A New Method for Noninvasive Quantitation of Segmental Myocardial Wall Thickening Using Technetium-99m 2-Methoxy-isobutyl-isonitrile Scintigraphy—Results in Normal Subjects

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A quantitative index of regional myocardial wall motion obtained from electrocardiogram-gated perfusion images has been assessed. The assumption for the proposed algorithm is that, according to the partial volume effect, the recovery counts by the instrumentation is a function of the object size. Systo-diastolic changes in the detected radioactivity would therefore reflect changes in myocardial wall thickness. Ten normal volunteers were studied in control condition by ^{99m}Tc 2-methoxy-isobutyl-isonitrile scintigraphy. Electrocardiogram (ECG)-gated images were acquired in multiple projections. End-diastolic and end–systolic activity was measured along radii from the center to the edge of the left ventricle. Data are displayed as circumferential profiles and the percent systolic thickening determined according to the formula (end-systolic profile − end-diastolic profile) (end-diastolic profile + background) × 100.) The intra- and interobserver variabilities were ±5.4% and ±4.1%, respectively. Analysis of regional systolic thickening showed a heterogeneous pattern, with a maximal and minimum value of 35% and 27% located to the infero-apical and to the proximal anterior wall, respectively. Our values correlate well with those reported for normals using cine computed tomography or nuclear magnetic resonance.

J Nucl Med 1990; 31:173–177

In recent years, myocardial imaging techniques have attempted to achieve the simultaneous assessment of regional perfusion and wall motion. Several imaging techniques, such as direct (*1*) and peripheral (*2*) contrast ventriculography, two-dimensional echocardiography (*3,4*) fast computed tomography (*5*) and nuclear magnetic resonance (*6*) are currently available for the regional evaluation of systolic wall thickening. However, none of these techniques is actually able to assess myocardial perfusion and wall motion simultaneously.

Received April 13, 1989; revision accepted Sept. 27, 1989.

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Recently, the new ^{99m}Tc-labeled tracer 2-methoxy-isobutyl-isonitrile (MIBI) has been proposed as a "multipurpose tracer", because first pass (*7*) and delayed static acquisitions (*8*) provide assessment of both global left ventricular (LV) function and regional perfusion. Furthermore, the ECG-gated acquisition of MIBI has been used to qualitatively evaluate regional myocardial wall motion.

Because of its kinetic characteristics, MIBI is trapped into the myocardium (*9*), with a steady state concentration into the organ in the first hours following injection. Therefore, systo-diastolic radioactivity changes recovered by the external counting depend upon variations in wall thickness, according to the partial volume effect (*10–12*). Application of this intrinsic limitation of nuclear devices may provide a useful tool to objectively evaluate regional wall motion. The aims of this study were twofold: (a) to develop a method for quantitating LV regional wall thickening by MIBI scintigraphy and (b) to assess the pattern of regional LV wall thickening in a group of normal subjects.

METHODS

Study Population

Our study population consisted of 10 normal volunteers (8 male, 2 female, mean age 45 ± 7, range 39–51 yr) with a low probability of coronary artery disease. Preliminary clinical evaluation was accomplished in all subjects by standard chest x-ray, two-dimensional echocardiography and bicycle maximal ergometric stress test. Echocardiography was performed in multiple views in order to evaluate all myocardial regions and showed normal ventricular function in all subjects. Maximal exercise stress test was negative in all subjects. Systemic hypertension, valvular or other cardiac abnormalities were excluded after this evaluation in all subjects. All subjects gave written, informed consent to participate in the study protocol. No adverse reactions have been reported in our laboratory in more than 120 patients studied with MIBI since 1987.

Clinical Protocol

All subjects were studied in the basal state after i.v. injection of 0.74 GBq (20 mCi) of MIBI (Cardiolite, Du Pont de Nemours, FRG). The tracer was injected in a fasting state; thereafter the subjects were invited to have a light meal and the images were collected 60–90 min later. Radioisotopic acquisitions were performed in anterior, 40° and 70° left anterior oblique projections. A small field, mobile gamma-camera (Apex 210-M, Elscint, Israel) equipped with a high resolution low energy parallel hole collimator was used, with the photopeak centered at 140 keV and a ±10% window. Sixteen frames (64 × 64 matrix) per R-R interval were acquired in list mode, with a hardware magnification factor of 1.3, collecting at least 100,000 counts/frame.

