: myocardial viability, thallium-201 with reinjection, gated blood pool scintigraphy, dobutamine, isosorbide dinitrate

INTRODUCTION

THE DIFFERENTIATION of viable from nonviable myocardium in patients with coronary artery disease and left ventricular dysfunction is an issue of increasing clinical relevance

in current era of reperfusion therapy.[1,2] A number of radionuclide imaging techniques have emerged for the detection of viable myocardium, in particular, reinjection of thallium-201 imaged by single photon emission computed tomography has been widely recognized as an accurate method by which to assess perfusion and sarcolemnal integrity, thereby addressing the problem of myocardial viability.[3-6] Assessment of regional left ventricular functional reserve by infusing cathecolamines such as dobutamine and epinephrine is also a potential

Table 1 Clinical characteristics of each patients

No.	age	sex	PIA	VD	IRA		stenosis	Collat	Tx	LVEF 1	LVEF 2
1	43	M	+	1	LAD	#6	100%	3+	PTCA	48.5	75.2
2	60	M	−	1	LAD	#7	100%	2+	PTCA	33.5	43.8
3	63	M	−	1	LAD	#7	99%	1+	PTCA	52.4	65.9
4	68	M	−	1	LAD	#7	100%	2+	PTCA	51.6	59.8
5	71	M	+	1	LAD	#6	99%	0	PTCA	36.5	50.2
6	78	M	−	2	RCA	#1	100%	2+	PTCA	38.9	57.6
7	50	M	−	2	RCA	#3	100%	2+	CABG	42.3	52.0
8	35	M	+	3	RCA	#2	99%	0	CABG	39.0	41.3
9	57	F	−	1	LAD	#6	100%	2+	PTCA	42.3	55.6
10	55	M	−	1	RCA	#3	99%	2+	PTCA	60.4	56.5
11	58	M	+	2	LAD	#6	100%	3+	CABG	38.2	63.9
12	72	F	−	1	LAD	#7	100%	3+	PTCA	61.7	66.2
13	52	M	+	2	LAD	#7	99%	2+	PTCA	49.4	63.4
14	69	F	+	1	LAD	#6	100%	2+	PTCA	32.1	58.2
15	49	M	+	1	LAD	#7	100%	2+	PTCA	48.2	56.8
16	67	M	−	1	RCA	#1	100%	3+	PTCA	55.2	58.6
17	68	M	+	2	RCA	#1	99%	3+	PTCA	49.6	52.3
18	71	M	−	1	RCA	#4	99%	2+	PTCA	58.2	56.2
19	45	M	−	1	LAD	#6	100%	3+	PTCA	42.3	45.0
20	51	M	+	2	LAD	#6	100%	3+	CABG	47.0	43.0
21	61	M	−	1	LAD	#6	100%	2+	PTCA	42.0	33.5
22	56	F	−	1	LAD	#7	99%	0	PTCA	42.3	55.7

PIA: post-infarction angina. IRA: infarct related artery. Collat: collateral flow, 0 none, 1 poor, 2 moderate, 3 good. Tx: therapy for infarct related artery. PTCA: percutaneous transluminal coronary angioplasty. CABG: coronary artery bypass grafting. LVEF 1: left ventricular ejection fraction before intervention. LVEF 2: left ventricular ejection fraction 1–3 months after intervention.

method for assessing viability and has gathered considerable interest especially in the field of echocardiographic study,[7-9] but some conceptual limitations have to be considered, because dobutamine may merely increase myocardial oxygen demand in the setting of exhausted coronary flow reserve, thereby producing myocardial ischemia and persistent regional dysfunction.[6] To overcome this possibility, we administered isosorbite dinitrate (ISDN) in addition to dobutamine for the evaluation of functional reserve to prevent myocardial ischemia resulting from dobutamine infusion. The values obtained by this method were compared with those for thallium scintigraphy with reinjection.

METHOD

Patient population
Thirty-eight consecutive CAD patients with severely stenosed infarct related artery and left ventricular dysfunction (32 men and 7 women; mean age, 59.9 ± 10.6) underwent pre-operative viability assessment. Each had one or more previous infarctions. Revascularization was attempted in all patients (34 patients by PTCA, 5 patients by CABG) irrespective of the results of the studies for assessing viability. Successful recanalization, which is defined as stenosis severity less than 75% in recanalized vessels by coronary angiograms performed at 3 months

after revascularization, was achieved in only 22 out of 38 patients. Of the 16 patients who could not be successfully revascularized, 13 patients reoccluded despite initially successful revascularization, and 3 patients could not be revascularized at all. Twenty-two patients who maintained successful revascularization (18 men and 4 women; mean age, 59.0 ± 10.7) were analyzed in this study and the clinical characteristics of these patients were shown in Table 1. All patients had subtotal or total occlusion in their infarct related arteries and left ventricular ejection fraction ranged from 32.1% to 60.4%.

