Regional Ejection Fraction: A Quantitative Radionuclide Index of Regional Left Ventricular Performance

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SUMMARY Radionuclide measurements of regional left ventricular ejection fraction were evaluated as a quantitative index of regional left ventricular function. Left ventricular regional ejection fractions were derived from background-corrected, time-activity curves in 43 patients assessed by both gated equilibrium radionuclide angiography and left ventricular contrast angiography. From a single, modified anterior oblique projection, the regional change in background corrected counts was determined in each of three anatomic regions. The normal range for regional radionuclide ejection fraction was determined in 10 patients with normal contrast ventriculograms and without obstructive coronary artery disease at coronary arteriography. Regional ejection fraction was compared with percent segmental axis shortening and extent of akinetic segments in corresponding regions of the contrast ventriculogram. Radionuclide and roentgenographic methods were in agreement as to the presence or absence of abnormal wall motion in 83 of 99 left ventricular regions (84%) in 33 patients evaluated prospectively. Comparison of regional ejection fraction demonstrated significant differences between regions with roentgenographically determined normokinetics (75 ± 3%, mean ± SEM), hypokinesis (44 ± 3%, p < 0.0005) and akinesis (24 ± 5%, p < 0.005). We conclude that the left ventricular regional ejection fraction provides a reliable quantitative assessment of regional left ventricular performance.

EQUILIBRIUM (gated) radionuclide angiography provides a noninvasive technique that can be applied to critically ill patients and can be performed serially, providing measurements under a variety of physiologic and pharmacologic states. Previous studies of regional left ventricular function using radionuclide angiography have utilized traditional angiographic methods of regional wall motion analysis based on segmental axis shortening or percent of akinetic segments. Attempts to quantify regional wall motion abnormalities have been hampered by suboptimal structural resolution and incomplete delineation of ventricular margins. A number of investigators have described quantitative global indices of left ventricular function based on changing count rates, a variable which is directly proportional to changes in ventricular blood volume. We have used this approach to quantitatively assess left ventricular wall motion using regionally derived radionuclide ejection fractions.

Materials and Methods

Patient Population

The study population consisted of 43 patients, 34 male and nine female, referred to the Peter Bent Brigham Hospital. The average age was 51 years (range 27–66 years). Of the 43 patients, 36 had coronary heart disease (32 obstructive and four nonobstructive); five with normal coronary angiograms had chest pain and two had valvular heart disease. Patients with congenital heart disease were excluded. All patients underwent both radionuclide angiography and cardiac catheterization with left ventricular and coronary angiography as part of routine clinical evaluation. Biplane contrast ventriculography (left and right anterior oblique projections) was obtained in 20 patients. The remaining 23 patients underwent single-plane (right anterior oblique) contrast ventriculography. All of the invasive studies were performed within 24 hours of the radionuclide evaluation.

Radionuclide Data Acquisition

In vivo red blood cell labeling was effected by antecubital intravenous injection of unlabeled stannous pyrophosphate (5 mg Pyrolite, New England Nuclear Corp) followed by 15–25 mCi of technetium-99m (99mTc) as pertechnetate 15–20 minutes later. Gated radionuclide angiograms were ob-
tained with an Anger scintillation camera with a high-sensitivity 30° slant-hole, straight-bore collimator (Engineering Dynamics Corp, Lowell, Massachusetts). Five minutes after injection of the radionuclide, the camera was positioned in the modified left anterior oblique (MLAO) projection (30° caudal tilt). The patient was positioned with the long axis of the left ventricle aligned vertically so that it would lie parallel to the y axis on subsequent computer matrix displays. Composite low-count (400 thousand counts) scintigrams were acquired until the camera obliquity demonstrating the greatest separation of the right and left ventricles was found (typically, a 35-45° MLAO).

After the radionuclide had equilibrated with the intravascular space (5 minutes), 6–10 million counts (approximately 1000 cardiac cycles) were acquired in list mode on magnetic tape with a digital computer (PDP 11/20, Digital Equipment Corporation). Counts were recorded from the area of the detector falling within an inscribed square such that the corners of the square approximated the outer perimeter of the detector field of view. Since the detector diameter was 25 cm, the length of each side of the inscribed square was 17.3 cm. Those photoevents falling within the inscribed square and within a 15% window centered on the photopeak of 99mTc were recorded. We recorded time marks and ECG amplitudes at 10-msec intervals, applying the method of Green et al.

