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Quantitative phase analysis of myocardial wall thickening by technetium-99m 2-methoxy-isobutyl-isonitrile SPECT

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Regional wall thickening was assessed by ECG-gated SPECT using technetium-99m 2-methoxy-isobutyl-isonitrile (^{99m}Tc-MIBI). For myocardial segments with an optimal short axis, regional count changes from end-diastole to end-systole were used to calculate the regional wall thickening. Functional images displaying amplitude, % wall thickening (%WT), and phase were generated by a fundamental Fourier analysis.

In the control subjects, %WT analysis showed heterogeneous contraction among the left ventricular wall segments. The amplitude values showed a similar pattern to the %WT values. Phase images demonstrated that the timing of ventricular contraction was almost homogenous between the various wall segments. In the CAD patients, regional decreases in amplitude and %WT corresponding to zones of reduced perfusion were shown in the ischemic segments. Phase images also indicated asynchronous contraction in these segments.

Phase analysis of regional wall thickening in ^{99m}Tc-MIBI scintigraphy seems to be useful for understanding regional myocardial function in combination with perfusion scanning.

Key words: wall thickening, myocardial perfusion, phase analysis, technetium-99m 2-methoxy-isobutyl-isonitrile (^{99m}Tc-MIBI), SPECT image

INTRODUCTION

THALLIUM-201 is the most important and widely used agent for the non-invasive detection of coronary stenosis by myocardial scintigraphy in patients with suspected coronary artery disease.[1–3] Technetium-99m 2-methoxy-isobutyl-isonitrile(^{99m}Tc-MIBI) is a recently developed ^{99m}Tc-labeled cardiac-imaging agent. The diagnostic ability of ^{99m}Tc-MIBI for assessing ischemic heart disease is reported to be almost the same as that of thallium-201.[4–9] This agent has several advantages over thallium-201 because of its ideal 140-keV photopeak for current imaging systems, the large injectable dose due to a 6-hour half-life, and its ready availability as a generator-produced agent. Also, in addition to improving the image quality and reducing image acquisition time in myocardial perfusion scintigraphy, other diagnostic procedures can also be performed simultaneously, such as the evaluations of cardiac function (left and right ventricular wall motion[10,11] and myocardial wall thickening.[12] In this study, the detection of regional wall thickening was performed using electrocardiographically gated single-photon emission computed tomography (ECG-gated SPECT) with phase analysis, and regional myocardial function was compared with regional myocardial perfusion.

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MATERIALS AND METHODS

Subjects

Nine patients with suspected ischemic heart disease were studied (7 males and 2 females with a mean age of 65±6 years, mean±SD) (Table 1). By coronary angiography and left ventriculography, 4 patients were diagnosed as having coronary artery disease (CAD) without previous myocardial infarction. Five subjects were categorized as normal because of the normal left ventriculography, no significant stenosis (<50%) in the main coronary arteries on coronary arteriography, and a normal thallium-201 stress test. The ^{99m}Tc-MIBI SPECT images showed no significant reduction in perfusion in these patients.

Data acquisition

For exercise imaging, an intravenous bolus injection of 740 MBq (20 mCi) of ^{99m}Tc-MIBI was performed while the patient was in a sitting position under maximal stress. One hour after injection of the radionuclide, 32-step SPECT images were acquired during 180° rotation from the right anterior oblique to the left posterior oblique projection (90 sec/view), using a rotating gamma camera (ZLC-7500, Siemens Co., Ltd.) with ECG signal gating (40 msec interval from the R wave). A high-resolution low-energy (HRLE) parallel collimator was used. Using ^{99m}Tc at 140 keV, the spatial resolution of this system with the HRLE parallel collimator was 6.3 mm.

Two days later, resting SPECT studies were performed without ECG gating using 370 MBq (10 mCi) of ^{99m}Tc-MIBI. The image acquisition time for each view was set at 30 sec.

Stress examination with thallium-201 scintigraphy was also performed by the same protocol as that for ^{99m}Tc-MIBI scintigraphy within 2 weeks. The injected dose was 74 MBq using the same SPECT system. Images were obtained soon after stress and 3 hrs after a thallium-201 injection. Ungated SPECT images were acquired by the same method as used in the resting ^{99m}Tc-MIBI study (30 sec/view).

Data processing

SPECT reconstruction was performed by using 9-point smoothing and a Shepp & Logan filter. Images of an optimal short axis were generated by a SCINTIPAC-700 (Shimadzu Co. Ltd., Japan). The distance of each slice is 6 mm.

