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Adenosine-Echocardiography for the Detection of Coronary Artery Disease

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Abstract

The use of adenosine-echocardiography to detect coronary artery disease was evaluated in 39 patients. Adenosine was infused intravenously at 0.14 mg/kg/min for 6 minutes with continuous recording of two-dimensional echocardiography. Three minutes after the start of adenosine infusion, thallium (^{201}Tl) was administered into a separate vein. Myocardial single photon emission computed tomography (SPECT) images were obtained 10 minutes and 3 hours after the ^{201}Tl injection. Transient reduction of systolic wall motion after adenosine infusion was considered an abnormal ischemic response. Echocardiography detected a wall motion abnormality after adenosine infusion in 17 of 39 patients. ^{201}Tl redistribution was observed in 28 patients. Agreements for the presence of myocardial ischemia or infarction between ^{201}Tl SPECT and echocardiography were 62% (24/39). The sensitivity of echocardiography in patients with single-vessel disease was 21%, but 76% with multi-vessel disease ($p < 0.01$ vs single-vessel disease). All side effects were tolerated well and disappeared within 1 or 2 minutes after stopping adenosine infusion.

Adenosine-echocardiography was particularly useful for the detection of multiple-vessel coronary disease. Simultaneous evaluation of wall motion and myocardial perfusion during adenosine-induced maximal coronary vasodilation may improve the functional description of diseased myocardial segments.

Key Words

adenosine, echocardiography, coronary artery disease, thallium-201 SPECT

INTRODUCTION

Thallium-201 (^{201}Tl) myocardial perfusion imaging with pharmacologic coronary vasodilation induced by dipyridamole has been accepted as an alternative to exercise stress imaging for the noninvasive diagnosis of coronary artery disease[1-3]. ^{201}Tl scintigraphy after dipyridamole infusion also provides powerful prognostic information for the risk stratification of patients with acute myocardial infarction and candidates for extensive vascular surgery[4,5]. However, dipyridamole has only an indirect vasodilatory effect through the blockade of cellular adenosine uptake[6]. Maximal coronary vasodilation cannot be achieved in a substantial number of patients using the standard dose of dipyridamole[7,8]. ^{201}Tl scintigraphy has recently been combined with intravenous infusion of adenosine, a direct and potent coronary vasodilator[9,10], and achieved good clinical results in the detection of coronary artery disease[11-14].

Two-dimensional echocardiography during dipyridamole infusion is also used for the detection of coronary artery disease[15]. However, the feasibility of using adenosine infusion during the echocardiography test for the detection of coronary artery disease has not been rigorously examined. Previous adenosine-echocardiography testing has shown that wall motion abnormality occurs in the areas of perfusion defects during adenosine infu-

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sion[16], but transient asynergy is observed in only 10% of patients with coronary artery disease[17]. Therefore, further evaluation is required before the value of adenosine-echocardiography for the detection of coronary artery disease can be accepted.

This study tested the use of adenosine-echocardiography in the detection of coronary artery disease.

METHODS

Subjects

Thirty-nine consecutive patients who underwent simultaneous ^{201}Tl myocardial single photon emission computed tomography (SPECT) imaging and two-dimensional echocardiography during adenosine infusion for the diagnosis of coronary artery disease at Yamagata University Hospital in the 6 months period from July to December 1991 were enrolled. There were 23 males and 16 females aged from 41 to 85 years (mean 63 ± 9 years). None had received percutaneous transluminal coronary angioplasty or aorto-coronary bypass grafting. Coronary arteriography revealed significant coronary artery stenosis in a single vessel in 14 patients, two vessels in 13, three vessels in four, and no significant coronary artery stenosis in eight. Significant coronary stenosis was defined as a 75% or greater narrowing of the lumen in either the main epicardial arteries or major branches. All imaging studies were performed for clinical purposes after informed consent was obtained. The study protocol was approved by the Yamagata University Committee on Human Research on June 20, 1991.

Adenosine infusion protocol

All cardiovascular medications were discontinued for at least 12 hours before the adenosine test, except for the short-acting sublingual nitrates. Adenosine was dissolved into physiological saline at a concentration of 2 mg/m*l*. Adenosine was infused intravenously at 0.14 mg/kg/min for 6 minutes[11] using an infusion pump (Nakagawa-Seikousha). Three minutes after the start of adenosine infusion, a dose of 111 MBq of ^{201}Tl was administered into a separate vein (**Fig. 1**). Blood pressure was measured at the left arm by a standard cuff method, 12-lead ECG and two-dimensional echocardiography were continuously monitored during the test.