Wall motion recovery by revascularization as the gold standard of viability
To assess regional wall motion, all patients underwent X-ray contrast ventriculography in right anterior and left anterior oblique projections before revascularization and 3 months after revascularization. The medication doses which may modify the myocardial contraction (beta-blocker, digitalis, Ca antagonist, diuretics, and nitrate) were kept constant during both ventriculographies. The left ventricle was divided into 5 regions: septal, apical, anterior, posterolateral and inferior. Wall motion was visually assessed by three experienced observers and graded on a scale of 0 to 4: 0 = normal, 1 = mild hypokinesis, 2 = severe hypokinesis, 3 = akinesis, 4 = dyskinesis). When the score of the wall motion increased by
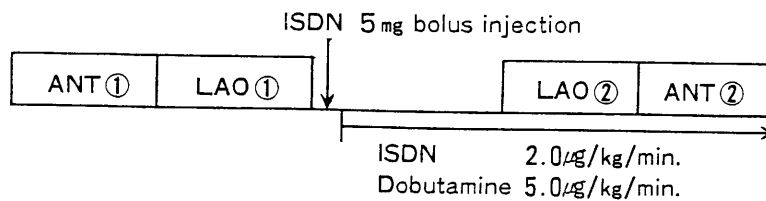
ISDN 5 mg bolus injection

ISDN   2.0 μg/kg/min.
Dobutamine 5.0 μg/kg/min.

Fig. 1 Schematic presentation of study protocol, illustrating the temporal sequence of ISDN and dobutamine infusion.

Gated Blood Pool Scintigraphy
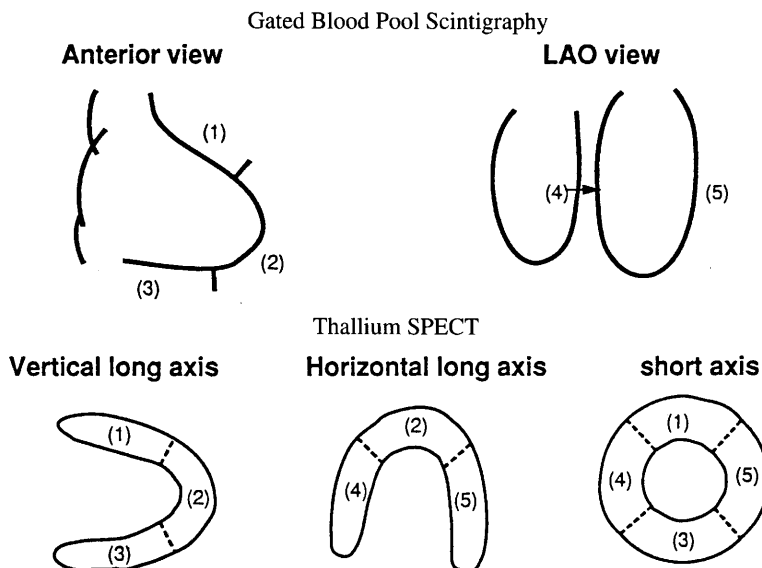**Anterior view**   **LAO view**

Thallium SPECT
Vertical long axis   **Horizontal long axis**   **short axis**

Fig. 2 Schematic representation of about the distribution of segments in gated blood pool scintigraphy, and corresponding portion of thallium SPECT for comparison are demonstrated. Left ventricle divided into 5 regions, which were assigned to anterior, apical, inferior, septal, and posterolateral regions. ANT: anterior view. LAO: left anterior oblique view.

one unit or more after revascularization, the segments were defined as having improved wall motion and viable segments. For patient analysis, if the score of wall motion in asynergic segments increased by one or more in at least one segment, the patient was regarded as having improved function.

Gated blood pool scintigraphy under isosorbide dinitrate + low dose dobutamine infusion

Each patient underwent radionuclide ventriculography at the baseline and after continuous infusion of ISDN and low dose dobutamine under the protocol shown in Figure 1. Red blood cells were labeled *in vivo* by injection of 1.5 mg stannous pyrophosphate, followed by 1110 MBq Tc-99m pertechnetate. At baseline and during pharmacological stress, electrocardiographically gated images were collected with the patients at supine rest. Images were obtained in both the anterior view and left anterior oblique projection that optimized separation of the ventricles with use of a gamma camera (STARCAM 300A) equipped with a high energy high resolution collimator, employing the 140 keV energy peak with a 20% window, and collecting for 10 min. Data were stored in a computer in

a 64 × 64 matrix, with 24 frames per cardiac cycle.

ISDN and low-dose dobutamine were infused through a 20 gauge intravenous cannula into an antecubital vein. 5 mg of ISDN was slowly injected for 3 minutes, followed by continuous infusion of ISDN at the rate of 2.0 μg/kg/min and dobutamine at the rate of 5.0 μg/kg/min simultaneously. After 15 minutes of equilibration, a repeat set of left anterior oblique and anterior images was collected. Heart rate and blood pressure were recorded at 1 minute intervals from the beginning of infusion to the end of data acquisition.

Analysis of wall motion response to ISDN and low dose dobutamine

The left ventricular ejection fraction was calculated with manufacturer's software. For analyzing regional wall motion, playback buffers were constructed with baseline images on the left and images under pharmacological stress on the right. All images were analyzed by two observers who were unaware of the patient information about catheterization and thallium scintigraphy. For analyzing regional wall motion (Fig. 2), wall motion abnormality in each segment was graded on a 5 point

scale: 0 = normal, 1 = mildly hypokinetic, 2 = severely hypokinetic, 3 = akinetic, 4 = dyskinetic. The analogous segments were compared at rest and during pharmacological stress. All changes in regional wall motion after ISDN and low-dose dobutamine infusion were recorded. Augmentation of contractile function of asynergic segments was defined as viable for the segmental analysis. For patient analysis, the presence of hibernating myocardium was defined as the presence of augmented contraction by gated blood pool scintigraphy under ISDN and dobutamine infusion in at least one severe asynergic segment.