Analysis of gated SPECT data

Myocardial wall thickening was analyzed for the optimal short axis images by a SCINTIPAC-2400 (Shimadzu Co. Ltd., Japan). First, the epicardial boundaries of the left ventricle were traced manually at end-diastole. Then the actual epicardial boundaries at every cardiac cycle were automatically determined using a cut-off threshold (40%) and fitting a fourth-order Fourier function. The cut-off threshold was set at 40% because the epicardial boundaries calculated by this threshold well fitted those of the original image and the epicardial boundaries in the region of mildly reduced perfusion did not produce defect changes. The boundary in the severely ischemic region was depressed markedly, so this boundary was recovered by 90% of the maximal margin of the circular radius. The area center of gravity of the left ventricular epicardial boundaries was calculated in every slice and for every cardiac cycle. From this center, 12 radii at 30-degree intervals were generated, and then an optimized short-axis image was divided into 12 segments shown in Fig. 1. Each area center of gravity of the left-ventricular epicardial boundaries at every cardiac cycle was normalized to a single point. The regional time-activity curve was calculated from these sequential images, and curve fitting was performed using the fundamental Fourier component. Then functional images of regional myocardial wall thickening were generated to demon-

Table 1 Clinical characteristics of the patients

Case	Age/Sex	CAG	LVG (LVEF)	Stress ECG	Chest pain
1. S.K.	74/M	LAD#8: 50%	Normal (EF=81%)	Negative	−
2. S.N.	67/F	RCA#1: 50%, LAD: #6: 25%, LCx#13: 50%	Hypokinesis slightly: #3 (EF=73)	ST ↓ : II, III, aVf (H) 0.025	−
3. I.H.	65/M	LAD#6: 50%	Normal (EF=73%)	Negative	−
4. S.I.	56/F	LCx#12: 25%, #14: 90%	Normal (EF=69%)	Negative	−
5. T.S.	64/M	LAD#7: 50%	Normal (EF=65%)	Negative	−
6. K.T.	61/M	LAD#6: 100%>collateral from RCA, LCx#13: 75%	Hypokinesis moderately #3 (EF=63%)	ST ↓ (H 0.10) II, III, aVf, V4–6	+
7. T.N.	63/M	RCA#1: 75%, LAD#6: 50%, #7: 75%, #9: 99% LCx#11: 75%, #12 & 13: 99%	Normal (EF=73%)	ST ↓ : II, III, aVf, V5–6 (Up slop) 0.05	+
8. K.S.	73/M	RCA#2: 75%, LAD#6: 90%, #10: 99%, #13: 75%	PVC (+)	Negative	+
9. Y.H.	73/M	RCA#1: 99%, LAD#6: 99%, #7: 100%, #9: 100% >collateral from LCx	Generalized hypokinesis slightly (EF=50%)	CRBBB, ST ↓ : V1–3 (0.1 DS) Borderline	+

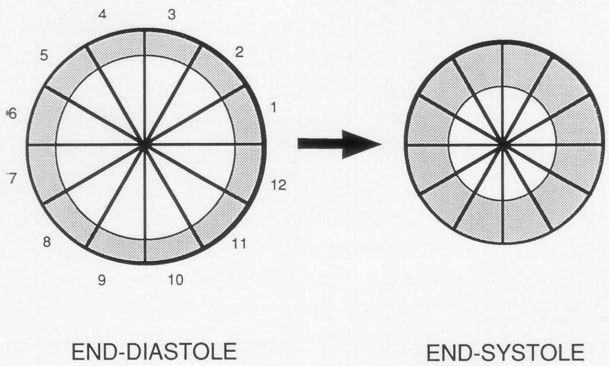

Fig. 1 Diagram of the method for measuring regional dimensions.

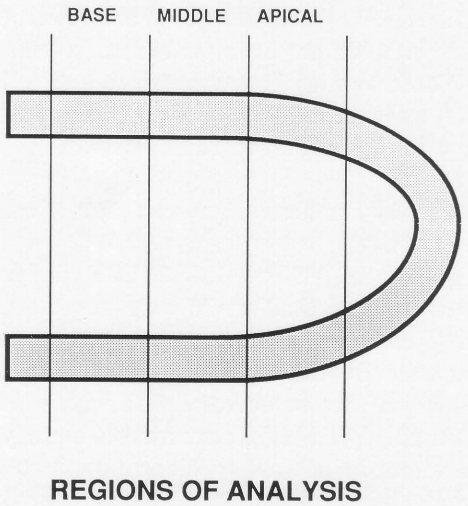

Fig. 2 Diagram of a vertical long-axis image showing the 3 segments used for quantitative analysis.

strate % wall thickening (%WT), amplitude (AMP), and phase.