**Radionuclide Data Processing**

The original list mode data collected on magnetic tape were reformatted by computer into 50-msec composite frames using a 64 × 64 matrix. The n th composite frame included those counts falling in a 50-msec window ending n × 50 msec from any ECG R wave. The resulting composite, dynamic study was stored on disc for further processing. Each reformatted 50-msec frame contained 300–600 thousand counts, with more than 30,000 counts within the left ventricle in the end-diastolic frame in patients with normal heart size.

Analysis of gated scintigraphic studies included determination of both global and regional left ventricular ejection fraction from the formula

\[
EF = \frac{ED - ES}{ED - B} \times 100\%
\]  

(1)

where EF is ejection fraction, B is the estimated background, and ED and ES are the end-diastolic and end-systolic counts, respectively. The boundaries of the global and intraventricular regions, as well as corresponding background estimates for each region, were determined by an empirically derived method described below.

To improve visualization of the left ventricular perimeter, the first two frames of the gated study were added and a 30% threshold was imposed (that is, matrix cells containing fewer than 30% of the maximum cell count in the image were set equal to zero). From this enhanced image, which corresponded to the first 100 msec after the R wave, the end-diastolic perimeter of the left ventricle was traced manually with an electronic cursor (fig. 1). This left ventricular region of interest represented a first approximation and was superimposed on the stroke volume image and ejection fraction image, which were used to confirm the perimeter of the left ventricle. Errors in the left ventricular outline were corrected and we made the final analysis of regional ejection fraction using the corrected left ventricular perimeter. The end-diastolic and end-systolic frames were defined as those frames with the maximum and minimum counts, respectively, within the left ventricular perimeter. These frames were selected from a time-activity histogram composed of all the composite frames within the representative cardiac cycle.

An automated computer algorithm was developed to define background regions and position them relative to the hand-drawn left ventricular perimeter (fig. 1). This algorithm has been described in detail elsewhere. Basically, three rectangular background regions were defined, each three matrix cells wide and with a length equal to one-half the longest vertical dimension of the end-diastolic left ventricular cavity. The background regions were positioned one cell removed from, and parallel to, the margins of an imaginary rectangle excribed about the ventricular perimeter. Individual background regions were centered along the lateral and apical side of the excribed rectangle and along the lower three-fourths of the septal side.

A left ventricular longitudinal axis was then constructed by connecting midpoints of the basal and apical sides of the excribed rectangle. Three quadrisecting transverse axes within the inscribed left ventricular perimeter completed demarcation of eight intraventricular subdivisions (fig. 2). This algorithm depends on carefully positioning the patient during data acquisition to ensure that the long axis of the left ventricle is aligned vertically on the matrix display.

The two intraventricular regions at the base of the heart (subdivisions 1 and 8, fig. 2) tended to overlie the region of the mitral and aortic valves. Furthermore, precise definition of the superior border of these regions was difficult because of the proximity to the left atrium and great vessels. As a result, background-corrected activity in these regions during end-diastole was less than background activity itself in the majority of patients, probably resulting from inclusion of adjacent structures into the region. These two regions were therefore not included in the subsequent analysis of regional ejection fraction.

The six remaining intraventricular subdivisions were grouped into three anatomic regions: anteroseptal (subdivisions 2 and 3), apical (subdivisions 4 and 5), and inferoposterior (subdivisions 6 and 7) (table 1).

The background (B,) for the three anatomic regions of the left ventricle was estimated using a weighted average of the counts per cell in each of the three background regions obtained in the end-systolic frame. The total background in the i th subdivision was estimated as
Figure 1. A) Modified left anterior oblique view of the end-diastolic image with the left ventricular perimeter indicated by the electronic cursor. B) Left ventricular perimeter with three background correction regions indicated. C) Excribed rectangle derived from left ventricular perimeter with eight subdivisions. D) Final regions of interest, with left ventricular perimeter and eight subdivisions.