Thallium-201 single photon emission computed tomography with reinjection
After an overnight fast, all patients underwent graded treadmill exercise testing according to the modified Bruce protocol. A 12 lead ECG was taken and blood pressure was monitered every minute. The test was considered ischemia positive when typical chest pain occurred, or there were ≥ 0.1 mV of horizontal or downsloping, or ≥ 0.15 mV upsloping ST-segment depression occurring at 0.08 second after the J point on any of the surface ECG. Criteria for the termination of exercise were severe chest pain, serious arrhythmia, hypotension, or when patients reached the age predicted heart rate or had severe fatigue. 111 MBq of thallium-201 was administered intravenously at peak exercise and exercise was continued for one additional minute. SPECT imaging was started 10 minutes after injection, and obtained with a wide field of view rotating gamma camera (ZLC-7500, Siemens Co., Ltd.) equipped with a low energy, high resolution collimator on the 70 keV photo peak with a 20% window. The camera was rotated through a 180° arc in an elliptical orbit about the patient's thorax from 40° right anterior oblique to 40° left posterior oblique at 6° increments for 30 seconds each. Redistribution images were obtained at rest 4 hours after the injection of thallium by identical imaging methods. During the period between the exercise and redistribution acquisition, patients were amburatory and remained in a fasting condition. Immediately after redistribution imaging, additional 37 MBq of thallium were injected into all patients at rest, and a third set of images was reacquired 15 minutes after second injection by use of the same imaging protocol. From the raw scintigraphic data, the exercise, redistribution and reinjection data were processed and reconstructed as tomographic images in an computer system (Scintipac 7000, Shimadzu Co., Ltd.). Standard back projection algorithm and Shepp and Logan filter were used to reconstruct the images. Transaxial slices were then reconstructed and realigned into frontal and sagittal sections with the manufacturer's software.

Analysis of thallium scintigraphy
For visual interpretation, all short axis and vertical long axis tomograms were displayed on transparency film with the intensity of each image normalized to the maximal pixel value in that image. Separate films were obtained displaying aligned slices of the post-stress and redistribution, post-stress and reinjection images.

The thallium-201 myocardial tomograms were divided into 5 segments for each patient as shown in Figure 2. These segments were assigned on the apical, anterior, septal, inferior, and posterolateral regions. All images were scored at separate times by consensus of 2 experienced observers using a 5 point scoring system (0 = normal, 1 = equivocal, 2 = mild, 3 = moderate, 4 = severe reduction in thallium-201 uptake) without knowledge of the clinical history or the results of gated blood pool scintigraphy. A post-stress perfusion defect was considered present when a myocardial segment had an initial post-stress score ≥ 3. Stress defects with a score ≤ 2 on the 4 hour redistribution image were called "reversible" and defects with a score ≥ 3 were "nonreversible." The nonreversible defects were further categorized according to their reinjection images: those with a score of ≤ 2 at reinjection images were "filled in," and those with a score ≥ 3 were "not filled in." Ischemic viable segments were defined as a reversible defect in redistribution images or as "filled in" in reinjection images. For patient analysis, ischemic viable myocardium was considered to include hibernating myocardium if there was redistribution and/ or "filled in" in at least 1 segments. Equivocal and mild defects were considered viable even if these segments accompanied no redistribution and "no fill in."

Statistical analysis
Student's paired t-test was used for the examination of differences in hemodynamic changes between the baseline and during pharmacological stress test. The chi-square test was used to determine the significance of difference in the rate of occurrence. A p value < 0.05 was considered significant.

RESULT

Effects of ISDN and low-dose dobutamine on hemodynamics and global ejection fraction
The effect of ISDN and low-dose dobutamine on the heart rate (HR), systolic blood pressure (SBP), and global ejection fraction are shown in Figure 3. Intravenous ISDN rapid infusion of 5 mg followed by continuous ISDN infusion at the rate of 2 μg/kg/min and dobutamine at 5 μg/ kg/min significantly increased the heart rate, systolic blood pressure and global ejection fraction at 15 minutes after the initiation of infusion. (HR: 69.1 ± 11.2 to 75.5 ± 11.5, $p < 0.01$, SBP: 117.8 ± 15.5 to 127.0 ± 17.1, $p < 0.01$, EF: 41.4 ± 12.1 to 46.2 ± 12.4, $p < 0.01$)