Perfusion was qualitatively assessed by two independent observers both on the static and gated images, according to previously described methods (*13,14*).

The Principle of the Partial Volume Effect

The basic principle for the quantitative wall motion analysis proposed in this study is similar to that used for radionuclide angiography, i.e. systo-diastolic changes in detected radioactivity. Interestingly, in ECG-gated flow images, the end-systolic counts obtained in a ventricular region of interest are higher than the end-diastolic ones in normal contracting segments. A steady state concentration of MIBI into the organ has been assumed because this tracer is trapped into myocardium and the washout rates in normal and in ischemic areas are negligible in the first few hours following tracer injection (*9*). The counts recovered by the external counting are influenced in this condition only by changes of cardiac thickness.

In imaging of the heart by means of nuclear medicine devices, the anatomical size of myocardial wall frequently falls below the image resolution of the instrument. Under these circumstances, the partial volume related effect (*10*) induces an apparent underestimation of the true tracer concentration. The recovery coefficient, i.e. the ratio of apparent to true isotope concentrations, has been calculated for the Anger camera used in the present study using a phantom formed by two eccentric cylinders of plexiglas, simulating myocardial wall with variable thickness. The volume between the two cylinders was filled with a homogeneous solution of ^{99m}Tc, to obtain a counting rate of about 1000 cps. This phantom allows the evaluation of object size in the range from 3 to 16.5 mm. In Figure 1, the demonstration of the partial volume effect in this phantom is shown. Plot of the recovery coefficient versus the object size, in units of the FWHM of our Anger Camera (8 mm), shows that normal systolic (15 mm) and diastolic (10 mm) thickness would have a recovery coefficient of 99% and 70%, respectively. This in vitro experiment demonstrates that in the range of physiologic thickening, the partial volume effect induces a 29% count loss from end-systole to end-diastole.

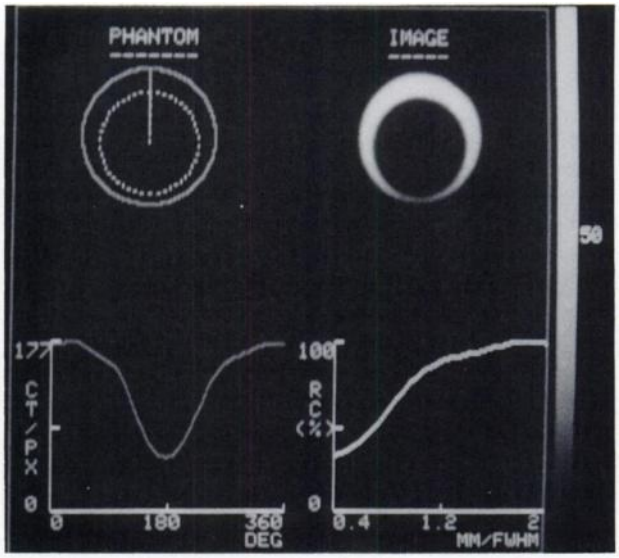

FIGURE 1
In vitro demonstration of the partial volume effect by the Anger camera used in this study. The phantom (upper left panel) filled with a solution of ^{99m}Tc that simulated myocardial thickness in a broad range of values (from 3 to 16.5 mm) is shown together with the relative image (upper right panel). An apparent loss of counts concomitant with the reduction of the object size is demonstrated by the angular profile generated clockwise from the top of the image (lower left panel). The lower right panel represents the recovery coefficient (RC%) versus the object size normalized to the image resolution of our Anger camera (8 mm) (MM/FWHM); the reduction of detected radioactivity as a function of thickness is particularly evident for thickness lower than 10 mm.