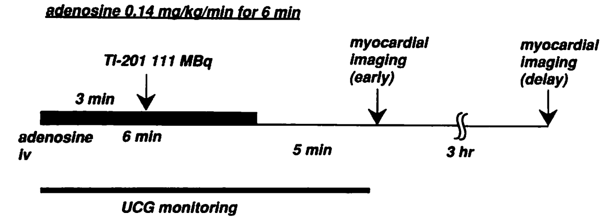

Fig. 1 Protocol for ^{201}Tl myocardial perfusion imaging and two-dimensional echocardiography during adenosine infusion
UCG = echocardiography

^{201}Tl myocardial SPECT imaging

Cardiac imaging was begun 10 minutes after the ^{201}Tl injection and repeated 3 hours later. All images were obtained on a large field-of-view rotating gamma camera (Siemens, ZLC-7500 Digtrac) equipped with a parallel hole, high resolution collimator. Thirty-two planar acquisitions were performed during a 180° rotation from the 30° right anterior oblique to the 60° left posterior oblique positions[18,19]. Each 64×64 matrix was collected for 30 seconds during each of the 32 acquisitions and contained 150,000 to 200,000 counts. Data were processed using a nuclear medicine computer system (Shimadzu, Scintipac-700). A series of contiguous transaxial images were reconstructed by means of a filtered back projection algorithm without attenuation correction[18,19]. Transaxial images were further processed according to the anatomical axis. Orthogonal tomograms, each 6 mm thick, were reconstructed parallel to the short-axis and vertical long-axis of the left ventricle.

For evaluating the regional ^{201}Tl uptake, two short-axis images at the basal and apical levels and a vertical long-axis image at the mid left ventricle were used. The regions with decreased ^{201}Tl uptake were assessed by two independent observers who did not know any information regarding the clinical history and angiographic findings of the patients. The left ventricular myocardium was divided into nine segments[20,21]. A 5-point scoring system was used to evaluate segmental ^{201}Tl uptake in the myocardium[20,21]: 4 = normal, 3 = slightly reduced, 2 = reduced, 1 = severely reduced, 0 = no activity. In interpreting early and delayed images, an uptake score on the early images of less than 2 was defined as an initial defect. An increase of one or more in the uptake score on the delayed images was defined as redistribution. The grading of myocardial ^{201}Tl uptake was settled by consensus between the two observers. When there was disagreement on the results, a third observer reviewed the study, and the majority opinion was taken.

Echocardiography

Two-dimensional echocardiography (Aloka, SSD-870) was continuously recorded before, during adenosine infusion and for 5 minutes after termination of infusion by a experienced cardiologist. Parasternal long- and short-axis views and the apical 4-chamber view were recorded on videotapes at rest as a baseline study and at the peak effect of adenosine. The echocardiograms were analyzed on a CRT by two independent observers. The left ventricle was divided into five segments in each view[15], and regional wall motion was graded by a semi-quantitative scoring system as follows: 3 = hyperkinesis, 2 = normal, 1 = hypokinesis, 0 = akinesis, −1 = dyskinesis. A transient wall motion abnormality, which was defined as a decrease of at least one point in the segmental wall motion score during adenosine infusion, was considered as an ischemic response. Inadequately visualized segments and the regions with dyskinesis in the baseline study were excluded from the analysis. The regional wall motion was graded by consensus between the two observers. However, there was disagreement on the results, a third observer reviewed the study, and his judgment was taken.

Statistics

The values of data were reported in terms of mean ± one standard deviation. The heart rate, blood pressure and rate pressure products were compared by a paired *t*-test. The chi-square test was used to compare the differences in proportion. A p value < 0.05 was considered significant.