The %WT was calculated by the following formula:

$$\%WT = \{[\text{End-systolic counts}] - [\text{End-diastolic counts}]/[\text{End-diastolic counts}]\} \times 100$$
$$= \{2[\text{AMP}]/[\text{End-diastolic counts}]\} \times 100$$

Functional images were displayed in 32 color steps. For %WT, the maximal upper range was set as 50% (1.56%/color step) from gray to red. For %WT (700), each color step was set as 2.19%/color step (Maximal value was 70%). For AMP, the maximal value was set as relative change normalized by the maximal value obtained at end-diastole (absolute value between ES counts and ED counts). In the phase image, each color step was set as 15.6 (msec/color step) and ventricular contraction was delayed from gray to red.

The normal range of %WT was calculated at 3 areas, as shown in Fig. 2.

Comparison between myocardial perfusion and % WT

When regional comparison was performed between the subjects, the 12 segments shown in Fig. 1 proved to be too detailed to align with the corresponding myocardial sites, so we established a 6-segment system instead (segments 2 & 3, 4 & 5, 6 & 7, 8 & 9, 10 & 11, and 1 & 12 were combined). The mid and apical regions were used for this study. Uptake of ^{99m}Tc-MIBI and thallium-201 was judged visually and scored as follows: normal perfusion (3+), low perfusion (2+), borderline defect (1+), and defect (0). The degree of %WT was judged in 3 steps as normal (2+), reduced contraction (1+), and no contraction (0) from the results of quantitative analysis obtained by control subjects.

Statistics

All results are reported as the mean±SD. Comparisons of means (%WT) were performed with the paired Student's t-test. The level of statistical significance was considered as $p<0.05$ for both analysis of variance and the paired t-test.

RESULTS

Sequential ECG-gated SPECT imaging and the functional imaging

The image quality of ^{99m}Tc-MIBI was superior to that of the thallium-201 images. Fig. 3A shows a control case (a 74-year-old male). The left ventriculogram was normal and the ejection fraction (EF) was 81%. Coronary arteriography showed 50% stenosis in the distal left anterior descending coronary artery (#8). Sequential ECG-gated SPECT images showed that the wall thickening appeared to be normal and no apparent perfusion defect could be observed. Functional images obtained in this case showed that the AMP and the %WT were heterogeneous. The degree of ventricular contraction was greater in the inferior wall. No significant regional contraction delay was noted on the phase image, but phase delay was shown slightly in apical mid-lateral wall (Fig. 4A).

Figure 3B shows a patient with severe ischemia (a 73-year-old male). Left ventriculography showed moderate hypokinesia in the septum and apex, and the EF was 50%. Coronary arteriography showed complete occlusion of segments #7 and #9, and 99% stenosis of segments #1 and #6. Prominent collaterals were observed from an atrial branch to segment #1, and from the posterolateral branches to segments #6, 7, and 9 (Fig. 5). Stress thallium-201 scintigraphy revealed incomplete redistribution in the left ventricular wall, except for the lateral wall. Sequential ECG-gated SPECT images showed good wall thickening in the lateral wall, whereas it was weak in the other parts of the ventricle. Functional images demonstrated these changes much more precisely (Fig. 4B). Quantitative analysis showed that the %WT in the anterior wall, septum and inferior wall was less than that in control subjects (reduced by more than 2SD) (Fig. 6). Asynchronous contraction was also noted in these reduced %WT regions.

Quantitative % WT analysis of the control subjects

Heterogeneity of %WT was observed among the wall segments in the control subjects (Fig. 7). The regional %WT in the mid-portion of the left ventricle was 52% for the lateral wall, 52% for the anterior wall, 75% for the septum, and 105% for the inferior wall. In the apical portion of the left ventricle, the %WT was 50% for the lateral wall, 52% for the anterior wall, 71% for the septum, and 105% for the inferior wall. The %WT of the septum and inferior wall was greater than that for the other segments (lateral wall vs. septum & inferior wall $p<0.05$, inferior wall vs. septum $p<0.05$). The changes in amplitude showed a similar pattern to the %WT value.

Comparative study

Using ^{99m}Tc-MIBI and thallium-201 scintigraphy, a comparison was performed between the %WT and myocardial perfusion on stress and delayed image. Regions of no contraction were not noted in the %WT study (Fig. 8). Data acquisition was performed 1 hr after the stress test. So this result was comparable with resting SPECT studies by thallium-201 and ^{99m}Tc-MIBI (coincidence 95.4% vs. 84.8%), but a slight disagreement was noted between the resting study with ^{99m}Tc-MIBI and the %WT data.