Calculation of Regional Wall Thickening

Before analysis, gated images were processed by nine-point spatial and temporal smoothing. No background subtraction was performed. The end-diastolic and end-systolic frames of the two oblique projections were analyzed. The anterior projection, because of the frequent superimposition of extra cardiac structures, was not used in the analysis. The end-diastolic frame was defined as the image acquired at the peak of the gated R-wave. The frame with the highest activity in the LV region of interest was considered as end-systolic; this was also checked by visual inspection of the LV cavity size in the cinematic display. The LV end-diastolic and end-systolic edges were manually drawn and the center of gravity of the LV was then automatically determined. Thereafter, 60 radii (one every 6 degrees) were automatically drawn from the centroid to the LV edge, the first radius being set in opposition to the apex. The distribution of MIBI activity was determined by calculating the average activity per pixel along each consecutive radius (*15*), in a clockwise fashion. The LV outflow region (5 radii corresponding to 30°) was not used in the analysis. Data were then displayed as "circumferential profile" curves by plotting MIBI activity against angular position and the end-diastolic and end-systolic profiles were realigned at the apex, set at 180°. Thus, the only operator-dependent procedure was the definition of the external edge of the LV.

The systolic wall thickening was then calculated according to the formula:

$$(\text{end-systolic profile} - \text{end-diastolic profile})/(\text{end-diastolic profile} + \text{background}) \times 100.$$

The count-based thickening profile quantitates the segmental wall motion as an angular function referenced from the center of gravity of the left ventricle. The values of percent thickening from all segments were averaged to ten anatomical regions (proximal and distal anterior, septal, postero-lateral

and inferior walls, infero-apical wall and the apex), each one consisting of 11 radii. The processing time averaged 10 min per patient.

Statistical Analysis

Correlations were determined by linear regression analysis. All data are given as mean ±1 standard deviation (s.d.). A probability value (p) < 0.05 was considered significant.

RESULTS

Reproducibility of Radioisotopic Thickening

The values of systolic thickening were recalculated in all subjects by the same observer in two occasions at least one wk apart and also by a second observer. The intraobserver variation of thickening measurements was ±5.4% ($y = 1.1x - 0.1$, $r = 0.86$, $p < 0.001$). The interobserver variation was ±4.1% ($y = 0.8x + 0.2$, $r = 0.93$, $p < 0.001$).

Radioisotopic Thickening in the Normal Subjects

All subjects showed homogeneous distribution of the tracer within the myocardial walls. The left ventricle was always well separated from the adjacent structure so that in all cases it was possible to draw the end-diastolic and end-systolic regions of interest. An average of 30,000 counts was collected in the LV region of interest in the end-diastolic frame; the average counts/pixel along the sampling radius ranged from 36 to 49 counts (42 ± 5). Analysis of the regional systolic thickening showed a heterogeneous pattern, with a maximal value of 35% located to the infero-apical region and a minimum of 27% to the proximal anterior segment and with a gradual increase from the base to the apex. Because of the superimposition in the LAO 40° projection of the apex and the inferior wall, the values of thickening obtained for the apex in the LAO 70° are likely to be the most reliable relative to this segment. Individual variation among a total of 100 LV regions analyzed ranged from 19% to 41%. The pattern of systolic thickening obtained in LAO 40° in a normal subject is reported in Figure 2. The values of systolic thickening in the different myocardial regions are shown in Figure 3.

DISCUSSION

In the present study, a new algorithm for quantitative analysis of regional myocardial wall motion from ECG-gated acquisition of MIBI scintigraphy is described. The proposed method is based on a physical limitation of most nuclear medicine devices, i.e. the partial volume effect, which occurs when the object size falls below the image resolution of the instrumentation.

The first observation on the relationship between the size of the myocardium and the appearance of myocardial images has been reported by Gewirtz and coworkers using ^{201}Tl myocardial scintigraphy (*16*). In that study, changes of left ventricular volume induced by partial aortic or coronary occlusion caused the appearance of perfusion defects without any change in tracer distribution, thus demonstrating the direct relationship between regional wall thickness and detected radioactivity. However, in that study, no correlation between reduction of wall thickening and the appearance of perfusion defects was reported.