\[
B_i = N_i \sum_{j=1}^{3} a_{ij} b_j \quad i = 1,8
\]

where \(N_i\) is the number of matrix cells in the \(i\)th subdivision, \(b_j\) is the mean background per cell in the \(j\)th background region, and \(a_{ij}\) is the assigned weight. The weights \(a_{ij}\), shown in Table 2 reflect the proximity of the \(i\)th subdivision to each of the three background regions. The background area lateral to the left ventricle (\(B_3\)) was weighted more heavily than the area over the septum (\(B_1\)) because a portion of the latter included counts from the right ventricle. Preliminary studies showed that global ejection fraction was overestimated when each background region was weighted equally. Thus, the background used for the anteroseptal region was two-thirds the average counts per cell in the septal background region (\(B_1\)) and one-third the average counts per cell in the lateral background region (\(B_3\)), while the background used for the inferoposterior region was derived only from \(B_3\). To establish the validity of the regional background selection technique with respect to a quantitative index of ventricular performance that could be obtained by an independent method, the global left ventricular ejection fraction derived from the contrast left ventriculogram was correlated with
the global ejection fraction obtained using regional background corrections.

Regional ejection fractions for the three anatomically defined regions of the left ventricle were computed by combining the counts from the appropriate subdivisions of the left ventricle shown in figure 2. The frames representing global end-diastole and end-systole were determined from the time activity curve derived from the left ventricular region. The ejection fraction for each anatomical region was calculated by using equation (1) and the total end-diastolic, end-systolic and background counts within that region.

To calculate global ejection fraction for the entire left ventricle, the global background (Bg) was calculated as

\[ Bg = \sum_{i=1}^{8} B_i \]  

Measurement of global ejection fraction was based on counts in all eight regions of the left ventricle. For global ejection fraction only, the background correction for region 1 was the average counts/cell in B1 and the background correction for region 8 was the average counts/cell in B8.

### Contrast Angiogram Analysis

For each contrast ventriculographic study, hand-traced right anterior oblique silhouettes of left ventricular end-diastole and end-systole were obtained by an independent observer from projected cineangiograms (16 mm or 35 mm) using previously described techniques. Only the first three beats after contrast injection were accepted for analysis. Beats immediately after a ventricular extrasystole were rejected. Global ejection fraction was determined for each ventriculogram by the area-length method of Dodge and associates. For 20 patients with biplane ventriculograms, ejection fraction was calculated by using the derived minor axis from each of the right and left anterior oblique views and the longest major axis. For 23 patients with single-plane right anterior oblique ventriculograms, ejection fraction was similarly calculated, assuming symmetry about the minor axes.

Regional ventricular function was assessed by determination of left ventricular hemiaxis shortening. After apposition of longitudinal axes of the right anterior oblique end-diastolic and end-systolic tracings, the end-diastolic axis was quadrisected by three perpendicular transverse axes (defining six segmental hemiaxes). The left ventricular hemiaxes were then assigned to three distinct anatomical segments: anteroseptal (hemiaxes H1 and H2), apical (hemiaxes H3 and H4), and inferoposterior (hemiaxis H5) regions (fig. 3). Hemiaxis 6, located at the basal portion of the inferior wall, was not used because prior analyses have demonstrated the unreliability of this hemiaxis in measuring inferior asynergy. An additional transverse axis at the junction of the middle and distal thirds of the end-diastolic long axis defined the distal margin of the inferoposterior region. This additional transverse axis was necessary to define the extent of inferoposterior akinetic segments, since this region contained only one hemiaxis (see below).

Evaluation of superimposed end-diastolic and end-systolic silhouettes allowed identification and localization of abnormally contracting wall segments. Systolic hemiaxis shortening <25% was considered abnormal (asynergy). Asynery was classified as hypokinesis (>5% shortening) or akinesis (<5% shortening and/or presence of a nonmoving or paradoxing wall segment). Hemiaxis shortening >25% was defined as normokinesis. Presence of both a normokinetic and asynergic hemiaxis within a ventricular region was interpreted as asynery. Coincidence of hypokinetic and akinetic segments within a single region was interpreted as akinesis. Akinesis was further classified as moderate (AKm) or severe (AKs). AKm indicated <5% shortening of both hemiaxes of a given region. AKs indicated that only one hemiaxis of a given region had <5% shortening. Since the inferoposterior region used only one hemiaxis (H5) for analysis, other criteria were required to subclassify inferoposterior akinesis. In this region, AKs indicated involvement of the entire regional wall segment, and AKm, less-than-complete involvement.