The contractile response of asynergic segments to ISDN and low-dose dobutamine
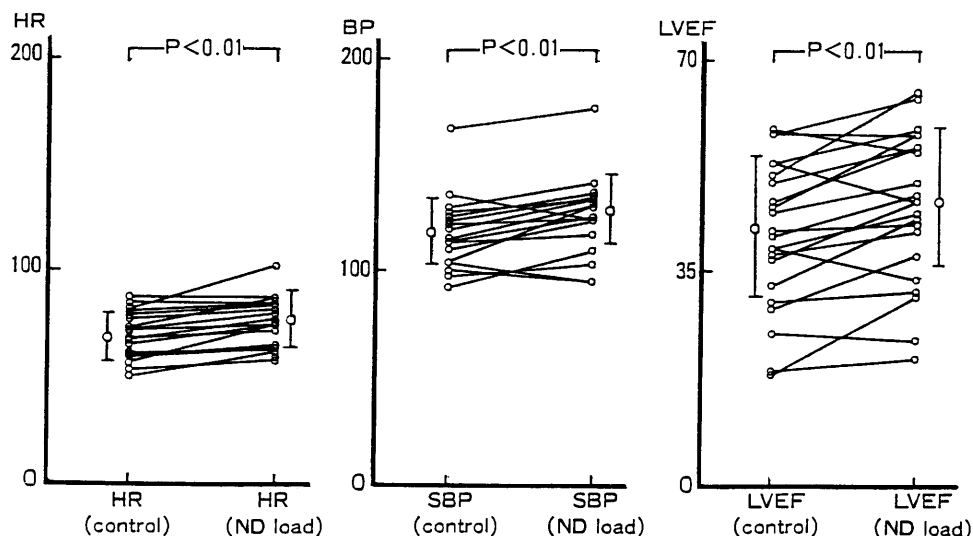The response of asynergic segments to ISDN and low-dose dobutamine are shown in Figure 4. Sixty-five of 110

Fig. 3 Changes in heart rate, systolic blood pressure, and left ventricular ejection fraction after infusion of isosorbide dinitrate and dobutamine. HR: heart rate. SBP: systolic blood pressure. LVEF: left ventricular ejection fraction. ND load: after ISDN and dobutamine infusion.
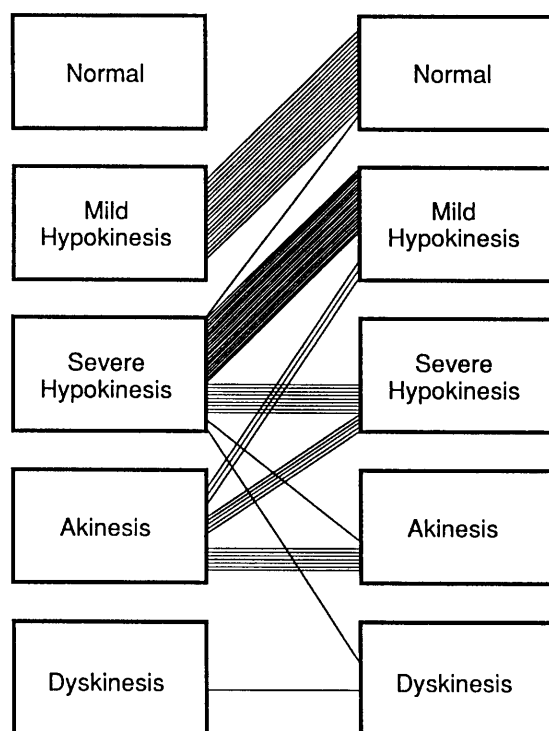

Fig. 4 The response of asynergic wall motion to ISDN and dobutamine.

Table 2 Number of severe asynergic segment on wall motion response to ISDN + dobutamine in relation to improvement in wall motion after revascularization

	Wall motion after RV	
	Improved	Not improved
Wall motion ↑ by ISDN + dobutamine	23	5
Wall motion →↓ by ISDN + dobutamine	7	12

Sensitivity: 76.7%, specificity: 70.6%, accuracy: 74.5%, positive predictive value: 82.1%, negative predictive value: 63.1%, RV: revascularization, ISDN: isosorbide dinitrate.

and changed to akinetic in 1 and 2 dyskinetic in 1 segment.

Functional reserve in severely asynergic segments in relation to wall motion improvement after revascularization

Severe wall motion abnormalities categorized as severe hypokinesis, akinesis and dyskinesis were observed in 47 segments. The relationship between the wall motion response to ISDN + dobutamine, and wall motion improvement by revascularization is shown in Table 2. Twenty-eight of 47 segments showed enhanced contraction, and 19 segments showed no enhancement. Wall motion improvement by revascuralization was observed in 23 of 28 segments (82.1%) with contraction enhanced by ISDN + dobutamine, and in only 7 segments of 19 segments (36.8%) without contraction enhanced by ISDN + dobutamine (p < 0.005). As for the 2 segments with deteriorated wall motion, 1 severe hypokinetic segment, which changed to dyskinetic after ISDN + dobuta-

segments had wall motion asynergy at the baseline. With ISDN and dobutamine, wall motion abnormalities improved in 46, remained unchanged in 17, and worsened in 2 segments. Furthermore, improved contractility by ISDN and dobutamine was observed in all of 18 mildly hypokinetic segments (100%), 20 of 31 severe hypokinetic segments (64.5%) and 8 of 16 akinetic and dyskinetic segments (50.0%). Two segments with worsened wall motion were initially severely hypokinetic

Table 3 Number of severe asynergic segment on thallium finding in relation to improvement in wall motion by revascularization

	Wall motion after RV	
	Improved	Not improved
Ischemia by Tl reinjection	25	2
Scar by Tl injection	5	15

Sensitivity: 83.3%, specificity: 88.2%, accuracy: 85.1%, positive predictive value: 92.6%, negative predictive value: 75.0%, Tl: thallium-201 scintigraphy, ISDN: isosorbide dinitrate.