The effect of object size on apparent regional myocardial tracer concentration has been intensively inves-

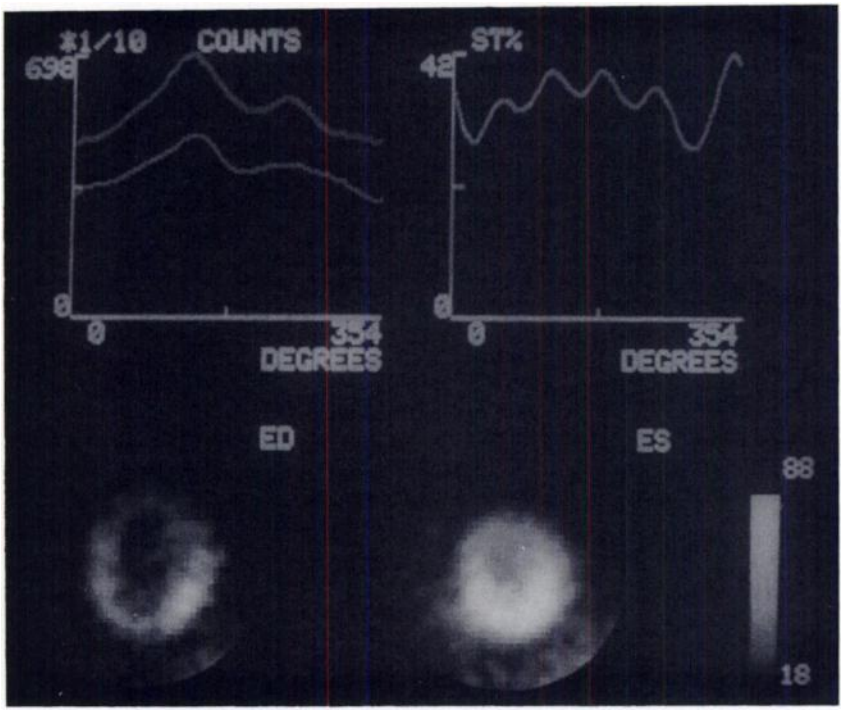

FIGURE 2
The systolic thickening profile (ST) obtained in LAO 40° projection in a normal subjects with the relative end-diastolic and the end-systolic count distribution angular profile are shown in the right and left upper panels, respectively. In the lower panels the end-diastolic (ED) and end-systolic (ES) frames are reported.

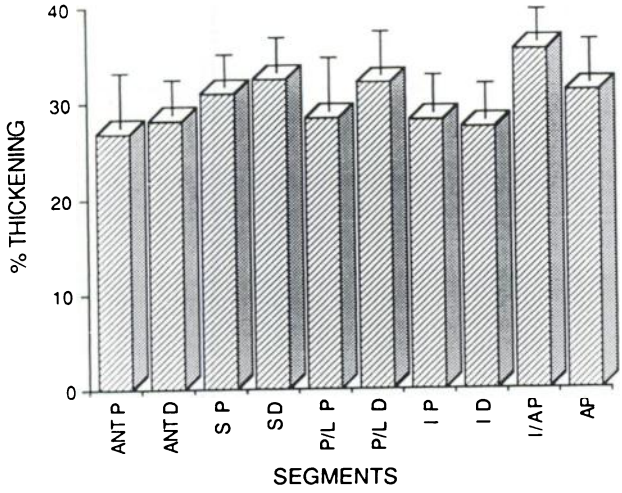

FIGURE 3
Regional differences in radioisotopic systolic thickening (% THICKENING) obtained in 10 normal subjects. Data are given as mean ± 1 s.d. of the mean. A heterogeneous distribution of regional thickening is observed with a maximum value encountered in the infero-apical wall and a minimum occuring in the proximal anterior region. (ANT = anterior; S = septal; P/L = posterolateral; I = inferior; I/AP = infero-apical; AP = apical; P = proximal; D = distal).