DISCUSSIONS

The evaluation of left ventricular function has gained increased importance owing to its high relevance to management choices and to the prognosis of patients.[13,14] Ventricular wall motion has usually been assessed by contrast left ventriculography (LVG), echocardiography (Echo), or radionuclide ventriculography, and more recently by cine computed tomography (cine CT) and nuclear magnetic resonance imaging (MRI). Using these methods, global and regional wall motion (except for wall thickening) are generally analyzed because of the ease and reliability of determining these parameters. However, the index of regional wall thickening is thought to be a more sensitive and precise estimate of regional myocardial ischemia than wall motion.[15–20] Some authors have used LVG,[20,21] Echo,[19,22–24] cine CT,[25] MRI,[26,27] and positron-emission computed tomography (PET)[28,29] to analyze regional wall thickening. Unfortunately, their methods cannot be used in routine clinical practice because of the long data acquisition time, non-optimal geometric analysis, difficulties in setting the ventricular boundaries, and the need for expensive equipment.

On the other hand, ^{99m}Tc-MIBI imaging can be performed with the commonly used SPECT system, and ECG-gated data acquisition can be undertaken easily. Thus, the use of this new tracer is expected to eliminate many disadvantages of the previously mentioned methods, and to open up new ways to evaluate the coronary artery disease (CAD) by the simultaneous estimation of ventricular function and perfusion. Using ^{99m}Tc-MIBI, the simultaneous evaluation of cardiac function (left and right ventricular wall motion[10,11] and myocardial wall thickening determined with planar images[12]) and regional myocardial perfusion has been performed. In this study, the regional wall thickening obtained by ECG-gated SPECT was assessed by phase analysis, and compared with regional myocardial perfusion.

Image quality and theoretical possibility of analyzing wall thickening

The quality of ^{99m}Tc-MIBI SPECT images was superior to the thallium-201, as reported previously.[4–7] ECG-gated sequential images showed an increase in the regional count and regional thickening of the myocardial wall with ventricular contraction. ^{99m}Tc-MIBI accumulates linearly in the myocardium in relation to blood flow in the same manner as microspheres. It exhibits slow myocardial clearance and shows little redistribution,[8,30] so its myocardial concentration is thought to be in a steady state during image acquisition. Therefore, the increase of the left ventricular regional count is thought to correspond to regional wall thickening according to the principle of partial volume effects on PET images.[31,32] This principle states that systolic wall thickening would be expected to be associated with an increase in regional count recovery. The relationship between wall thickness and the recovery coefficient is linear for a wall thickness range of 8–20 mm and could potentially be used to estimate the increase in wall thickness during systole from changes in regional count recovery. The LV wall thickness is usually <20 mm and lies within the resolution of our SPECT system. Thus, the regional wall thickening could be analyzed as sequential changes in counts from end-diastole (ED) to end-systole (ES).

Control subjects

The subjects classed as normal showed a regional myocardial count increase from ED to ES and a