### Radionuclide-Angiographic Comparison

To determine the utility of regional ejection fraction in assessing regional ventricular performance, the radionuclide-derived ejection fractions were compared with corresponding angiographically determined segmental wall motion in each of three regions: anteroseptal, apical and inferoposterior (table 1). From 10 patients with normal contrast ventriculograms and no evidence of obstructive coronary artery disease (group 1), values for regional ejection fraction were calculated for each of the three ventricular regions as mean regional ejection frac-
Regional ejection fractions more than 2 SD below the mean for each region were considered abnormal. Agreement of radionuclide and angiographic methods regarding the presence or absence of asynergy, as well as severity of asynergy, was then determined in the subsequent 33 patients by comparing angiographic and radionuclide analyses of each ventricular region. To facilitate comparison, the 33 patients were divided into two groups based on roentgenographic findings. Group 2 (normals) consisted of 12 patients with normokinesis of all three contrast ventriculographic regions. Group 3 (abnormals) consisted of the remaining 21 patients with asynergy of one or more of the three ventricular regions evaluated.

Reproducibility of Radionuclide Method

Reproducibility of the radionuclide method was evaluated in 12 patients who consented to a repeat study 40–120 minutes after the initial data acquisition. Each restudy was performed after repositioning of both patient and scintillation camera, but without significant change in systemic blood pressure or heart rate. From initial and repeat studies of each patient, regional and global ejection fraction reproducibility was evaluated by comparing values obtained in each of the three left ventricular anatomic regions. The left ventricular region of interest and, hence, the background regions and the ventricular subdivision, were defined independently for the first and second studies.

Results

Global Ejection Fraction

Average global ejection fraction for 22 patients with normal contrast ventriculograms (groups 1 and 2) was 65 ± 8% (mean ± SD) by radionuclide evaluation and 69 ± 7% by contrast ventriculography. All 22 patients demonstrated roentgenographic global ejection fractions >50%.

Range of global ejection fractions for group 3, the 21 patients with contrast angiographic evidence of regional asynergy, was 43 ± 17% (range 14–64%) by the radionuclide method and 42 ± 16% (range 13–69%) by contrast ventriculography. Comparison of global ejection fractions of all 43 patients showed excellent agreement between radionuclide and contrast methods, with mean values of 53% and 56%, respectively. The relationship between ejection fraction determined from contrast ventriculography (EFc) and radionuclide ventriculography (EFn) was

$$EF_c = 0.95(\text{EF}_n) + 5.46 \quad r = 0.91 \quad S_{(x,y)} = 6.34 \quad (4)$$

As might be anticipated, the agreement was best when the comparison was limited to the 20 patients who underwent biplane oblique contrast ventriculography, where the relationship was

$$EF_c = 1.1(\text{EF}_n) - 0.76 \quad r = 0.95 \quad S_{(x,y)} = 4.67 \quad (5)$$

Contrast-Radionuclide Comparison

Normal values for regional ejection fraction, determined from radionuclide studies of the 10 patients with normal contrast left ventriculograms and without significant coronary artery disease, are listed in table 3. Comparing regional ejection fraction from each of 99 regions (three per patient) in the 33 patients in groups 2 and 3 with the normal regional ejection fraction values revealed 32 abnormal (asynergic) and 67 normal (normokinetic) regions, compared with 44

<table>
<thead>
<tr>
<th>Region</th>
<th>REF (%)</th>
<th>mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anteroseptal</td>
<td>66 ± 13</td>
<td></td>
</tr>
<tr>
<td>Apical</td>
<td>85 ± 12</td>
<td></td>
</tr>
<tr>
<td>Inferoposterior</td>
<td>74 ± 16</td>
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asynergic and 54 normokinetic regions noted on contrast ventriculograms. Contrast and radionuclide assessment agreed in 83 of 99 instances (84%). By contrast standards, radionuclide assessment was falsely positive (asynergy) in two of the 16 discordant regions and falsely negative (no asynergy) in 14 ventriculographic regions.