Table 4 Number of severe asynergic segment on wall motion response to ISDN + dobutamine in relation to thallium findings

	Thallium findings	
	Viability +	Viability −
Wall motion ↑ by ISDN + dobutamine	24 (22)	4 (1)
Wall motion →↓ by ISDN + dobutamine	3 (3)	16 (4)

Number in parenthesis showing the segments with improvement in wall motion after revascularization.

Fig. 5 Wall motion response of infarcted myocardium to ISDN + dobutamine infusion and the effect of revascularization. ND: ISDN and dobutamine.

Fig. 6 The assessment of myocardial viability by exercise thallium with reinjection and the effect of revascularization.

mine infusion, was improved to hypokinetic by revascularization, but another severe hypokinetic segment with deteriolation to akinesis showed no improvement at all following revascularization. Gated blood pool scintigraphy during ISDN and dobutamine was 76.7% sensitive and 70.6% specific.

Thallium-201 finding in relation to wall motion improvement after revascularization

Thallium scintigraphy showed perfusion abnormality in all of 47 severe asynergic segments, including 27 segments with redistribution or "filled in" and 20 segments with neither redistribution nor "filled in" (Table 3). Post-revascularization improvement in wall motion was observed in 25 of 27 segments (92.6%) with redistribution or "filled in," while only 5 of 20 patients had a persistent defect even after reinjection. Thallium scintigraphy with reinjection was 83.3% sensitive and 88.2% specific for the prediction of wall motion recovery by revascularization.

Functional reserve assessed by wall motion response to ISDN + low-dose dobutamine in relation to perfusion scintigraphy (Segmental analysis)

The correlation of interpretation of viability for each severe asynergic segment by wall motion response to ISDN + dobutamine and thallium perfusion scintigraphy
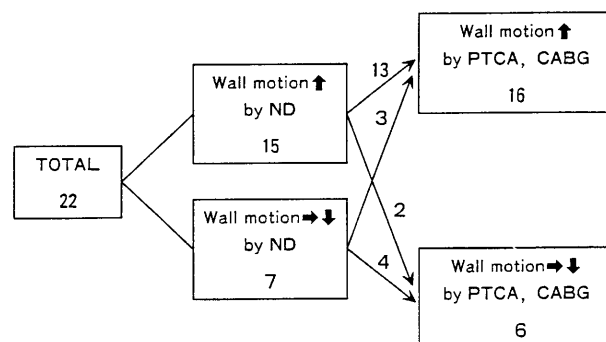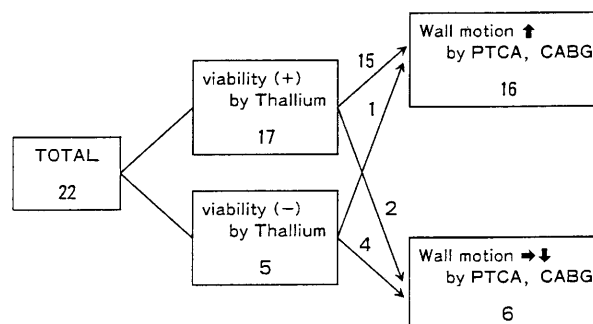
is summarized in Table 4. Of 47 segments with severe wall motion abnormality, both studies indicated hibernation in 24 segments (51.1%), and scarring in 16 segments (34.0%). Thus these two interpretations were matched in 40 segments (85.1%). The condition of 22 of 24 segments (91.7%) judged as hibernating in both studies was reversible, but that of only 4 of 16 segments (25.0%) judged as scarred in both studies was reversibly asynergic. There were 3 segments (6.4%) showing no enhanced contraction caused by ISDN + dobutamine but judged as ischemic and viable myocardium by thallium scintigraphy. Wall motion abnormality was significantly improved in all 13 segments after revascularization (100%). On the other hand, of 4 segments showing enhanced contraction caused by ISDN + dobutamine, and no redistribution and "filled in" in thallium scintigraphy, only 1 segment (25.0%) improved after revascuralization.

Predictive accuracy of ISDN + low-dose dobutamine gated blood pool scan and variables derived from thallium reinjecton scintigraphy for the presence of hibernating myocardium (patient analysis)

Gated blood pool scintigraphy with ISDN + dobutamine infusion identified improved wall motion in 15 of 22 patients. Among segments functionally responsive to ISDN + dobutamine, 13 patients (86.7%) had improved
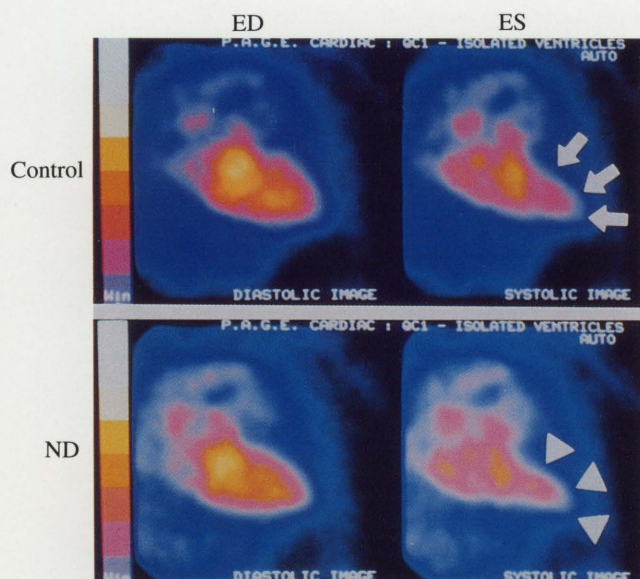
ED   ES