A

B

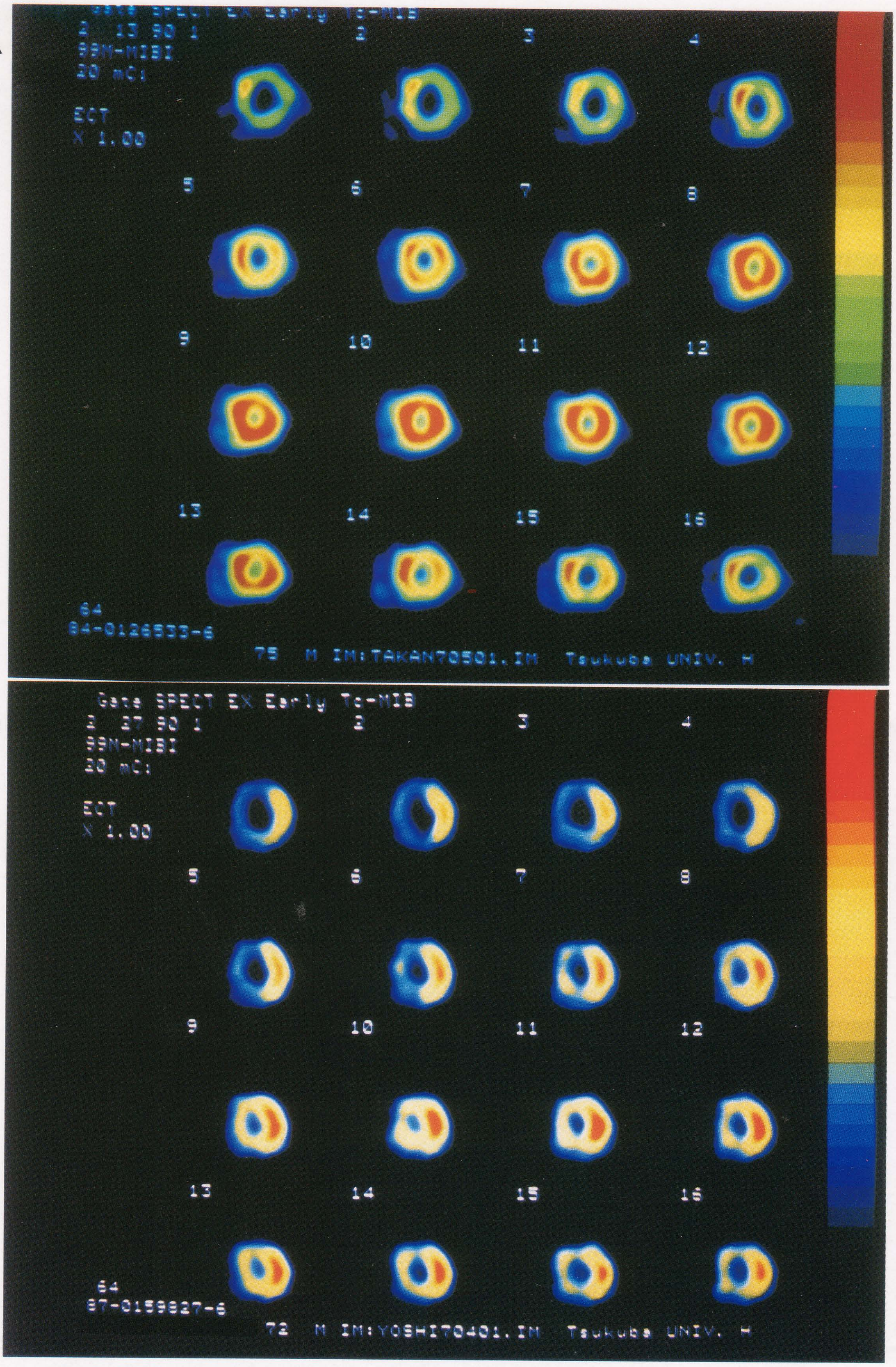

Fig. 3 ECG-gated short-axis images of the left ventricular myocardium in a control subject (A) and in a patient with severe ischemic heart disease (B). Sequential images obtained at the mid-ventricle are shown from end-diastole (1 frame) to end-systole (9 frames & 11 frames) in a control subject and CAD patient respectively.

