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# Clinical application of three-dimensional myocardial imaging: Evaluation of efficacy of medical treatment on myocardial perfusion

Junichi YAMAZAKI,* Hiromitsu HOSOI,* Satoshi ISHIGURO,* Hiroshi MUTO,* Hisayo YAMASHINA,* Takeshi MORISHITA,* Masaaki TAKANO,** Junichi SUGITA*** and Munehiro TAKAHASHI****

*First Department of Internal Medicine, School of Medicine, Toho University,
**Radioisotope Inspection Laboratory, School of Medicine, Toho University,
***K.G.T. Corporation and ****Shimadzu Corporation

To investigate the clinical applicability of the three-dimensional (3D) myocardial imaging using a newly developed system (the Application Visualization System-Medical Viewer), thallium-201 myocardial single photon emission computed tomography was performed in 19 patients with previous myocardial infarction before and after treatment with nisoldipine. We have developed a new method for automatically reconstructing 3D imaging for the stereoscopic evaluation of myocardial perfusion. The left ventricular myocardial volume with a radioisotope count ≧ 50% of maximum was calculated by using the conventional surface rendering method. With these images, the effect of nisoldipine on myocardial perfusion was assessed and the myocardial volume with a radioisotope count ≧ 50% of maximum was compared. In fifteen (88%) of 19 patients, myocardial perfusion increased in the infarct areas after nisoldipine treatment. Nisoldipine significantly increased the myocardial volume with a radioisotope count ≧ 50% of maximum from 141 ± 17 to 153 ± 18 m*l* on the stress 3D imagings. These findings indicate that nisoldipine improved myocardial perfusion during exercise. 3D imaging provided stereoscopic assessment of the changes in myocardial perfusion following treatment with nisoldipine and also detected transient enlargement of the left ventricular lumen induced by exercise.

**Key words:** three-dimensional myocardial imaging, thallium-201 myocardial single photon emission computed tomography, myocardial perfusion, nisoldipine, surface rendering

## INTRODUCTION

THALLIUM-201 MYOCARDIAL SCINTIGRAPHY is useful for assessing the outcome of surgical and medical treatment for ischemic heart disease as it allows the noninvasive measurement of myocardial perfusion.[1] Scintigraphic data are currently analyzed by the bull's eye method,[2] but this method is likely to underestimate the ischemic area at the apex and overestimate basal ischemia since it involves displaying short axis images on a polar map. Three-dimensional (3D) myocardial imaging has the potential to provide more accurate information on the extent of ischemia and the changes in cardiac morphology, such as transient enlargement of the left ventricle with exercise, which cannot be detected by two-dimensional polar mapping.[3–8] We have recently developed a new software program for 3D imaging by using the Application Visualization System-Medical Viewer (AVS-MV: K.G.T. Corp., Tokyo, Japan).[9] In the present study, we performed thallium-201 myocardial single photon emission computed tomography (myocardial SPECT) following exercise in ischemic heart disease patients before and after treatment with nisoldipine,[10–15] a calcium antagonist, and then evaluated the effect of therapy on myocardial perfusion by 3D imaging. A change in the left ventricular myocardial volume with a radioisotope count ≧ 50% of maximum by the conventional surface rendering method was observed before and after administration of nisoldipine.

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For reprint contact: Junichi Yamazaki, M.D., First Department of Internal Medicine, School of Medicine, Toho University, 6–11–1 Ohmori-Nishi, Ohta-ku, Tokyo 143, JAPAN.

