

Non-invasive quantification of exercise-induced changes in regional left ventricular function in normals and patients with one vessel coronary artery disease using radionuclide ventriculography

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KEY WORDS: Regional ejection fraction, radionuclide ventriculography, exercise testing, one vessel coronary artery disease, ischemia, scar, reproducibility.

To quantitate changes in regional left ventricular function induced by ischemia or scar, rest and exercise equilibrium radionuclide studies of 26 patients with one vessel coronary artery disease and 12 normal individuals were analysed with a new method for regional ejection fraction determination. A computer algorithm provided observer-independent segmental analysis from a centre of gravity of the left ventricular activity at end-diastole (left anterior oblique projection). Special segments were assigned for anteroseptal, inferoapical and posterolateral areas corresponding to the three main coronary arteries. Reproducibility using an unchanged camera positioning was excellent even for 2 min acquisition studies ($r=0.93$) and still good after repositioning ($r=0.80$ to 0.87). In normal areas, regional ejection fraction increased or showed no change during exercise. In contrast, it decreased significantly in regions supplied by stenosed coronary arteries (ischemia) and remained depressed in scar zones. The method proved to be valid for regional changes induced by left anterior descending and left circumflex coronary obstructions, but less for right coronary artery lesions. Global ejection fraction reflected a sum of all regional changes implying that regional analysis should be more sensitive in detecting coronary artery disease.

Assessment of regional left ventricular performance and wall motion is of particular interest in patients with coronary artery disease (CAD), in whom areas with normal contraction can be found next to hypo- or akinetic segments. In some of these patients, regional abnormalities may be detected only during exercise. With the introduction of radionuclide angiography, assessment of global left ventricular ejection fraction at rest and during exercise has become a widely accepted method in the evaluation of patients with CAD^[1-4].

Attempts have been made to describe regional changes of left ventricular function in radionuclide studies. They range from qualitative visual inspection of end-systolic and end-diastolic images or an equilibrium study in movie format^[1,5-8] to

description of functional scintigraphic images^[9-11] and to quantitative measurement of regional ejection fraction^[12-14]. Quantitative analyses have so far been restricted to resting studies of 5-15 min acquisition^[9,11,12]. The results of these different scintigraphic approaches have traditionally been compared with wall motion abnormalities as found with standard contrast ventriculography despite some major differences between the two methods. With contrast ventriculography tangential changes of a two-dimensional body are observed in each projection and certain geometrical assumptions made to describe wall motion abnormalities^[15,16]. In contrast, in a count-based analysis of equilibrium radionuclide ventriculography, regional ejection fraction provides a measure of change in regional function of a three-dimensional body or sector. While a comparison of global ejection fraction results by both methods is valid, regional changes described by contrast ventriculography (wall motion) and radionuclide ventriculography (func-

Received for publication 30 June 1981; and in revised form 8 October 1981.

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tion) are different. Since localized CAD is the common denominator of these different regional parameters, normal, ischemic and scar contraction patterns should be studied and validated in patients with well defined localized coronary artery lesions.

The aim of our investigation was therefore:

- (1) to describe a count-based observer-independent computer method to measure regional ejection fraction from short acquisition equilibrium radionuclide ventriculography,
- (2) to define normal values of regional ejection fraction at rest and during exercise,
- (3) to describe changes in regional ejection fraction at rest and during exercise in patients with one vessel CAD with and without previous myocardial infarction, and
- (4) to assess the reproducibility of such regional ejection fraction measurements in view of later intervention studies.

Methods

PATIENT SELECTION

Twenty-six patients with angiographically documented one vessel CAD and 12 normal subjects were included in this study. There were 24 male and two female patients between the ages of 23 and 64 years. Of 16 patients with left anterior descending (LAD) coronary artery disease, nine had proximal >75% stenosis with angina pectoris but without previous myocardial infarction. Seven patients had subtotal or total LAD occlusion with documented previous transmural myocardial infarction but without further angina. In the remaining 10 patients the right coronary artery (RCA) was involved in six and the left circumflex coronary artery (LCX) in four. Five of these 10 patients complained of chest pain during the study and five of them gave a history of previous myocardial infarction. All anti-anginal drugs were stopped four days (nitrates 24 h) prior to the study in order to avoid drug-effects on global or regional left ventricular function^[17,18].