RESULTS

Adenosine infusion caused a slight reduction in systolic blood pressure and an increase in heart rate (**Table 1**). The rate pressure products increased slightly (9,314±2,377 vs 10,360±2,148, $p < 0.001$). Side effects during adenosine infusion are summarized in **Table 2**. Headache and nausea were the frequent side effects. Transient prolongation of the PR interval (first-degree atrioventricular block) was observed in three of 39 (8%) patients. Transient second-degree atrioventricular block developed in seven of 39 (18%) patients. Thirteen patients (33%) experienced chest pain, and ischemic ST depression, defined as horizontal or downsloping ST depression of greater than or equal to 1 mm, occurred in 17 patients (44%). All symptoms and hemodynamic changes were tolerated well and disappeared within 1 or 2 minutes after discontinuing adenosine infusion. Intravenous infusion of aminophylline was necessary to reverse the side effects of adenosine in only four patients (10%).

Table 1 Hemodynamic changes during adenosine infusion

	Basal	Adenosine
Heart rate (beats/min)	66±13	84±12*
Systolic blood pressure (mmHg)	141±19	123±20*
Rate pressure products (beats/min × mmHg)	9,314±2,377	10,360±2,148*

* $p<0.001$ vs basal value

Table 2 Side effects of adenosine infusion

	Patients (%)
Chest pain	13 (33)
Headache	4 (10)
Nausea	3 (8)
Flushing	2 (5)
Abdominal discomfort	1 (3)
Dyspnea	1 (3)
ST depression	17 (44)
AV block I°	3 (8)
AV block II°	7 (18)

Echocardiograms of a patient with angina pectoris are shown in **Fig. 2**. The patient had 90% coronary stenosis in the left anterior descending artery and the left circumflex artery. Transient reduction of regional wall motion during adenosine infusion was observed at the anteroseptal wall of the left ventricle.

Fig. 3 compares the echocardiography and ^{201}Tl SPECT images in the presence or absence of myocardial ischemia or infarction. Complete agreement between the echocardiograms and ^{201}Tl images occurred in 24 of 39 (62%) patients. Adenosine-induced wall motion abnormality was observed in 17 of 39 patients (44%), 16 of the 17 had ^{201}Tl redistribution and angiographically proved coronary artery disease.

Fig. 4 shows the sensitivity and specificity for the detection of patients with coronary artery disease. The sensitivity was lower in echocardiography than

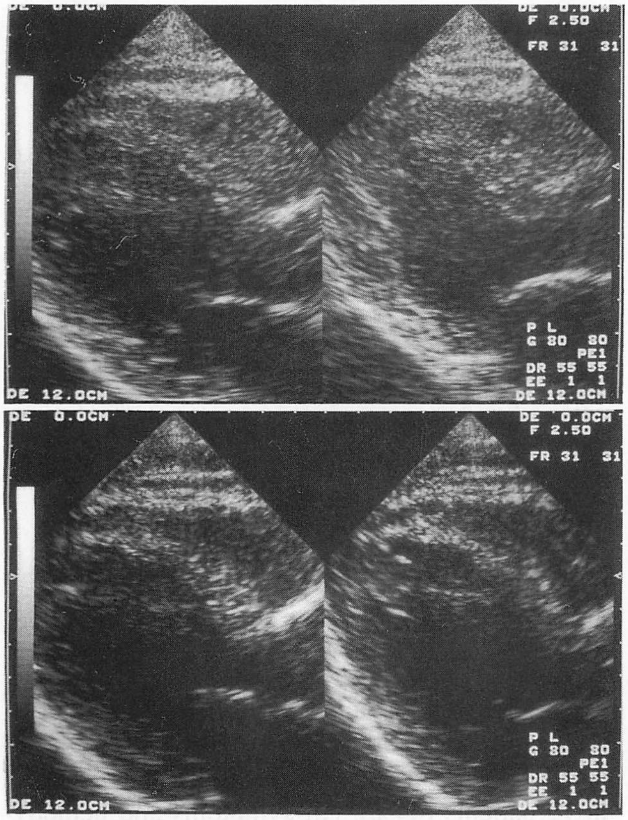

Fig. 2 Adenosine-echocardiograms of a patient with angina pectoris
The parasternal long-axis views of the baseline study (*upper*) and during adenosine infusion (*lower*). Transient reduction of systolic wall motion is seen at the anteroseptal wall of the left ventricle during adenosine infusion.