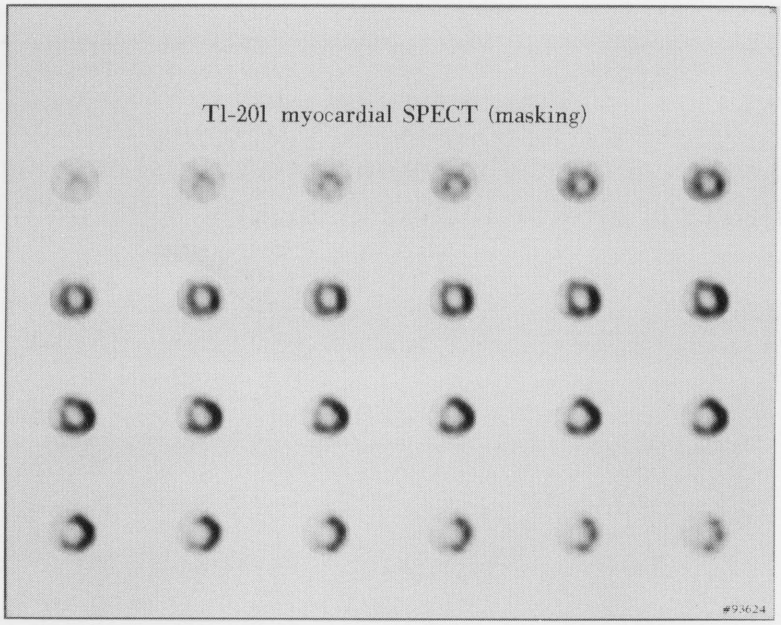


**Fig. 1** Procedure for constructing 3D myocardial imagings: Short axis images are masked.

## METHODS

*Study population*

The subjects were 19 patients with previous myocardial infarction (15 men and 4 women with a mean age of 62.4 ± 8.5 years). All the patients had a history of prolonged chest pain, and developed sequential electrocardiographic changes and myocardial enzyme changes consistent with myocardial infarction. The patients with previous myocardial infarction imprised 14 cases of antero-septal (A/S) infarction with ST-segment changes in precordial leads $V_1$ through $V_6$, and 5 cases of infero-posterior (I/P) infarction with ST-segment changes in leads II, III and $aV_F$. Fifteen of the 19 patients underwent coronary angiography and all had significant stenosis (a percent luminar diameter narrowing of 50% or more in either main epicardial artery) on the infarct-related coronary artery. Eleven patients had one vessel stenotic lesion, and 4 had two vessel stenotic lesions. In the remaining four of the 19 patients, a treadmill ECG test showed significant ST segment depression. Ten of the 19 patients had ST-segment depression with chest pain, although 9 patients had ST-segment depression without chest pain. In all 19 patients, incomplete redistribution was noted in the infarct area on myocardial SPECT prior to treatment with nisoldipine, confirming the occurrence of ischemia and myocardial viability in the patients with previous myocardial infarction.

*Test drug and administration*

Nisoldipine was administered at a dose of 10 mg/day for 3–6 months. During the treatment period, concomitant use of nitrates (except for occasional sublingual nitroglycerin or isosorbide dinitrate during angina attacks), other calcium antagonists, β-blockers and other antiangina agents was prohibited. Tranquilizers, hypnotics, antihyperlipidemic agents, and antiplatelet agents could be administered provided that there was no modification of the dosage throughout the study and provided their use had been instituted prior to the study. All of the patients had stable symptoms throughout the study.

*Data collection and processing*

Myocardial SPECT was performed before and after nisoldipine therapy with a dedicated 3-detector imaging system equipped with general-purpose low-energy collimators (PRISM-3000: Ohio Imaging, Cleveland, Ohio/Shimadzu Corp., Kyoto, Japan). The exercise load was gradually titrated upward through multiple levels with a bicycle ergometer: exercise was started at 25 watts, and increased in increments of 25 watts every 3 minutes. During the exercise, standard 12-lead electrocardiogram and blood pressure levels were monitored at 1 minute intervals. $^{201}$TlCl 74–148 MBq (2–4 mCi) was injected intravenously at peak exercise with such signs as chest pain, shortness of breath, fluctuation in blood pressure/heart rate, and significant ST-segment changes on electrocardiogram as the end points, and exercise was continued for 60 seconds after the injection of $^{201}$TlCl. A stress image was taken 5 minutes after intraveneous injection of $^{201}$TlCl, and the delayed image 4 hours later. The gamma camera was peaked on the 80 KeV X-ray peak (15% window). Data were collected under the camera by the continuous mode, with a 5 degrees step, and 24 steps for each of the three detectors in a short distance noncircular rotation system through 360 degrees. Images were acquired for 37.5 seconds/view, with a total imaging time of approximately 15 minutes. The projection data were obtained

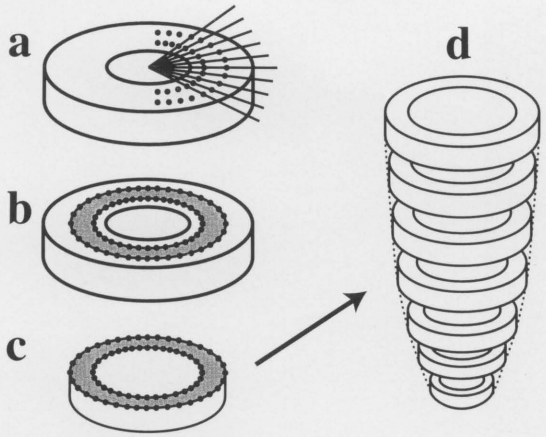


**Fig. 2** Procedure for constructing 3D imagings. Radial lines are drawn from the center of the short axis image and the maximum thallium-201 count on each line is determined [a]. The points with the maximum counts are taken as the outer border of the left ventricular myocardium, and the inner border is decided [b, c]. Following subtraction of the ventricular lumen, the short axis images of the left ventricle thus obtained are used to construct a 3D imaging [d].