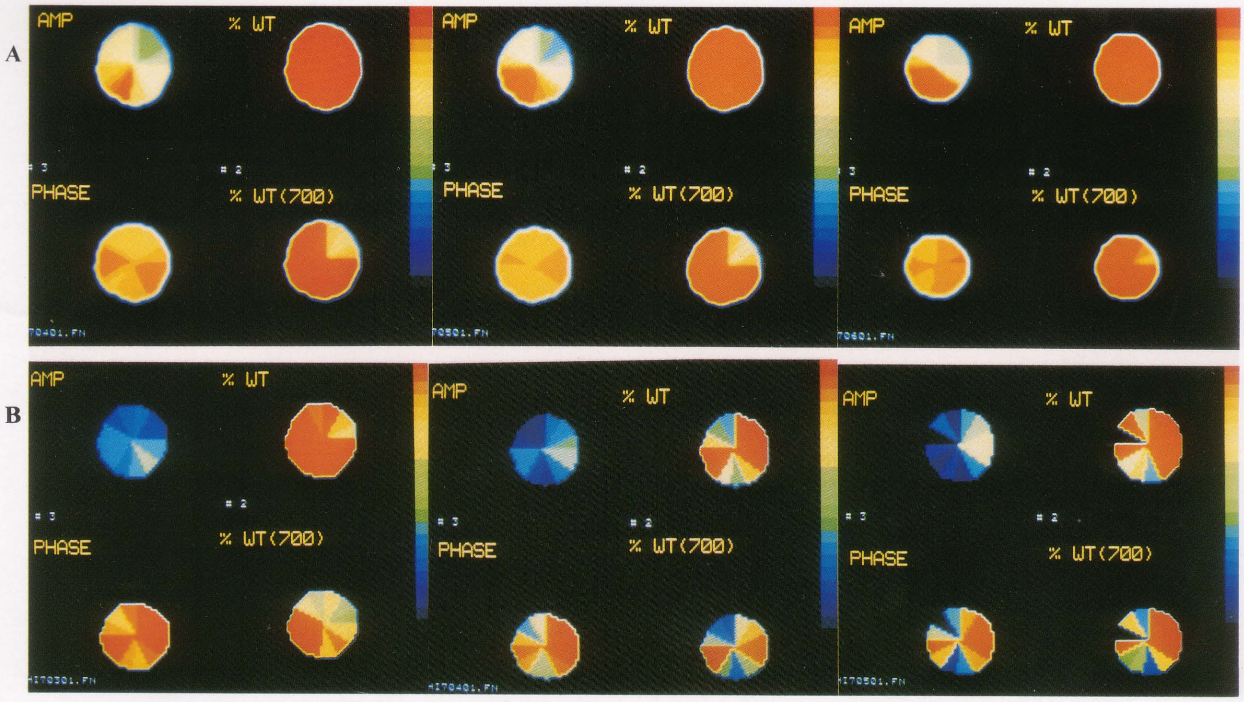

Fig. 4 Functional images produced for the control subject (A) and the ischemic patient (B) shown in Fig. 3. Images of 3 slices at the mid-ventricle are demonstrated. Images of the middle slice correspond to the sequential image shown in Fig. 3. Right side images are 6 mm forward to apex, whereas left-side images are 6 mm forward to base.

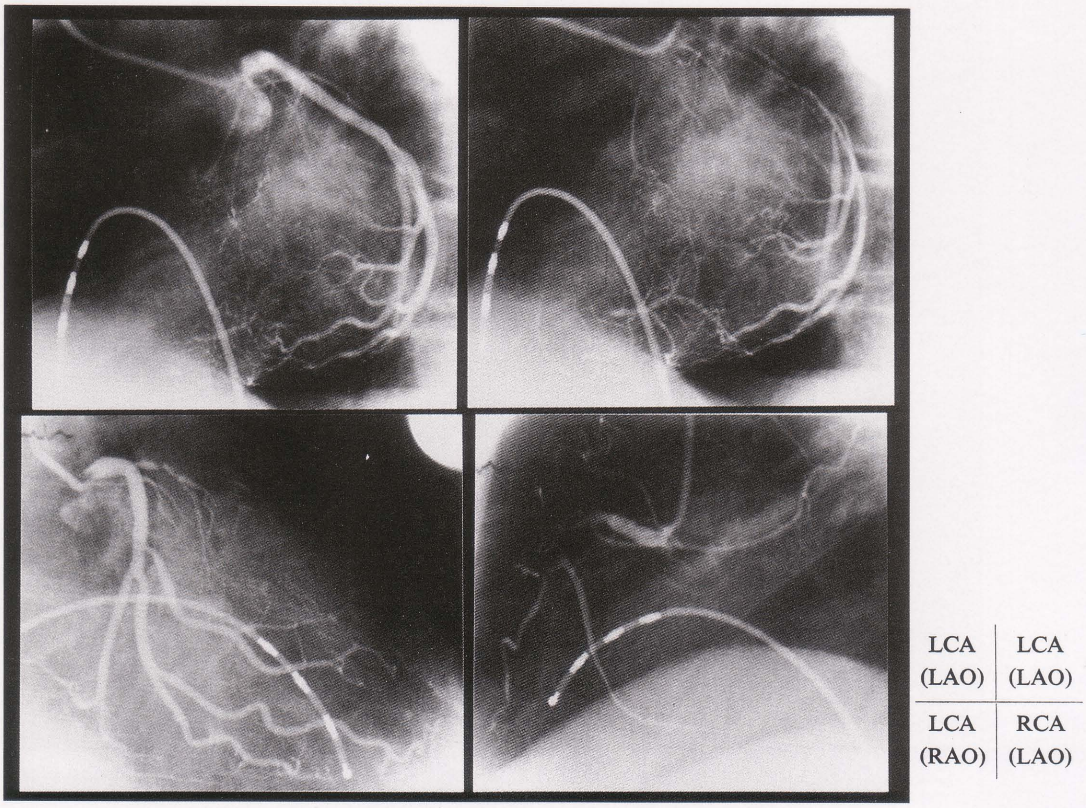

Fig. 5 Coronary arteriograms of the patient shown in Fig. 3B.

thickening with a gradual enhancement from the base to apex was noted, confirming the findings in previous studies.[25,26] Marked heterogeneity of %WT values was identified among the various wall segments. The %WT values for the inferior wall was greater than that for the other segments. In a previous study of normal controls by other methods, the %WT was smallest for the septum and greater for the lateral and inferior walls.[22–29] In previous ECG-gradual decrease from ES to ED. Heterogeneous wall

gated PET studies, the percent of count increase (corresponding to our %WT) was lowest (32.9±7.2%) for the septum and highest (72.8±26.5%) for the lateral wall.[28,29] However, in contrast to our method the external and internal areas of the LV wall were excluded from analysis, and the transaxial section was used in these PET studies. In our study using an optimized short axis, the %WT value for the septum was greater than that for the lateral wall, a result slightly different from that reported previ-