Tl-201 imaging \ echocardiogram	N	IS	MI
N	6	1	1
IS	11	16	1
MI	1	0	2

24 / 39 : 62%

Fig. 3 The presence of myocardial ischemia or infarction detected by ^{201}Tl SPECT images and echocardiograms
N=normal; IS=ischemia; MI=myocardial infarction

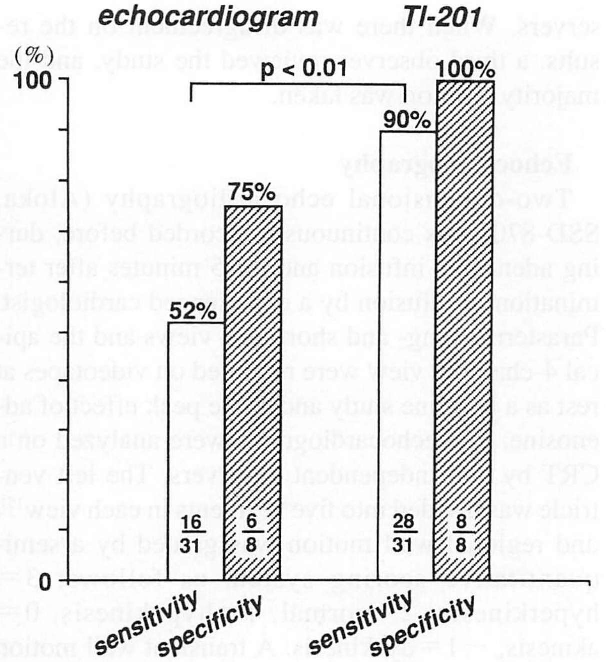

Fig. 4 Sensitivity and specificity for the detection of patients with coronary artery disease

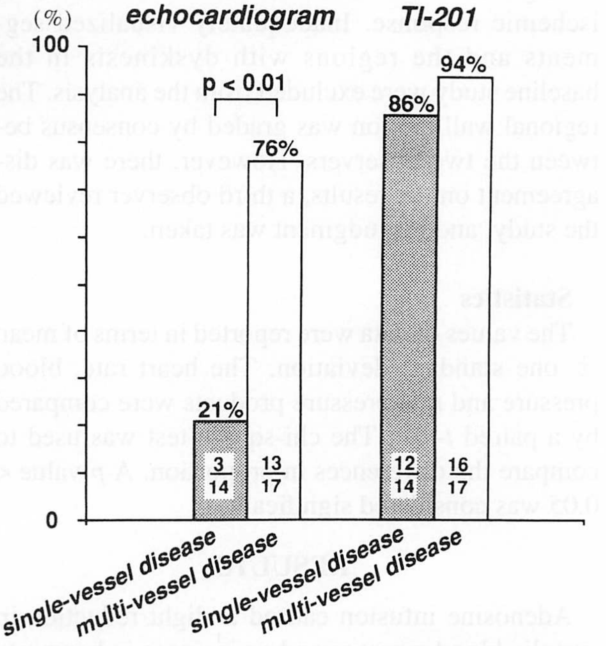

Fig. 5 Comparison of sensitivity between the patients with single- and multi-vessel coronary disease

in ^{201}Tl imaging (52% vs 90%, $p < 0.01$), although the specificity was not different between the two tests (75% vs 100%).

Then, 31 patients with coronary artery disease were divided into two groups according to the findings of coronary arteriography: single-vessel disease ($n=14$) and multi-vessel disease ($n=17$).

For patients with single-vessel disease, echocardiography had a sensitivity of 21% (**Fig. 5**). However, for patients with multi-vessel disease, the sensitivity of echocardiography was 76% ($p < 0.01$ vs single-vessel disease). The sensitivity of ^{201}Tl SPECT imaging was similar for patients with single- and multi-vessel disease (86% vs 94%).

DISCUSSION

This study showed that adenosine-induced transient wall motion abnormality could be detected by two-dimensional echocardiography. The adenosine-echocardiography test was safe and useful for the diagnosis of coronary artery disease, especially in patients with multi-vessel disease.

In exercise stress testing, the level of exercise affects the ability to detect myocardial ischemia[22)]. Inadequate exercise results in "false negative" images and underestimation of the extent of coronary artery disease. However, pharmacological stress tests can achieve a more uniform level of stress[23)]. Currently, dobutamine and dipyridamole have been practically applied as a pharmacological stress testing[15,23,24)]. Dobutamine has positive inotropic and chronotropic effects on the heart and results in an increase in myocardial oxygen demand. Thus, in the presence of fixed coronary stenosis, a supply-demand mismatch occurs, and myocardial ischemia ensues[24)]. In contrast, dipyridamole increases coronary blood flow, but not myocardial oxygen demand. The predominant mechanism causing ^{201}Tl perfusion defects during dipyridamole infusion is flow heterogeneity between territories supplied by the normal and stenotic coronary arteries[25)].