Control

ND

Fig. 7 End-diastolic (ED) and end-systolic (ES) frame images of illustrative gated blood pool scintigraphy at control state (upper raw) and during ISDN and dobutamine infusion (lower raw). Severe hypokinesis of anterolateral wall and akinesis in apex was evident at baseline, but wall motion improvement of these asynergic segments become apparent with ISDN and dobutamine. ND: images during ISDN and dobutamine infusion.


LA   TA   SA

EX

RD

RI

Fig. 8 Thallium with reinjection scintigraphy obtained in the same patient as in this figure 8. Severe hypoperfusion in anteroseptal and apex was noted with definite redistribution in anteroseptal and apical region. Upper, middle, lower column showing exercise images (EX), 4 hour redistribution images (RD), reinjection images (RI) respectively. LA: long axis view. SA: short axis view. TA: transverse axis view.

wall motion after revascularization. In contrast, among 7 patients whose asynergic segments remained unchanged even after ISDN + dobutamine infusion, only 3 patients (42.8%) improved after revascularization (Fig. 5).
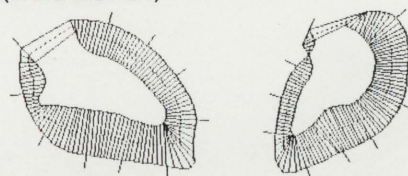
Before PTCA
(WALL MOTION)
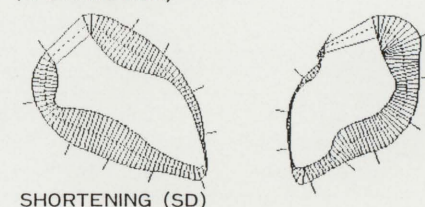
SHORTENING (SD)

3M after PTCA
(WALL MOTION)

SHORTENING (SD)

Fig. 9 Left ventricular silhouettes of the ventriculographies obtained before and 3 month after revascularization in the same patient as in Figure 8. Wall motion improvement in anteroseptal and apical region was apparent by revascularization.
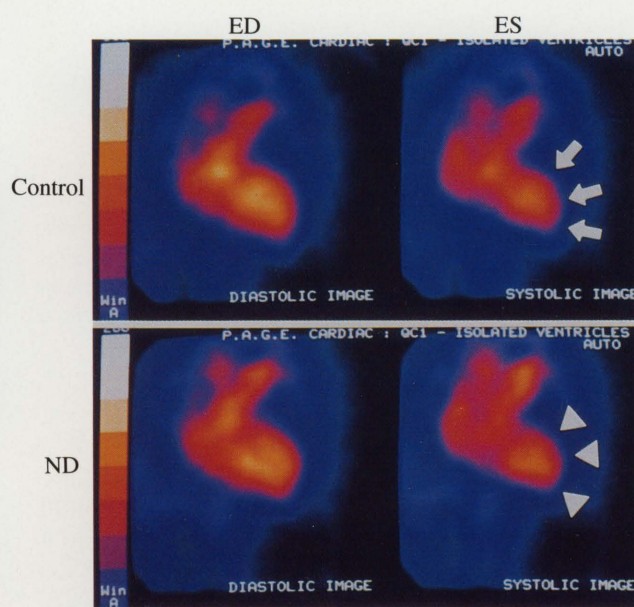
ED   ES

Control

ND

Fig. 10 End-diastolic (ED) and end-systolic (ES) frame images of illustrative gated blood pool scintigraphy at control state (upper raw) and during ISDN and dobutamine infusion (lower raw) in another patient. Akinesis in anterolateral and apical region was evident at baseline, and wall motion remained unchanged irrespective of ISDN and dobutamine infusion.

Thallium with reinjection identified 17 patients with hypoperfused ischemic segments. Fifteen of 17 patients had improved wall motion after revascularization. In contrast, of 5 patients with persistent perfusion defect

Table 5 Pre-operative predictive accuracy for wall motion reversibility with gated blood pool scintigraphy during ISDN and dobutamine compared with the indexes derived from thallium scintigraphy with reinjection

	Symptom	ECG	Tl (EXRD)	Tl (EXRI)	GBPSND
PPV	75.0	73.3	92.3	88.2	86.7
NPV	28.6	28.6	55.6	80.0	57.1
ACC	45.5	59.1	77.3	86.4	77.3