The 12 normal subjects who were all studied for exclusion of CAD, were men between the ages of 31 and 53 years. They were all free of clinical signs or symptoms of disease and had normal ECGs and myocardial perfusion scintigraphy with thallium-201 both at rest and during exercise. In addition, they all had a normal global ejection fraction response to exercise^[3] and eight of them had angiographically documented normal coronary arteries.

RADIONUCLIDE VENTRICULOGRAPHY

Radionuclide data were accumulated at rest and continuously during exercise for left ventricular ejection fraction determination as previously described^[19]. Multiple gated equilibrium radionuclide angiograms were performed by *in vivo* labeling of red blood cells with 20 mCi technetium-99 m after cold pyrophosphate had been injected 20–30 min earlier. Imaging was then performed with a single crystal scintillation camera of the Anger-type equipped with a high sensitivity collimator in a 40° to 50° left anterior oblique and 5°–10° caudal tilt projection which best allowed separation of the left ventricle from other heart chambers. Data acquisition was accomplished with a commercially available nuclear medicine computer system (Medtronic/MDS-A² system). The cardiac cycles of a 2 min acquisition period at rest or peak exercise were assembled at corresponding times to generate composite images throughout the heart cycle.

In order to calculate ejection fraction, a rectangular region of interest was arbitrarily placed around the left ventricle at end-diastole. A computer algorithm (MUGE) was used to determine automatically the left ventricle at end-diastole using the second derivative of the count profile. Each subsequent frame was processed at the same threshold level to determine the changing count rate within the left ventricle ('variable' region-of-interest). A computer-assigned background region-of-interest outside the left lower quadrant of the left ventricle was used to correct for non-cardiac activity. Ejection fraction (EF) was then calculated from the time-activity curve according to the formula: $EF (\%) = [(CED - CES) : CED] \times 100$, where CED = left ventricular counts at end-diastole and CES = left ventricular counts at end-systole, each corrected for background.

Ejection fractions calculated by this technique have been shown to correlate well with those determined from biplane cine-angiography^[19], the correlation coefficient in our laboratory being $r = 0.90$. The reproducibility of ejection fraction measurements by this technique has been shown to be excellent^[20].

REGIONAL ANALYSIS

For regional analysis the computer determined a center of gravity of the left ventricular activity at end-diastole (MDS algorithm). From this center, eight radial sectors of 45° were defined. Because of overlap with aorta and/or left atrium, three of these eight sectors were excluded from further analysis

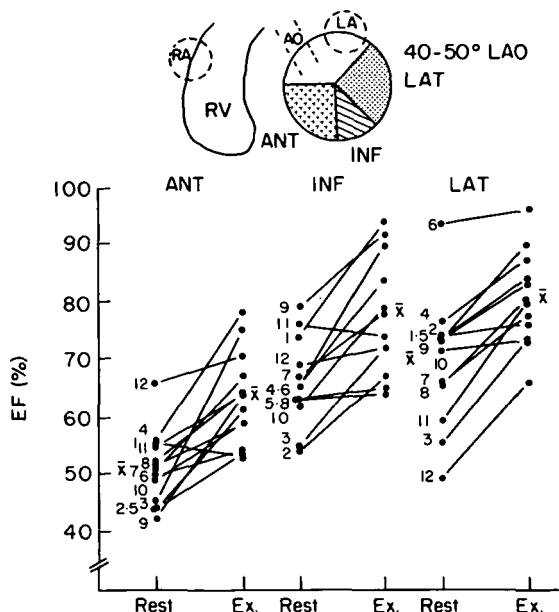


Figure 1 Regional ejection fraction (REF) analysis and normal values at rest and during exercise. Left ventricular activity at end-diastole is divided into eight equal sectors using the center of gravity as starting point. Three sectors are excluded from analysis because of overlap with the aorta (AO) or the left atrium (LA). The remaining five sectors form three regions (ANT=anteroseptal; INF=inferoapical; LAT=posterolateral) reflecting areas normally perfused by the three main coronary arteries. RA=right atrium; RV=right ventricle; Ex.=exercise; LAO=left anterior oblique projection; \bar{x} = mean value; n=12.

(Fig. 1). The remaining five sectors were assigned to the three main coronary arteries: two anteroseptal sectors to the LAD and two posterolateral sectors to the left circumflex (LCX) coronary artery, while there was only one inferoapical sector in the left anterior oblique view which is normally perfused by the right coronary artery (RCA; Fig. 1). The change in counts from end-diastole to end-systole in each sector was used to calculate regional ejection fraction similar to the calculation of global ejection fraction. The same background value determined for global ejection fraction measurement was used for each individual sector.