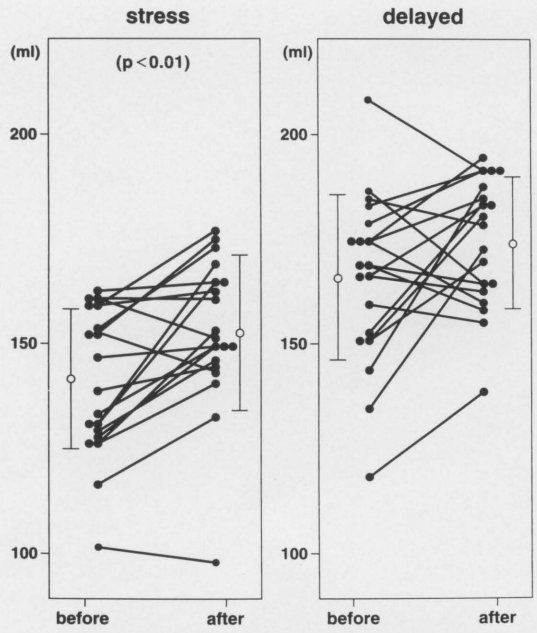


**Fig. 3** Myocardial volume with a radioisotope count ≧ 50% of maximum before and after administration of nisoldipine in 19 patients with previous myocardial infarction. The volume is significantly increased on stress images and also shows a non-significant increase on delayed images.

upon data acquisition with a 64 × 64 matrix, and projection images were reconstructed with a 1.33 × zoom. Transaxial images were reconstructed by a filtered back projection method, with a Shepp & Logan filter, and attenuation correction was not applied. These transaxial images were then reoriented in the short axis. The data were then analyzed with ODYSSEY software (Titan 750: Ohio Imaging, Cleveland, Ohio/Shimadzu Corp., Kyoto, Japan) for myocardial SPECT imaging. Subsequently, 3D myocardial imagings of the left ventricle were constructed, displayed, and analyzed with a new system (the Application Visualization System-Medical Viewer: AVS-MV; Titan 2).[9] Various software modules required for the construction of 3D imagings of the left ventricular myocardium were made with the AVS-MV.

*Construction of three-dimensional imagings*

3D imagings were constructed for stereoscopic evaluation of myocardial perfusion and the extent of ischemic lesions. First, short axis images of the left ventricle were masked to eliminate the background (Fig. 1). After determining the central point of the left ventricular lumen on the masked short axis images, the peak point was detected automatically on a radial line which was drawn on the left ventricular myocardium from the central point. After a total of 72 peak count points were detected by changing the angle in the radial line in 5 degree increments, the line connecting these points of each slice was defined as the outer border of the left ventricular myocardium. When the peak count point could not be detected on a radial line, it was determined with reference to the position of the peak point on the adjacent line (Fig. 2a). Seventy-two points shifted 3 pixels inwards from the outer border points on the radial lines were determined. The line connecting these points in each slice was defined as the inner border of the left ventricular myocardium (Fig. 2b). After determining the outer and inner borders of the myocardium, 3D imaging was reconstructed by three-point spatial smoothing between the slices from the apical to basal lesion selected visually (Fig. 2c, 2d). Then the radioisotope counts for each pixel of the newly reconstructed 3D imaging were determined, and taking the maximum value as 100%, the radioisotope counts were mapped in color on the 3D image. In this way improvement in myocardial perfusion after treatment with nisoldipine was evaluated visually and numerically in terms of changes in the findings in 3D images. In patients with severe defects in the infarct area, the region of interest of the outer border was visually determined by manual setting of the lateral margin of the left ventricle.