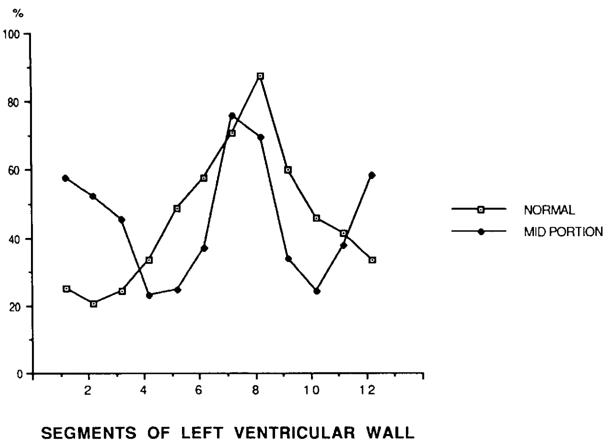

Fig. 6 Regional differences in the % wall thickening around the circumference at the short axis of the left ventricle in the patient shown in Fig. 3B.

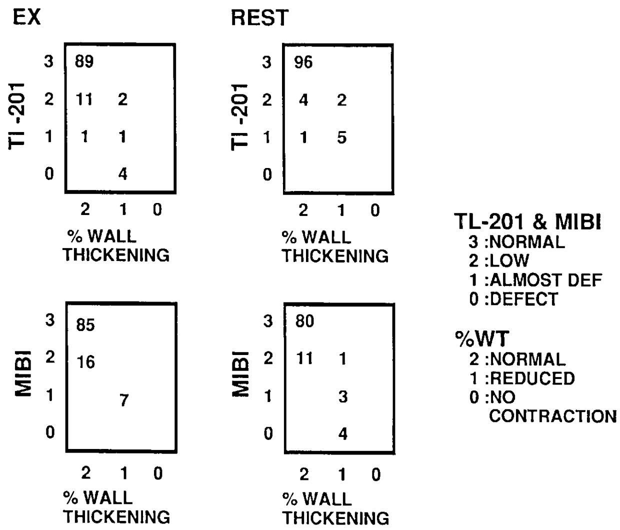

Fig. 8 Comparison between regional myocardial perfusion and regional wall thickening under exercise and resting conditions on both ^{201}Tl and ^{99m}Tc-MIBI scintigraphy.

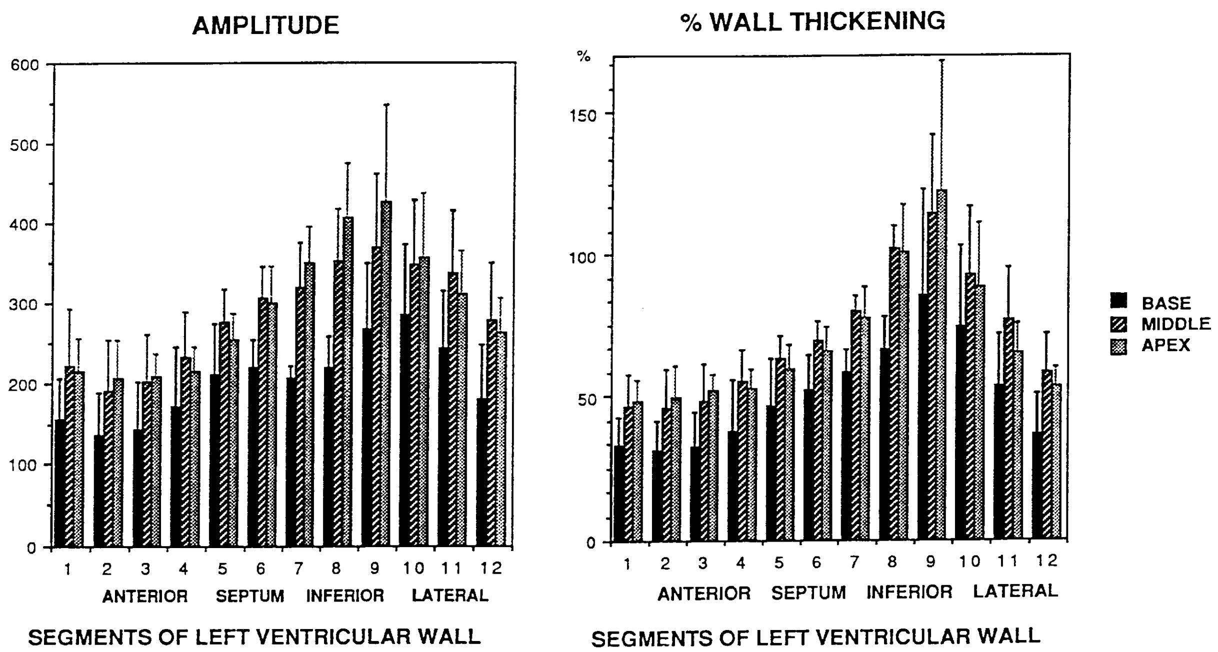

Fig. 7 Regional differences in the % wall thickening around the circumference at the short axis of the left ventricle in 5 control subjects.

ously. This might have been due to the following reasons.