Severity of Asynergy

Of 44 regions designated asynergic by contrast evaluation, 27 were hypokinetic and 17 akinetic. Regional ejection fractions of 75 ± 3% (mean ± SEM) for group 1 patients and 67 ± 2% for group 2 patients were significantly greater than values for either hypokinetic (44 ± 3%) or akinetic (24 ± 5%) regions (p < 0.0005) in group 2 and group 3 patients. Hypokinetic and akinetic regions also differed significantly (p < 0.0005). The mean normal value for regional ejection fraction varied from region to region (table 3). To compare values from different regions, the regional ejection fraction was normalized by dividing it by the mean normal ejection fraction for that region. There was a significant difference in normalized ejection fraction in normokinetic, hypokinetic (p < 0.0005) and akinetic (p < 0.00125) regions (fig. 4). Moderate (AK1, n = 8) and severe akinesis (AK2, n = 9) corresponded to regional ejection fractions of 34 ± 7% and 15 ± 4%, respectively (p < 0.0125). The normalized values are depicted in figure 5.

**Background Correction**

Background activity contained within the regions of interest used for background correction averaged 65 ± 6% of the total counts contained within the left ventricular perimeter (mean ± SD) for the 43 patients studied. The percent background within specific background regions was 49 ± 8%, 59 ± 9% and 89 ± 15% for regions B2, B3, and B1, respectively (fig. 2).

**Reproducibility of Radionuclide Methods**

The reproducibility of the technique, determined in 12 patients undergoing repeat radionuclide studies, is depicted in figure 6. There was excellent correlation between the regional ejection fractions obtained from the first and second study (r = 0.98; S(x,y) = 5.93; slope = 1.0) and between global ejection fractions obtained from the first and second study (r = 0.99; S(x,y) = 1.48).

**Discussion**

Assessments of wall motion by radionuclide methods have used standard contrast angiographic methods of analysis.2-6 These angiographic analyses (segmental axis shortening, extent of akinetic segments) require precise identification of both end-diastolic and end-systolic chamber margins and are thus limited by the structural resolution of...
radionuclide studies. In addition, angiographic analyses ignore the three-dimensional perspective provided by cyclic variation in radioactivity.

Use of the Anger scintillation camera for measurement of ejection fraction by changing count rates was reported by Van Dyke and co-workers in 1972. Applying an empirically derived background correction to time-activity curves obtained during initial transit of a \textsuperscript{99m}Tc-human serum albumin (HSA) bolus through the central circulation, these investigators obtained values for global ejection fraction which compared favorably with those obtained with standard contrast angiographic methods. Also in 1972, Parker et al.\textsuperscript{7} described a computer-assisted application of the Anger camera which provided global ejection fraction from gated measurements of \textsuperscript{99m}Tc-HSA blood pool at equilibrium. Using an empirical background correction, they determined the global ejection fraction by assuming proportionality of volume to recorded ventricular count rates. Refinements of these methods for determining global ejection fraction have subsequently been reported by Schelbert et al.\textsuperscript{20} for initial pass studies, and Green et al.,\textsuperscript{12} using equilibrium blood pool methods.

The background-corrected activity recorded from the region of the left ventricle is directly proportional to its blood volume. While the radionuclide method has limited spatial resolution and edge definition, it does provide an accurate measure of the activity viewed by the detector or a region of the detector. Therefore, assessment of global and regional ventricular function based on changing count rates has inherent advantages over the geometric approaches borrowed from contrast angiography. First, the geometric approaches assess only the ventricular wall which is tangential to the detector. Techniques based on left ventricular activity assess the three-dimensional space viewed by the corresponding region of the detector, assessing ventricular function regardless of its orientation to the detector. Techniques based on activity need not make assumptions concerning left ventricular shape. This consideration is particularly important in patients with asynergy when these geometric assumptions may not be valid. Second, the need for defining the margins of the left ventricle during end-systole is eliminated with the count-rate method. During end-systole, the difference between ventricular and background activity may be small and edge resolution particularly poor.

**Technical Considerations**

Distribution of radioactivity throughout the intravascular space in equilibrium studies necessitates accurate background correction. Activity arising from the blood pool of the chest wall, pulmonary circulation, myocardium or cardiac structures and great vessels adjacent to the left ventricle is not only heterogeneously distributed in each study, but inconsistent in distribution from one patient to the next.

Significant variation in ejection fraction values resulting from slight variation in designation of background regions has been reported for initial pass studies.\textsuperscript{20} The higher levels of background activity encountered in equilibrium studies only intensify the importance of minor differences in background selection. The accuracy with which we measured global ejection fraction.