*Calculation of myocardial volume based on conventional surface rendering*

Myocardial volume with a radioisotope count ≧ 50% of maximum was calculated by using the surface rendering method. The maximum radioisotope count per voxel on the 3D imagings was designated as 100%, and thresholds were set at 5% intervals below this count. Then the myocardial volume with a radioisotope count above each of the threshold values was calculated. SPECT images with a 64 × 64 matrix obtained with ODYSSEY had an area of 3.5 × 3.5 $mm^2$ pixels. The volume (voxels) was calculated by multiplying the area by the slice interval. In this way, the changes in myocardial volume with a radio-

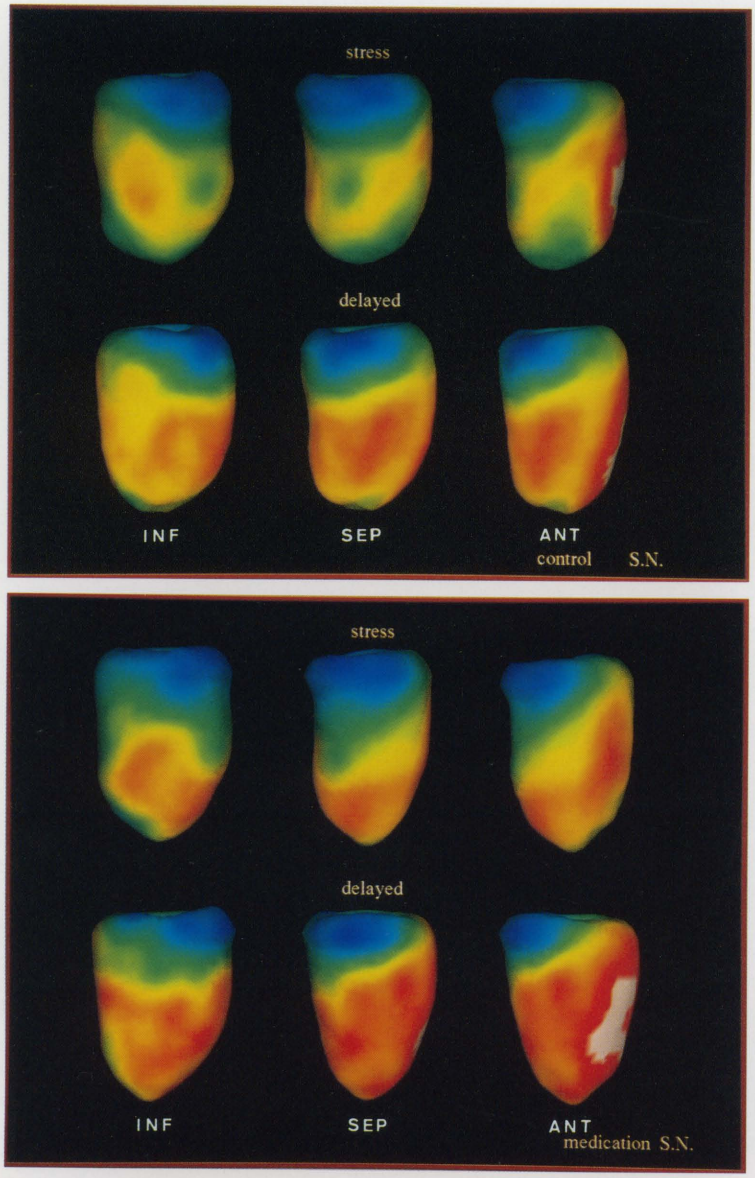


**Fig. 4** 3D imagings obtained from a patient with previous myocardial infarction, showing improved perfusion of the apex, anterior wall, and septum following treatment with nisoldipine (a; control: before treatment, b; medication: after treatment; INF: inferior view, SEP: septal view, ANT: anterior view).

isotope count ≧ 50% of maximum were compared before and after administration of nisoldipine.

*Statistical analysis*

Results were expressed as the mean value ± S.D. and the paired t-test was used for analysis with the level of significance being set at $p < 0.05$.

## RESULTS

*Visual findings in three-dimensional images before and after administration of nisoldipine*

The duration of exercise stress was significantly prolonged at 582 ± 121 sec. to 646 ± 118 sec., but the systolic pressure, heart rate and pressure rate product remained unchanged after nisoldipine administration compared to pretreatment. On the exercise myocardial SPECT after nisoldipine administration, chest pain decreased to 2 out of ten patients who had chest pain in the control period before nisoldipine. The existence of viable myocardium and myocardial ischemia were suggested in the infarct area. In fifteen of the 19 patients, nisoldipine treatment significantly increased the thallium-201 myocardial perfusion on 3D images in the infarct areas. Before nisoldipine therapy, transient enlargement of the left ventricular cavity with exercise was observed on 3D imagings obtained from 4 patients with two vessel stenotic lesions or extent infarct lesions.