EXERCISE STUDIES

All patients and normals underwent supine bicycle exercise on a electronically braked Elema-Schönander ergometer (type EM 350) up to a predetermined exercise level known to produce exercise limiting symptoms. The detector of the scintillation camera was not changed between rest

and exercise studies. ECG and blood pressure were monitored during the exercise test. Data of the last 2 min of exercise were used to calculate global and regional ejection fraction. We have previously shown that this study protocol provided reproducible results for global ejection fraction^[20,21].

REPRODUCIBILITY

To assess reproducibility of two serial measurements of regional ejection fraction at rest, 16 patients selected at random, were studied twice with identical camera positioning. To determine the influence of camera repositioning on regional ejection fraction results, 15 other patients were studied twice with a time interval of 45-90 min between the studies. Both patient and camera were then repositioned according to the same anatomical criteria as used initially. Care was taken that no angles or similar numbers could be noted during the first positioning procedure. In addition, 10 of these 15 patients had submaximal exercise studies twice.

LEFT HEART CATHETERIZATION

Left heart catheterization was performed in all patients and in eight normal subjects using the transfemoral Judkins technique. Each coronary artery was filmed in at least two, usually three and sometimes four projections. Biplane contrast ventriculography and left ventricular pressure measurements also belonged to the routine left heart catheterization procedure.

STATISTICAL ANALYSIS

Ejection fraction results are reported as mean \pm 1 standard error of the mean. Regression analysis was performed using the least squares method and Student's t-test for paired and unpaired samples were employed to assess the significance of differences between rest as well as rest and exercise values.

Results

NORMAL VALUES

Global ejection fractions of all normal subjects increased during exercise from 56.9 ± 1.3 to $66.4 \pm 1.1\%$ ($P < 0.001$). In each individual, exercise ejection fraction was at least 10% higher than the resting value^[3,20].

Normal values of regional ejection fraction at rest and peak exercise are shown in Fig. 1 and summarized in Table 1. At rest, regional ejection fraction

Table 1 Global and regional ejection fraction measurements at rest and peak exercise of all four patient groups in comparison to the normal values

	$\bar{x} \pm 1 \text{ s.e.}$	Global ejection fraction		Regional ejection fraction					
		Rest	Ex.	Anteroseptal		Inferoapical		Posterolateral	
				Rest	Ex.	Rest	Ex.	Rest	Ex.
Normals (n=12)	56.9 ± 1.3 P	66.4 ± 1.1 0.001	63.3 ± 3.2 0.001	50.9 ± 2.5 0.001	63.3 ± 3.2 0.001	66.0 ± 2.9 0.001	77.6 ± 3.9 0.001	69.7 ± 4.4 0.001	80.3 ± 2.9 0.001
LAD-stenosis (n=9)	64.7 ± 2.2 P	56.7 ± 4.1 0.05	35.8 ± 6.5 0.001	60.4 ± 3.5 0.001	67.4 ± 4.5 NS	67.4 ± 4.5 NS	68.9 ± 4.9 NS	72.3 ± 3.2 0.01	77.6 ± 2.7 0.01
LAD-occlusion (n=7)	41.9 ± 4.8 P	42.7 ± 6.7 NS	26.7 ± 8.8 NS	26.4 ± 7.9 NS	26.7 ± 8.8 NS	39.9 ± 8.5 NS	48.6 ± 9.8 NS	58.1 ± 8.6 0.05	68.9 ± 8.2 0.05
LCX-disease (n=4)	45.3 ± 3.3 P	40.8 ± 4.5 NS	40.9 ± 3.3 NS	38.9 ± 5.2 NS	40.9 ± 3.3 NS	41.3 ± 10.7 NS	43.3 ± 9.9 NS	59.6 ± 10.4 NS	41.3 ± 10.7 NS
RCA-disease (n=6)	58.8 ± 3.9 P	57.7 ± 3.2 NS	58.3 ± 2.4 NS	53.4 ± 3.0 NS	58.3 ± 2.4 NS	65.3 ± 5.2 NS	62.0 ± 4.6 NS	62.0 ± 6.2 0.025	72.9 ± 4.6 0.025

P values pertain to changes from rest to exercise. Because there were patients with and without previous myocardial infarction and/or angina pectoris in the LCX- and RCA-disease groups, statistically significant differences did not appear as easily as in patients with LAD disease. Abbreviations: LAD = left anterior descending; LCX = left circumflex; RCA = right coronary artery; Ex. = exercise.