PPV: positive predictive value. NPV: negative predictive value. ACC: overall accuracy. ECG: electro-cardiography. Tl (EXRD): conventional (exercise-redistribution) thallium scintigraphy. Tl (EXRI): thallium scintigraphy with reinjection. GBPSND: gated blood pool scintigraphy with ISDN and low-dose dobutamine.
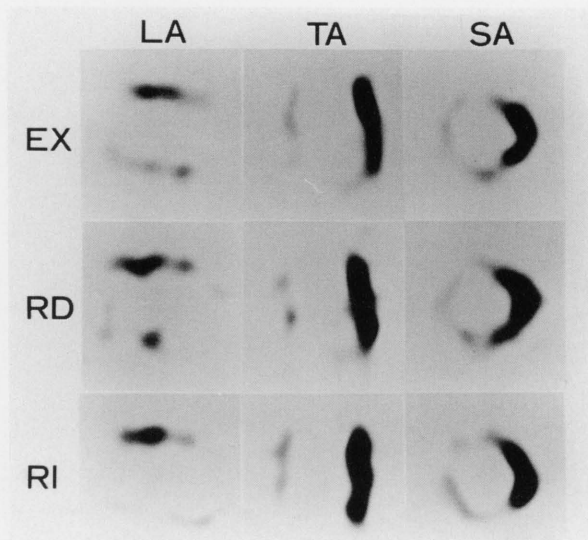

Fig. 11 Thallium with reinjection scintigraphy obtained in the same patient as in figure 11. Severe hypoperfusion in anteroseptal, apical and inferior region was noted with neither redistribution nor "fill in" even after reinjection. Abbreviation is the same as Figure 9.

Fig. 12 Left ventricular silhouettes of the ventriculographies obtained before and three months after revascularization in the same patient as in figure 11. Despite successful recanarization, severe asynergy remained unchanged.

without fill in, 4 patients (80.0%) had unchanged wall motion even after complete revascularization (Fig. 6).

The preoperative predictive accuracy of wall motion reversibility with gated blood pool scintigraphy during ISDN + dobutamine infusion and variables derived from thallium scintigraphy is shown in Table 5.
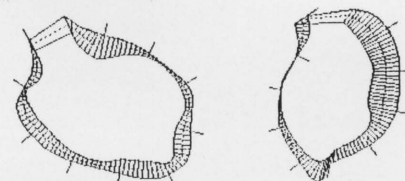
Positive predictive values for all variables were fairly high in symptom, ECG, conventional thallium scan, thallium with reinjection, and gated blood pool scintigraphy with ISDN and dobutamine, but negative predictive values were fairly low except thallium reinjection (28.6% by symptomatic and electrocardiographic criteria, 55.6% by conventional thallium, 57.1% by gated blood pool scintigraphy and 80.0% by thallium reinjection). Thallium with reinjection scintigraphical criteria showed the best overall accuracy among these valuables.

Case presentation
Figure 7 shows end-diastolic and end-systolic blood pool

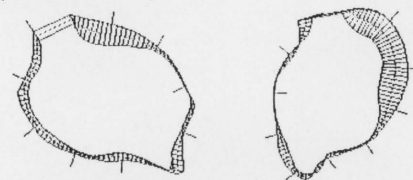images for a patient with anteroseptal myocardial infarction before and after ISDN + low-dose dobutamine infusion. Significant asynergy was observed in the anterior wall and apex at baseline and improved after ISDN + dobutamine infusion. A thallium perfusion scan of the same patient is shown in Figure 8, suggesting transient perfusion abnormality in the anteroseptal wall and apex. The wall motion abnormality in this patient was significantly improved by revascularization as shown in Figure 9.

Figure 10 shows blood pool images of a patient with obstruction of the left anterior descending artery and the right coronary artery. No difference was seen between the baseline and after ISDN + dobutamine infusion. In a thallium scan with reinjection, neither redistribution nor "fill in" was seen in the anteroseptal, apical or inferior wall (Fig. 11). In this patient, no improvement in function was observed at all despite successful recanalization as shown in Figure 12.

DISCUSSION

This comparative study demonstrated that wall motion response to ISDN + low-dose dobutamine assessed by qualitative gated blood pool scintigraphy provided as a high positive predictive value as does thallium with reinjection, but a lower negative predictive value than thallium with reinjection for predicting reversible asynergic myocardium, even in patients with severely reduced flow reserve and severe left ventricular dysfunction with the possibility of induction of myocardial ischemia by positive inotropic drugs. In the segments which remained unchanged even after ISDN + dobutamine infusion, no return of contractile function was observed on late contrast ventriculography in most segments. Conversely, most segments exhibiting improvement in regional function resulted in recovery by revascularization.

The meaning of ISDN in addition to dobutamine as the pharmacological stress for assessing viability

Dobutamine has been widely used for the detection of coronary stenosis by inducing myocardial ischemia. Coronary hyperemia occurs during dobutamine infusion because of increased myocardial oxygen demand.[12] Theoretically, at flows exceeding myocardial demand, hyperkinetic wall motion is seen during dobutamine infusion, but at flows below myocardial demand, myocardial ischemia is induced and results in failure of contraction. Therefore, in the setting of chronically hypoperfused hibernating myocardium with limited coronary flow reserve, the conceptual limitation that dobutamine may merely increase myocardial demand, thereby producing myocardial ischemia has to be taken into consideration. The effectiveness of nitrates for the treatment of myocardial ischemia has been established by many studies.[13,14] Several mechanisms have been proposed to explain the beneficial effects of nitrate in relieving myocardial ischemia including 1) decrease in myocardial oxygen consumption due to reduction of preload and afterload, 2) increase in collateral blood flow or decrease in collateral resistance, 3) stenosis vasodilatation, and 4) dilatation of vasospastic vessels. By these theoretical backgrounds, ISDN was administered in addition to dobutamine in this study to prevent myocardial ischemia. In this study, 1 segment strongly suggestive of ischemic response was observed despite the use of ISDN in addition to low-dose dobutamine, indicating the possibility of ischemia induction by low-dose dobutamine.