*Change of the left ventricular myocardial volume*

In the 19 patients with previous myocardial infarction, the left ventricular myocardial volume with a radioisotope count ≧ 50% of maximum was significantly increased from 141 ± 17 m*l* to 153 ± 18 m*l* on stress images ($p < 0.01$), and also increased from 166 ± 20 m*l* to 175 ± 15 m*l* on delayed images (Fig. 3).

## CASE REPORTS

A 50-year-old man with previous myocardial infarction in the anterior wall and septum showed complete occlusion of the left anterior descending artery (LAD: #7) and collateral vessel from the right coronary artery on coronary angiograms. A treadmill test performed after a 48-hr drug-free period showed significant ST depression in leads $V_{4-6}$, but no chest pain was induced during or after exercise. The 3D stress imaging obtained prior to nisoldipine therapy showed thallium-201 defects and impaired perfusion at the apex, anterior wall, and septum, as well as slightly impaired perfusion of the posterior wall (Fig. 4a). Incomplete redistribution was noted in the anterior wall and the septum on the delayed 3D imaging. Myocardial SPECT was performed after treatment with nisoldipine for about 6 months. Perfusion of the septum and apex was improved by nisoldipine therapy (Fig. 4b). The stress 3D imaging showed transient enlargement of the left ventricular cavity prior to nisoldipine treatment, but this was absent after treatment (Fig. 4a, 4b). Figure 5 shows the distribution of myocardial volume versus the radioisotope count threshold at 5% intervals in a patient with previous myocardial infarction. Treatment with nisoldipine increased the myocardial volume with a count of 60–70% on the stress image and a count of 75–90% on the delayed image, suggesting improvement in myocardial perfusion.

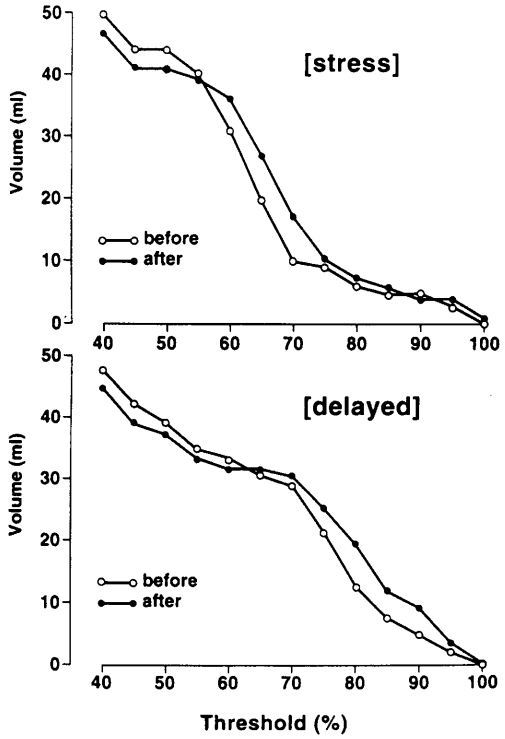


**Fig. 5** Myocardial volume with a radioisotope count above each threshold value set at 5% intervals. Treatment with nisoldipine improved myocardial perfusion, increasing the myocardial volume with a count of 60–70% on initial images and a count of 75–90% on delayed images.

## DISCUSSION

The SPECT unit with a three-head camera (PRISM-3000) has an advantage over the conventional one-head camera SPECT unit because the non-circular orbit of the camera heads fitting the individual form of the body within a short time has improved the spatial resolution.

In the present study, 3D myocardial imaging was obtained in patients with ischemic heart disease by using the AVS-MV. The AVS-MV has a library function which converts the geometry into an equivalent polytriangle geometry to create 3D models from SPECT, CT and MRI. For this reason, besides applying the volume algorithm to surface files, we have been able to compute the volume of any AVS geometry that represents a closed surface. The purpose of this study was to investigate the clinical applicability of 3D imaging for visually assessing changes in myocardial perfusion as well as changes in the left ventricular myocardial volume with a radioisotope count above various threshold levels by the surface rendering method. Another purpose was to evaluate the effect of nisoldipine on myocardial perfusion following exercise by means of 3D imaging in patients with previous myocardial infarction.