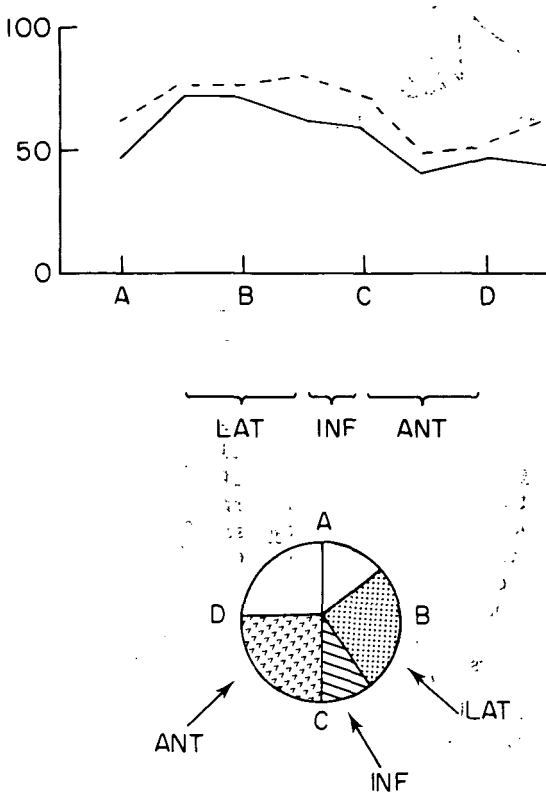


Figure 2 Regional ejection fraction analysis of a normal individual (R.R., male, 37 years). The values of all eight sectors are shown graphically (clockwise) at rest (solid line) and during exercise (dotted line). Regional ejection fraction increases in all sectors. Global EF: rest=52%; exercise=66%. Abbreviations as in Fig. 1.

was significantly lower in the antero-septal than in the other two areas ($P < 0.001$). During exercise, regional ejection fraction increased significantly in all sectors ($P < 0.001$). Looking at the 36 individual areas of the 12 normal subjects, however, there was a significant improvement of $\geq 10\%$ only in 26 (72%). On the other hand, regional ejection fraction did not decrease in any normal subject during exercise. Figure 2 shows the computer analysis of all eight segments in a normal subject.

PATIENTS WITH ONE-VESSEL CAD

In Table 1 and Fig. 3 results of global and regional ejection fraction of 16 patients with single LAD disease are shown in comparison to normal values. In patients with previous myocardial infarction, global ejection fraction was depressed at rest and remained unchanged during exercise. In patients with LAD stenosis and angina, global

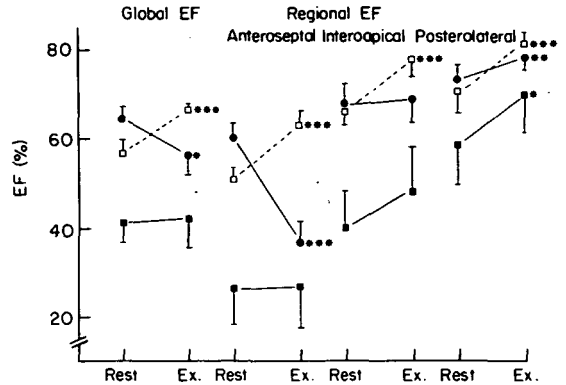


Figure 3 Global and regional ejection fraction in 16 patients with single LAD disease (nine with LAD stenosis and seven with LAD occlusion) in comparison to normal values at rest and during exercise. Note that the main differences between the three groups appear in the involved antero-septal area whereas all groups showed a normal increase postero-laterally. Abbreviations as in Fig. 1. \square = Normals ($n=12$); \bullet = LAD stenosis ($n=9$); \blacksquare = LAD occlusion ($n=7$); * $P < 0.05$; ** $P < 0.001$; *** $P < 0.005$. Values are $\bar{x} \pm s.e.m.$

ejection fraction was normal at rest and decreased significantly ($P < 0.05$) during exercise.