First, the energy of ^{99m}Tc is relatively high compared to that of thallium-201, but the attenuation of γ-rays in the deep parts of the septum and inferior wall might not be negligible, because the segmental %WT value was greater than that of amplitude in these segments. Second, the inclusion of an anterior papillary muscle may have also decreased the change in counts in the lateral wall. Third, our control subjects were not completely normal, and myocardial damage due to CAD might have existed in the anterior and lateral ventricular walls. In patients with CAD, it was reported that the %WT delineated minimal wall motion abnormalities (a 20% reduction compared to normal subjects) despite a normal LVG and normal resting perfusion.[28,29] Therefore, wall segments showing this type of decrease in the %WT may contain ischemic myocardium. Fourth, the SPECT data was obtained 1 hour after the stress test, so this change may be partly due to prolonged post-ischemic myocardial dysfunction, so-called "stunned myocardium".[33] Fifth, a greater underestimation of the regional count may occur in myocardium that has become significantly thicker at end-systole owing to incomplete counts acquisition and non-linearity for wall thickness due to partial volume effects.

Phase images in the control subjects showed no significant delay in contraction among the various wall segments. The use of phase analysis to assess regional wall thickening has been tried in animal experiments by means of sonomicrometry.[34,35] It has been reported that phase is an excellent index for the evaluation of ischemic myocardium without knowing the baseline normal %WT in the ventricular wall segments. Thus, the third possible explanation suggested above might not contribute much to the discrepancy in segmental %WT between our study and previous reports. But the effects of normal electrical conduction and abnormal electrical conduction must be considered because the contraction delay occurs in distal parts of the electrical route on the left ventricle. In future, normal control studies must be done to determine the normal %WT and phase ranges more precisely.

CAD patients

In the subject shown in Fig. 3B, regional wall thickening was observed in the segment that showed significantly reduced perfusion on visual analysis, suggesting that regions with a severe reduction in ^{99m}Tc-MIBI uptake at rest may contain viable myocardium. Rocco, et al.[7] showed that in approximately 50% of myocardial regions for which ^{99m}Tc-MIBI uptake at rest was graded visually as markedly reduced, wall motion was detected by radionuclide ventriculography. Also in 25% of such cases, the regional contraction was normal. In this subject, the %WT was decreased below the normal range in quantitative analysis, and phase delay also occurred in ischemic segments when compared to the normal perfused segments.

The comparative study showed that the %WT was significantly decreased as resting perfusion decreased, as did a previous study with PET.[28] A significant asynchrony was also noted in the ischemic regions. Thus, segments showing decreased %WT and asynchrony must contain ischemic myocardium. In addition, our findings may be partly explained by the presence of stunned myocardium in areas of ischemic myocardium.[33,36,37] Heyndrickx, et al. were able to demonstrate the impairment of regional myocardial function for up to 3 hours following five minutes of coronary occlusion.[38] Also, the phenomenon of postejection thickening occurs in acute and prolonged myocardial ischemia.[34,35] In an animal experiment, postejection thickening increased with the increasing severity of ischemia and was greatest during complete coronary occlusion. In addition, the progressive phase delay of first Fourier harmonics reflected an increase in postejection thickening with progressive myocardial ischemia, and there was an inverse linear relationship between the %WT and the phase delay. Thus, the degree of regional myocardial ischemia could be assessed precisely by using the two indices of %WT and phase value.

Limitations of this method

The normal %WT value may be influenced by inclusion of the papillary muscles and by decreased attenuation of γ-rays in the deep parts of wall segments in our method. Accordingly, the value of %WT might be relatively reduced in the lateral wall. A hypertrophic heart must not be analyzed without correction, because of non-linear count changes corresponding to the %WT.[28] The data acquisition time required (about 1 hr) was also relatively long, but this problem might be solved by using a new SPECT system with triple sensors that allows data accumulation within 20 min under ECG-gating conditions. Furthermore, some errors in calculation might occur from problems with curve fitting to the original curves.

CONCLUSION

The present study performed with ^{99m}Tc-MIBI SPECT suggests that phase analysis of wall thickening provides a new method for evaluating regional myocardial mechanical function in combination with regional myocardial perfusion. Functional images

(%WT and phase) could demonstrate the state of regional myocardial contraction quite clearly. However, further assessment in normal subjects and CAD patients is required to fully determine the clinical validity of this method. In future, this type of quantitative analysis of regional wall thickening may become a useful tool for monitoring myocardial function in CAD patients during various physical and pharmacological interventions.

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