tigated by Hoffman et al. (*10*) using positron emission tomography (PET). These authors showed that, when the object size falls below the image resolution of the instrument, the object only partially fills the sensitive volume of the detectors viewing that dimension. Reconstruction of these images resulted in an underestimation of the true isotope concentration in the structure (the partial volume effect). Wisenberg et al. (*12*) showed that artifactual reductions in tissue tracer concentrations, due to the partial volume effect, can be minimized by ECG-gated image acquisition. Parodi et al. (*11*) demonstrated that myocardial wall motion abnormalities cause underestimation of regional $^{13}NH3$ concentration; regional fractional shortening closely correlated with counts recovered by the PET system (FWHM 17 mm). Although the new generation of gamma-cameras provides a better spatial resolution, minimizing the partial volume effect, an underestimation of tissue tracer concentration in cardiac images still occurs. This is clearly shown in our phantom study, where a significant underestimation in true isotope concentration was observed relative to object sizes lower than 10 mm (Fig. 2).

Comparison with Other Techniques

Our data on the pattern of LV regional wall thickening in normal subjects are similar to the echocardiographic results reported by Haendchen et al. (*3*) and Zoghbi et al. (*4*) both in normals and in the conscious dog. These studies showed heterogeneous wall thickening in normal segments with a gradual enhancement from the base to the apex. Similar values have been reported by Lanzer et al. (*5*) using cine computed tomography. Comparable values for systolic thickening were also obtained by Sechtem et al. (*6*) by nuclear magnetic resonance imaging, showing the lowest values of thickening in the posterior segments and the greatest in the lateral and apical regions.

Discrepancies occur in comparison with contrast ventriculography. Using this technique, wall thickening in normals ranges from 30% to 150% in control conditions and exceeds that measured directly by implanted radiopaque markers (*17*). This discrepancy might be due to the possible inclusion of trabeculations and papillary muscles in end-systolic measurements and in uncertainties in the identification of endocardial borders. These findings suggest that contrast ventriculography should not be considered as the "gold standard" for the assessment of regional systolic thickening.

Technical Considerations

Some limitations of our method should be mentioned. First of all, results may be influenced by background activity. In particular, according to the formula used for calculation, an increase in the background activity would induce a reduction in the measured wall thickening. However, in the range of heart to background ratio from 2:1 to 3:1 the calculated wall thickening would change no more than 10%.

The effect of a marked perfusion defect must also be taken into account. In this circumstance, the background would have a greater influence than for a normal region, because of a lower target-to-background ratio.

Ad hoc experiments are needed in order to better clarify the effect of these factors on count-based thickening calculation.

Clinical Implications

The results of the present study should be of interest to laboratories performing nuclear cardiac imaging, because they demonstrate the possibility of obtaining simultaneous information on regional perfusion and wall motion. An important feature of this radioisotopic analysis is that our method, based on systo-diastolic radioactivity changes, represents a non-geometrical approach for the assessment of wall thickening. Moreover, it operates on a regional basis and can characterize patients with ischemic heart disease, in whom the functional impairment is typically regional, better than the evaluation of global left ventricular function by the geometrical analysis of gated flow images (*18*). Our method overcomes the limitation of a qualitative analysis of ECG-gated MIBI acquisitions (*8*) for the detection of wall motion abnormalities.

The method of analysis is simple enough for widespread use without the need for complex computer algorithms, requires minimal operator interventions and can be easily applied on an outpatient basis. Ap-

plied to patients with coronary artery disease and regional wall motion abnormalities, it can provide useful information about the relationship between site and extension of perfusion defects and myocardial dysfunction.

Results from the present study support the utilization of the proposed method to evaluate both regional myocardial perfusion and wall motion. However, further evaluations in normal subjects and in patients are required in order to fully understand the clinical validity of this approach. Quantitative analysis of MIBI images could represent a new tool for monitoring of myocardial function in patients with ischemic heart disease during physical and pharmacological interventions.

ACKNOWLEDGMENTS

This study was supported in part by a research grant from the Ministero Della Pubblica Istruzione, Italy, and by National Research Council (Cardiorespiratory group) Grant 87.00446.04.

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