Significant differences in regional ejection fraction became apparent in the involved antero-septal area, while postero-laterally all patients showed a normal behavior in regional ejection fraction. In the antero-septal sector, patients with scar due to LAD occlusion showed a depressed regional ejection fraction which did not change significantly during exercise. Patients with LAD stenosis, on the other hand, had a normal regional function at rest but a highly significant decrease of the antero-septal regional ejection fraction during exercise. In the small infero-apical sector in between there was no significant change in either group.

Figures 4 and 5 show computer analyses of all eight sectors in two patients with LAD stenosis (Fig. 4) and LAD occlusion (Fig. 5), respectively, at rest and during exercise. These individual cases demonstrate how global ejection fractions may remain unchanged despite exercise-induced ischemia and depression of the involved regional ejection fractions due to compensatory increase in regional ejection fraction in non-involved normal areas.

Four patients with single LCX disease followed a very similar pattern of their regional ejection fraction response to exercise in 'opposite' regions compared to those with LAD disease (Table 1):

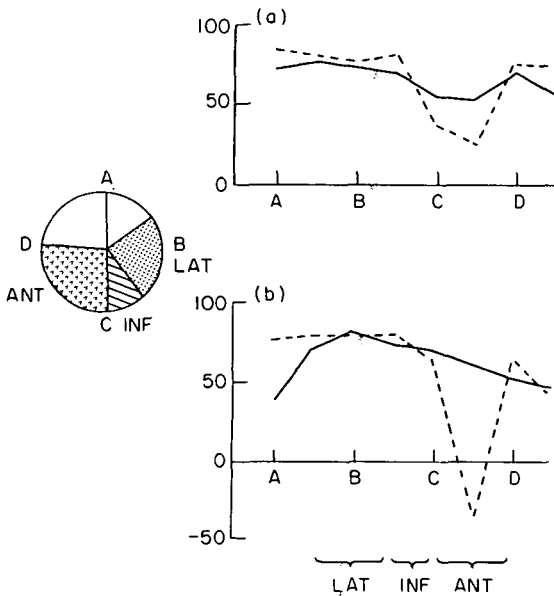


Figure 4 Regional ejection fraction analysis in two patients with single high grade LAD stenosis and exercise-induced ischemia. Note the marked decrease in regional function in the anteroseptal area. Global ejection fraction did not change significantly due to improvement of regional function in normal regions. Presentation and abbreviations as in Fig. 2. (a) H.M., male, 41 years; global EF: rest=63%; exercise=66%. (b) K.B., male, 58 years; global EF: rest=61%; exercise=58%.

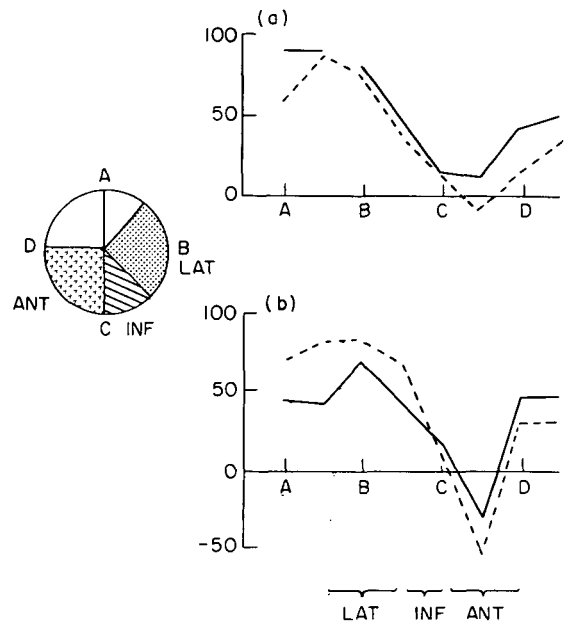


Figure 5 Regional ejection fraction analysis in two patients with single LAD occlusion due to previous myocardial infarction. Note the depressed regional function in the anteroseptal area at rest which was reduced only a little more during exercise. Presentation and abbreviations as in Fig. 2. (a) D.B., male, 40 years; global EF: rest=65%; exercise=34%. (b) R.K., male, 58 years; global EF: rest=33%; exercise=34%.

during exercise, all patients demonstrated a decrease in the posterolateral area and three out of four patients showed some increase anteroseptally. Again in the small inferoapical region in between there was no significant change during exercise.

Six patients with involvement of the right coronary artery showed no significant change in the inferoapical region; regional ejection fraction decreased by more than 10% in only two of them. A normal increase was found in three patients in the anteroseptal area and in all patients posterolaterally (Table 1).