![Figure 6. Comparison of regional ejection fraction (REF) from two consecutive studies (study 1 and study 2) in 12 patients.](image)
fraction and detected regional asynergy provides an indirect test of the regional background correction technique which cannot be validated directly.

The high degree of reproducibility of global ejection fraction determined from sequential studies was comparable to results obtained by other investigators using radionuclide techniques. The reproducibility is also comparable to that noted by Cohn et al. in a study of reproducibility of angiographically derived left ventricular ejection fraction. Cohn emphasized the importance of consistency of method in both data acquisition and analysis, as well as hemodynamic stability, to ensure agreement of sequential contrast studies.

Automation of background region selection and systematic patient positioning were techniques used in this study to minimize observer bias and improve reproducibility of background selection. Proper alignment of the left ventricle with respect to the detector was achieved by obtaining ungated, low-count density images and aligning the long axis of the left ventricle into a vertical orientation. This process required two to four images and took 5–10 minutes. Collection of the 10 million count, gated study took an additional 12–15 minutes.

The time to reformat the studies after list mode data acquisition was approximately 30 minutes. We are currently using commercially available software for data acquisition (Gamma-11, Digital Equipment Corporation) and collect in matrix mode (64 × 64 picture elements) using 50-msec frames. Data analysis is otherwise identical to the method described. By eliminating the reformatting time, analysis requires approximately 10 minutes after the study has been acquired.

Fifty-millisecond frames were used so that as many counts as possible could be included in each frame to improve the counting statistics without jeopardizing the accuracy of the measurements. Since there was excellent correlation between contrast and radionuclide measurements of global left ventricular ejection fraction, the frame length did not compromise the accuracy of the regional measurements in the population studied.

The left ventricular outline drawn manually from the composite image of the first 100 msec after the R wave tended to underestimate the size of the ventricle, particularly at the posterior base. This error may have occurred if the ventricle had already begun to contract by 100 msec and because the number of counts is lowest at the edge of the ventricle where ejection is greatest. We corrected the left ventricular outline by superimposing it on the ejection fraction and stroke volume images that were obtained with the initial analysis. We used the corrected outline to calculate regional ejection fraction.

The modified left anterior oblique projection was used because the separation of the left ventricle from the right ventricle and left atrium is greatest in this view. It does result in some superimposition of anterior and diaphragmatic left ventricular walls, however. As a result, isolated abnormalities of either anterior or inferior wall motion may be obscured by compensatory hyperkinesis of the opposite wall. Furthermore, in cases of combined asynergy (both anterior and diaphragmatic walls), the relative contribution of each to changing volume must be discerned. Localization of anterior and inferior wall asynergy in this study was probably enhanced by association of inferior wall asynergy with abnormalities of posterior and posterolateral segments and association of anterior wall asynergy with compromised motion of the interventricular septum. These frequently associated abnormalities have been described in roentgenographic studies.

Contrast-Radionuclide Agreement

Sensitivity of the right anterior oblique contrast angiogram to the presence and location of left ventricular asynergy has been established, although the full extent of wall motion abnormalities may be more apparent with biplane views. Comparing single-plane right anterior oblique and biplane oblique contrast ventriculograms in a series of patients with abnormalities of regional wall motion, Cohn et al. noted no instance in which regional asynergy was apparent exclusively in the left anterior oblique view. Extent of dysfunction was less apparent in the right anterior oblique than in biplane views, however, resulting in less reliable estimation of global ejection fraction from uniplane calculations.

Thus, close agreement might be expected between contrast and radionuclide methods in the detection of asynergy, but the differing sensitivities of the techniques to motion of nontangential wall segments, as well as the arbitrary nature of segmental axis construction, might lessen agreement regarding the extent and severity of dysfunction. Results of this study are consistent with those assumptions.

Measurement of regional ejection fraction provides a quantitative method to assess regional left ventricular wall motion. Because the technic is noninvasive, sequential analysis is possible in acutely ill patients; because data processing is automated, patient analysis can be performed within a few minutes after data acquisition. Regional ejection fraction determinations may prove useful in assessing the natural progression of coronary artery disease, or changes resulting from pharmacologic, surgical or physiological interventions.

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