*Construction of three-dimensional imaging*

Conventional methods of 3D imaging establish the threshold for visualization at 40–60% uptake.[6] With such methods, the region under the threshold is visualized as a complete defect, so the severity of the ischemia cannot be assessed. The new system employed in the present study constructed 3D imagings without establishing a threshold. With this system, short axis images of the left ventricle were masked to eliminate the background, and the outer border margin of the left ventricular myocardium was determined with a program for automated setting of the region of interest, but in the case of images featuring severe defects, it proved impossible to visualize the outer border surface of the myocardium with this program and it had to be determined manually. Because $^{201}$TlCl was used as the tracer and there was no synchronized ECG, the maximum count on radial lines drawn from the center of the short axis images was regarded as representing the lateral margin of the left ventricular myocardium in order to allow for of left ventricular wall motion. Manual setting of the lateral margin of the left ventricle was slower than the automated method, but still took only 5 minutes. This deficiency is therefore unlikely to preclude clinical application of the present system, but in the patients with a radioisotope count $\leqq$ 20–25% of maximum in the infarct area, it proved impossible to visualize the outer border of the myocardium with this program. In such a patient with a complete defect in the infarct area, 3D imaging estab-

lishing a threshold based on the conventional surface rendering method is useful for clinical application.

*Calculation of myocardial volume by the surface rendering method*

The volume of ischemic myocardium cannot be calculated by two-dimensional imaging. In the present study, the left ventricular myocardial volume showing a radioisotope count ≧ 50% of maximum was calculated on 3D imagings by using the conventional surface rendering method to determine the number of voxels as well as the radioisotope count per voxel. The maximum radioisotope count per voxel was set at 100% and thresholds were set at 5% intervals below this. Then the number of voxels and the radioisotope count above each threshold were determined and used to prepare a frequency curve that allowed perfusion to be assessed objectively. Although this method may not reflect the true left ventricular myocardial volume because the 3D imagings were constructed from $^{201}$TlCl uptake data obtained without ECG synchronization, it is probably useful for longitudinal assessment of the changes in myocardial perfusion. This conclusion is supported by our detection of a significant increase in left ventricular myocardial volume with a radioisotope count ≧ 50% of maximum on the stress images obtained after nisoldipine therapy in the patients with previous myocardial infarction. Recently, $^{99m}$Tc-labeled high-energy products which facilitate ECG-synchronized 3D imaging have come into widespread clinical use. With these agents it should be possible to calculate the actual myocardial volume in the left ventricle.[7,8]

*Improvement in myocardial perfusion with nisoldipine*

Like other calcium antagonists, nisoldipine exerts an antianginal effect by reducing afterload and myocardial oxygen demand through peripheral and coronary vasodilation,[11,12] but it has greater coronary selectivity and a longer duration of action than other calcium antagonists.[13,14] In the present study, the effect of nisoldipine on total left ventricular myocardial perfusion was evaluated by 3D imaging. The administration of nisoldipine improved myocardial perfusion in the stress and delayed images. The thallium-201 uptake of infarct area in the stress image was increased by nisoldipine therapy, suggesting that this drug also improved myocardial perfusion during exercise.[14–17] It is therefore possible that nisoldipine suppresses the increase in coronary tone at sites of organic stenosis, which has been suggested to be responsible for the reduction in myocardial perfusion during exercise.

In summary, 3D imaging revealed the beneficial effect of nisoldipine on myocardial perfusion as a decrease in ischemic left ventricular myocardial volume after exercise. There was another finding that was also of interest. Before nisoldipine therapy, transient enlargement of the left ventricular cavity with exercise was observed in 3D images obtained from 4 patients with previous myocardial infarction, especially those with two vessel stenotic lesions or a history of severe infarction. An increase in left ventricular end-diastolic pressure associated with ischemia may play a role in the development of such exercise-related enlargement. This finding suggests that 3D imaging may also facilitate morphological assessment of the left ventricle. 3D mapping allowed stereoscopic evaluation of myocardial perfusion and the extent of ischemic lesions.

## CONCLUSION

1. Myocardial SPECT was performed in 19 patients with previous myocardial infarction before and after treatment with nisoldipine to investigate the clinical applicability of 3D imaging with the AVS-MV.
2. 3D imaging provided information on the pattern of improvement in myocardial perfusion in the infarct area after nisoldipine treatment.
3. 3D myocardial imaging by the conventional surface rendering method made it possible to calculate the myocardial volume. Nisoldipine increased the left ventricular myocardial volume with a radioisotope count ≧ 50% of maximum in the patients with previous myocardial infarction.
4. Nisoldipine improved myocardial perfusion during and after exercise, probably by dilating the coronary arteries and reducing myocardial oxygen demand in association with a reduction in afterload.
5. The AVS-MV increased the clinical applicability of 3D imaging and also facilitated morphological assessment of the left ventricle.

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