REPRODUCIBILITY

Reproducibility of two serial regional ejection fraction analyses covering all three areas are shown in Fig. 6 in comparison to that of global ejection fraction. Reproducibility was excellent in all three regions although it was clearly worse than that of global ejection fraction. The mean difference between two serial measurements of regional ejection fraction was 0.16 ± 5.17 (1 s.d.) implying that a change in regional ejection fraction would

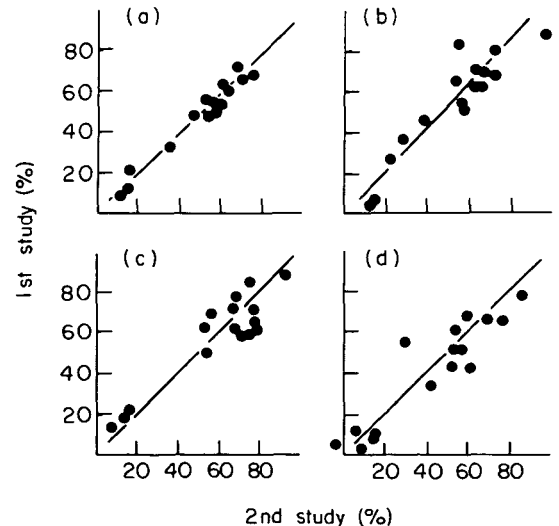


Figure 6 Reproducibility of global and regional ejection fraction measurements of two consecutive studies of 2 min data acquisitions with unchanged camera position. (a) EF global: $r=0.987$; $y=1.05x-1.5$. (b) REF inferior: $r=0.931$; $y=0.90x+3.2$. (c) REF lateral: $r=0.925$; $y=0.99x+1.8$. (d) REF anterior: $r=0.916$; $y=0.96x+3.9$.

have to be $\geq 10\%$ (2 s.d.) in an individual patient to be 'significant'.

After repositioning, reproducibility was somewhat reduced in all three regions: the corresponding r values ranged between $r=0.80$ and $r=0.87$ while reproducibility of global ejection fraction was still excellent ($r=0.97$). Variability between two measurements was somewhat larger after repositioning: in anteroseptal and posterolateral areas the mean difference was 0.19 ± 7.19 and reached 0.71 ± 9.97 inferoapically. Under these circumstances a change in regional ejection fraction in a single patient could be considered to be 'significant' only if it were $\geq 14\%$ (2 s.d.; anteroseptal and posterolateral regions) and $\geq 20\%$ (2 s.d.; inferoapical segment), respectively.

Discussion

In patients with CAD, quantitative assessment of regional changes in left ventricular contraction has become very important in differentiating between normal, ischemic and scar segments. Area, chord and radial methods have been compared for contrast ventriculography each showing advantages and disadvantages^[15,16,22,23]. Some of these analyses have been applied to radionuclide ventriculography at rest^[11,12]. In the present investigation, we have validated a radial method for regional ejection fraction calculation from short acquisition equilibrium radionuclide ventriculography in normal subjects and patients with one-vessel CAD. Comparing rest and exercise measurements, we could separate regions with normal, ischemic and scar myocardium and relate these findings to coronary anatomy. For validation purposes we have studied regional changes in normal subjects and patients with one-vessel CAD thereby avoiding a comparison between regional function (radionuclide ventriculography) and wall motion (contrast ventriculography).

The results of regional ejection fraction at rest showed lower values for anteroseptal as compared to other regions. Others have described a similarly reduced motion of the septal wall in radionuclide studies^[5,8,16] or noted a somewhat lower function in that region^[12,13], but it remains unclear whether this is a true finding or rather due to the technique applied. In our analysis two possible reasons could be found for a methodological explanation of lower regional function in the anteroseptal area: first, we have used a center of gravity fixed at end-diastole while in reality this center should move during

systole towards the septum and aortic valve plane. This movement would reduce regional end-systolic volume and increase regional ejection fraction in the anteroseptal sector and have opposite effects on posterolateral measurements. Due to increased difficulty in accurately defining end-systolic regions we did not attempt to correct for this factor. A second reason may lie in background subtraction: for all regional ejection fractions, we used the same computer-assigned background region-of-interest outside the left lower quadrant of the left ventricle used for global ejection fraction determinations. Actually, background is higher in the septal as compared to the lateral area due to scatter from right ventricular activity^[24]. A higher background subtraction in the septal region would result in higher regional ejection fraction values there. Since background is not uniform in this area and since manually assigned regions show larger variability^[24], we used only one standard background region-of-interest. This observer-independent method could thus be used both for rest and exercise studies of only short acquisition times.