The incidence of myocardial ischemia provoked by adenosine or dipyridamole infusion, in which transient reduction of systolic wall motion or ST depression were a positive finding, varies from 10% to 89%[7,15-17,26)]. In the present study, adenosine-induced wall motion abnormality was observed in 16 of 31 patients (52%) with coronary artery disease, while positive ^{201}Tl SPECT was noted in 28 of 31 patients (90%). These discrepancies of sensitivity between ^{201}Tl redistribution and wall motion abnormality suggest a physiological inequality between heterogeneous flow distribution and myocardial ischemia.

In myocardial regions perfused by normal coronary arteries, adenosine increases the coronary blood flow, reflecting normal coronary flow reserve[9,10)]. Since the presence of coronary stenosis limits the level of coronary flow reserve, a flow tracer, ^{201}Tl, can detect the heterogeneous distribution of coronary blood flow as perfusion defects[25)]. Therefore, the presence of myocardial ischemia is not essential to image perfusion defects by ^{201}Tl SPECT. When adenosine is administered in the setting of critical coronary artery stenosis, coronary blood flow decreases absolutely as well as relatively due to the "coronary steal" phenomenon[27)]. Transient reduction of wall motion thus occurs as a result of myocardial ischemia. These discrepancies in the mechanisms for the positive test between ^{201}Tl imaging and echocardiography may be the relevant cause of the differences in sensitivity found by the present study. Fung *et al.* Showed in animal experiments that regional wall motion at the area perfused by a stenotic coronary artery deteriorated after dipyridamole along with absolute reduction in subendocardial blood flow[27)]. Nabeyama *et al.* clearly showed dipyridamole-induced wall motion abnormality in the area perfused solely by the collateral vessels[28)]. These lines of evidence suggest that dipyridamole induces myocardial ischemia in the presence of critical coronary stenosis or collateral vessels. This may explain our results that adenosine-induced wall motion abnormality was more frequently observed in patients with multi-vessel disease than those with single-vessel disease.

Continuous echocardiographic monitoring of left ventricular wall motion during adenosine infusion can provide complimentary functional information to myocardial ^{201}Tl SPECT imaging. Simultaneous evaluation of the wall motion by echocardiography and myocardial perfusion by ^{201}Tl will enhance the characterization of myocardial ischemia.

要　約

アデノシン負荷断層心エコー図法による冠動脈疾患の評価

竹石　恭知　　千葉　純哉　　阿部　真也　　池田こずえ　　友池　仁暢

冠動脈疾患の診断におけるアデノシン負荷断層心エコー図法の有用性を検討した．冠動脈疾患の疑われる39例にアデノシン0.14 mg/kg/minを6分間持続静注し，その間，断層心エコー図と^{201}Tl心筋イメージングを同時に行って，前者により左室壁運動を連続的に観察，アデノシン投与による一過性壁運動異常の出現を虚血と判定した．また111 MBqの^{201}Tlを，アデノシン静注開始3分後の時点で別の静脈ラインより投与し，10分後と3時間後に心筋SPECT像を撮像，左室短軸，長軸断層像を再構成し，再分布の有無を視覚的に判定した．アデノシン投与により17例(44%)に左室壁運動異常が出現し，^{201}Tlの再分布は28例(72%)に認められた．正常，虚血，梗塞の判定は，断層心エコー図と^{201}Tl心筋像で，62% (24/39)で一致し，冠動脈疾患検出の感受性，特異性はそれぞれ，前者では52% (16/31), 75% (6/8)，後者では90% (28/31, $p < 0.01$ vs 断層心エコー図), 100% (8/8)であった．断層心エコー図の陽性率は，1枝病変よりも多枝病変で高かった(21% vs 76%, $p < 0.01$).

アデノシン負荷心エコー図法により冠動脈疾患の検出が可能であり，とくに多枝病変例での有用性が示唆された．このように心エコー図法を^{201}Tl心筋イメージングと併用することにより，負荷中の左室壁運動と心筋灌流の同時評価が可能であり，冠動脈疾患の評価に有用と考えられた．

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