Contractile response to ISDN and dobutamine as a method differentiating asynergic but viable myocardium from scarring

The response of reperfused, stunned myocardium to inotropic stimulation has been widely reported concerning animal models[15–17] and human subjects,[10,18] but in the chronically hypoperfused, functionally depressed hibernating myocardium, only preliminary data demonstrate that the application of dobutamine unmasks the contractile reserve of hibernating myocardium.[8,9] Our results showing 76.7% sensitivity and 70.6 specificity are in agreement with these previous clinical studies which demonstrated contractile response assesed by dobutamine as a potential method to distinguish hibernation from scarring. Although only a small number of patients were analyzed, Lau et al. reported that contractile response to low-dose dobutamine assessed by echo cardiography was 93% sensitive and 45% specific for predicting post-CABG wall motion improvement. Furthermore, dobutamine echo identified 59% of PET viable segments and 73% of PET nonviable segments.[8] Charney et al. reported that dobutamine echo provides 74% sensitivity and 100% specificity for the prediction of wall motion recovery 7 days (not enough time for the complete recovery) after revascularization, and concluded that this method is a potentially exciting approach for assessing asynergic viable myocardium.[9] Metabolically, dobutamine activates oxidative metabolism measured by C-11 acetate and PET.[19–21] Ono et al. reported that severely hypoperfused segments with preserved FDG uptake (hibernating myocardium) demonstrated improved Ac clearance, so oxidative metabolic reserve is a marker of viability.[21] But they did not evaluate contractile reserve to dobutamine. Further evaluation of the relation between the oxidative metabolic reserve and functional reserve is necessary.

Thallium with reinjection as a method for assessing viability

It has been demonstrated that 38–47% of myocardial regions with irreversible perfusion defects according to exercise-redistribution thallium scintigraphy are metabolically active.[22,23] The reinjection of thallium after delayed imaging may enhance detection of viable myocardium in areas of no redistribution on routine thallium scan, and this imaging option shoud be of choice for the assessment of inducible ischemia and myocardial viability.[3–6] Tamaki reported, however, that 7 of 28 segments with persistent defect even after reinjection showed metabolical activity, so reinjection thallium imaging still underestimates the extent of tissue viability compared to metabolic imaging.[4] Our data are compatible with their findings clearly showing that 5 of 20 segments with persistent defect by thallium criteria had function improved by revascularization.

Concordance and discordance between contractile response to ISDN + dobutamine and thallium scintigraphy with reinjection

Interpretation of both studies was concordant in 40 segments (85.1%), and mismatched in 7 segments (14.9%), so exellent agreement was obtained, but all 3 segments with thallium viable but no contraction reserve improved in function after revascularization, and 3 of 4 segments

with contractile response to ISDN + dobutamine and persistent defect even after reinjection showed no functional improvement. Thus, in 6 of 7 discordant segments, thallium with reinjection identified tissue viability correctly. Although the mechanism responsible for the depressed contractile function has not been established, this may be a protective response to reduce oxygen demand in the setting of reduced oxygen availability, thereby establishing perfusion-contraction matching. Under these circumstances, it is unclear whether signal transduction of beta-receptor stimulation leading to contractile augmentation is still working or not, because no animal model of hibernating myocardium to clarify this hypothesis has not been established.

Another possible explanation of discordance between these two tests is based on the effect of the neighboring normal myocardium, by which even the necrotic area could be dragged in part. Only the anterior and LAO views were assessed for gated blood pool scintigraphy in this study, and the difficulty in discriminating infarct zone from the nonischemic zone might be a reason for the positive response of the irreversibly asynergic zone to ISDN and dobutamine.

Study limitations
Our study limitation was the inability to quantitatively compare the true myocardial thallium concentration and wall motion change caused by ISDN and dobutamine. Although the observers who graded thallium activity and wall motion score achieved a high level of agreement, reliance on visual determination of thallium-201 redistribution and fill in was unclear because no calibration of redistribution was defined. As for the wall motion analysis of gated blood pool scan, poor spacial and temporal resolution compared to echocardiography was a problem, so we compared the cine loop scintigraphy during control and ISDN + dobutamine infusion side by side, and a 5 grade scale was used to evaluate the subtle change in wall motion, and there was close agreement.

Another study limitation which should be taken into consideration is the reliability of wall motion improvement as a reliable standard for assessing viability. Despite the constant use of medications during this study, the degree of asynergy may be influenced not only by myocardial contractility but also by loading conditions such as the blood pressure and left ventricular end diastolic volume. This means that improvement in wall motion may not always imply improvement in contractility, but in a clinical situation, the change in the asynergic degree of the left ventricular wall could be regarded as the best end point for assessing the result of interventional therapy.

Clinical implications
Our findings indicate that the differentiation of asynergic viable myocardium from scarring may be possible by wall motion response to ISDN + low-dose dobutamine. However, the problem of some underestimation of the prediction of reversibility remains to be solved. Thallium with reinjection is superior to ISDN + dobutamine gated blood pool scintigraphy in both sensitivity and specificity, and should therefore be the method of choice.

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