With the method of regional analysis used, the base of the heart was excluded due to anatomic overlap with the left atrium and due to interference with activity of the aortic root. The remaining five sectors were assigned to three regions corresponding to the myocardium perfused by the three main coronary arteries. While a greater number of segments might have been more sensitive to small areas of abnormality, this advantage would have been lost by the smaller number of counts and the worse statistics in each segment — especially in view of short acquisition times (exercise)^[25]. In the present study this problem was exemplified by the increased variability of regional ejection fraction in the small inferoapical segment compared to the larger anteroseptal and posterolateral regions (two segments). Thus, the method used represents a practical compromise between the number of regions analysed and acceptable count statistics despite short acquisition time.

Reproducibility of regional ejection fraction measurements proved to be excellent, but our r values were somewhat lower than those of another report^[12], probably due to the short acquisition times used (lower count statistics). One important factor influencing regional analysis of left ventricular function proved to be camera positioning: reproducibility was worse, especially in the inferoapical segment — but still acceptably good — if patient and camera were repositioned for a second

study. For intervention studies, this implies that small changes can be detected more easily with an unchanged camera position. With proper equipment this can also be achieved during rest-exercise studies.

During exercise, regional ejection fraction increased in normal subjects in all areas, but there were important interindividual variations. Only 26 out of 36 regions in the 12 normal subjects showed a significant increase of >10%, but there was no decrease. In contrast, in patients with ischemic segments we found a highly significant reduction in regional ejection fraction in the involved area. In normal regions, they showed generally a normal increase in regional function during exercise. This could explain why global ejection fraction did not fall during exercise in some patients despite regional ischemia. Patients with previous transmural myocardial infarction had depressed regional function in the involved area with no change during exercise. In normal regions, these patients also showed a normal improvement in regional function during exercise.

With regard to coronary anatomy, the study demonstrated that changes in regional function in the anteroapical and posterolateral sectors were related to obstruction of LAD and LCX coronary arteries, respectively. On the other hand, lesions of the right coronary were detected by significant changes in the inferoapical sector only in a minority of cases. In some of these patients, depressed function in the inferoapical segment was associated with depressed regional ejection fraction in the adjacent segments, mainly the inferoseptal region. Because other investigators have found similar difficulties in detecting inferior wall motion abnormalities, right anterior oblique and 70° left anterior oblique projections have been proposed for this regional analysis^{6,7}. The relative insensitivity of the inferoapical sector to lesions of the right coronary artery may explain the false negative global ejection fraction results observed in these patients^{2,3,21}. In addition, in a grossly enlarged left ventricle and especially in the presence of left ventricular aneurysm the center of gravity of end-diastolic activity is markedly displaced and therefore the methodological approach used is no longer valid. Despite the fact that none of our patients with previous transmural infarction had a left ventricular aneurysm, it is possible that in enlarged hearts such a mechanism might have been responsible for the moderately reduced regional function observed in normal areas of some of these

patients. Thus, this methodological limitation in patients with left ventricular aneurysms which is similarly true for other approaches has to be kept in mind in the application of such a regional function analysis.

This study demonstrated that normal, ischemic and scar myocardial regions could be differentiated by non-invasive assessment of left ventricular regional function using equilibrium radionuclide ventriculography. The global ejection fraction response to exercise reflected a sum of all regional changes implying that regional analysis should be more sensitive in detecting CAD. In normal areas, regional ejection fraction increased or showed no change during exercise whereas it decreased in regions supplied by stenosed coronary arteries (ischemia) and remained depressed in scar zones. Thus, in patients with CAD, normal regions could be found next to ischemic or scar areas. The method presented proved to be valid for regional changes induced by LAD and LCX coronary obstructions, but less for right coronary artery lesions. Reproducibility of regional ejection fraction was excellent despite short acquisition times, especially if the camera position was unchanged for baseline and exercise measurements. The implication is that this non-invasive method should be suitable for the quantification of regional changes observed during different drug intervention studies or early after acute myocardial infarction.

We express our thanks to the nuclear medicine technicians of our hospital for their excellent assistance and to H. E. Schmitt, M.D., and his angiographic team for their help in the catheterization procedures.

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