Left ventricular ejection fraction from gated SPET myocardial perfusion studies: a method based on the radial distribution of count rate density across the myocardial wall

Hendrik Everaert[1], Philippe R. Franken[1], Patrick Flamen[1], Michael Goris[2], Afsana Momen[1], Axel Bossuyt[1]

[1] Division of Nuclear Medicine, Univesity Hospital, Free University of Brussels (AZ VUB), Brussels, Belgium
[2] Division of Nuclear Medicine, Stanford University School of Medicine, Stanford, California, USA

Received 6 June and in revised from 20 August 1996

Abstract. Left ventricular ejection fraction (LVEF) can be derived from gated single-photon emission tomographic (SPET) myocardial perfusion studies using either manual or edge detection techniques. In the presence of severe perfusion defects, however, difficulties may be encountered. In this article a method based on the assumption that the average position of the myocardial wall can be localized by means of statistical analysis of the distribution count density, and not on edge detection, is used to measure LVEF. SPET myocardial perfusion images, gated in eight time bins, were recorded in 50 patients 60 min after the injection of 925 MBq technetium-99m tetrofosmin. Masking of non-myocardial structures and thresholding resulted in images in which only myocardial walls had significant non-zero values. The distance of the wall relative to the centre of the cavity was calculated in the three-dimentional space as the first moment of the count rate distribution along radii originating in the centre of the cavity. LVEF was calculated using, for each time bin, the sum of the cube of all distances as an estimate of the cavity volume. The method required minimal operator interventions and was successful in all patients, including those with severe perfusion defects. Intraobserver and interobserver variability was excellent, with regression coefficients of 0.97 and standard deviations of 4.5% and 4.7%, respectively. For 30 patients, the measurements were validated against planar equilibrium radionuclide angiography (ERNA) that was obtained within an interval of 1 week. LVEF ranged from 12% to 88%. Agreement between the two methods was excellent ($LVEF_{ERNA}$=1.05+0.92 $LVEF_{GSPET}$, r=0.93, P=0.023, SEE=7.06). The Bland-Altman analysis did not show any apparent trend in the differences between ERNA and gated SPET over a wide range of ejection fractions. The standard deviation of the differences was 3.1%. In addition no relationship was found between the two methods and the severity of perfusion defects. In conclusion, accurate measurements of LVEF are obtained from gated SPET perfusion images using a method based on statistical analysis of the count rate density. This method did not deteriorate even in the presence of severe perfusion defects and could therefore be used in following patients after myocardial infarction.

Key words: Ejection fraction – Gated single-photon emission tomography – Myocardial perfusion

Eur J Nucl Med (1996) 23:1628–1633

Introduction

Several recent studies have shown that left ventricular ejection fraction (LVEF) can be measured with reasonable precision from gated single-photon emission tomographic (SPET) myocardial perfusion images [1–5]. In these studies, the limits of the left ventricular cavity were outlined either manually following arbitrary thresholds [1] or by using edge [2, 4] or surface [5] detection algorithms. Although these techniques provide satisfactory results in many cases, difficulties may be encountered in the presence of severe perfusion defects where the myocardial contours cannot be identified accurately. In addition, estimation of the cavity volume requires additional geometric approximations.

A new approach to characterize myocardial wall kinetics from gated perfusion SPET studies has recently been developed at Stanford University [6]. In this method the location of the myocardial wall is defined by statistical parameters and not by edge detection. The algorithm operates in the three-dimensional space, radially from the centre of the left ventricular cavity. The sum of the cube of all distances to the myocardial wall is used to calculate the volume of the cavity.

Correspondence to: P.R. Franken, Division of Nuclear Medicine, Academic Hospital, Free University Brussels (AZ VUB), Laarbeeklaan 101, B-1090 Brussels, Belgium

The aim of this work was to determine the feasibility, reproducibility and accuracy of this method for measuring global LVEF in patients with coronary artery disease. The results were validated against LVEF measured on conventional planar equilibrium radionuclide angiocardiography (ERNA).

Materials and methods

Patient population

Included in this study were 30 consecutive patients with known or suspected coronary artery disease who underwent, for clinical purposes, both myocardial SPET imaging and radionuclide angiocardiography within an interval of 1 week. All patients were in a clinically stable condition and were in sinus rhythm at the time of the investigation. There were 13 men and 17 women with a mean age of 69.1±11.5 years. Twenty-one patients (70%) had a history of previous myocardial infarction. There were ten patients with anterior infarction and 11 with inferior infarction. Eighteen patients showed evidence of transmural (Q waves) infarction on standard 12-lead ECG.

Gated SPET myocardial perfusion studies from 20 patients with a less than 5% likelihood of coronary artery disease were also analysed [7]. These patients comprised seven men and 13 women with a mean age of 47.0±9.9 years. All of them had normal rest and exercise ECG, normal chest X-rays and normal 2D-echocardiographic studies.

Measurement of LVEF from gated SPET perfusion images

Gated SPET acquisition. Patients received 925 MBq of technetium-99m tetrofosmin intavenously at rest. Studies were acquired 60 min after tracer administrationon a triple-head gamma camera (MultiSpect3, Siemens, Inc., Hoffman Estates, Ill.) equipped with low-energy high-resolution collimators. Acquisition parameters were 360° rotation, 32 views per head (96 angles), 64×64 format, zoom 1.23 (pixel size: 4.96 mm×4.96 mm), stop and go, 40 s per stop, 8 time bins, forward/backward framing by 75% and beat acceptance window at 20% of the average RR interval calculated just before starting the acquisition. Patients with more than 15% rejected beats were not included in the study.

Image preprocessing. Gated projections were first normalized to the one containing the largest number of accepted beats. Transverse slices were then reconstructed by using the filtered backprojection method (Butterworth filter, cut-off frequency 0.4 cycles/pixel, order 5) and reoriented with respect to the left ventricular long axis. For each time bin, the images were then interpolated in the three-dimensional space by a factor 4 and displayed in the three orthogonal planes with the apex pointing downwards.

Masking and thresholding. Gated images were masked and thresholded in order to obtain data in which only the left ventricular wall had significant non-zero values. The right ventricle and non-cardiac structures were masked out by using a three-dimensional ellipsoidal mask fitted manually around the left ventricle. Thresholding was performed by subtracting from each pixel the average count density measured in a small region of interest (5×5 pixels) drawn at the base of the left ventricular cavity on the end-diastolic bin.

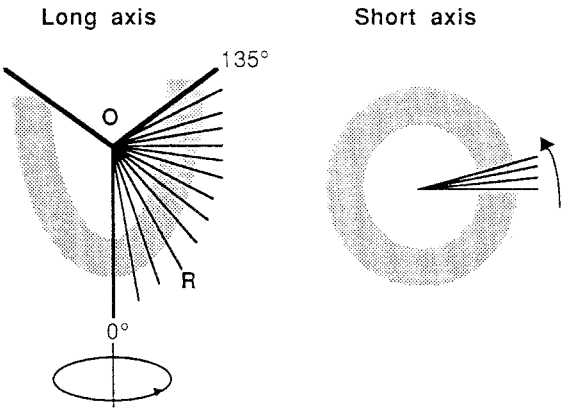

Fig. 1. Illustration of the way in which the myocardial wall is sampled. (For abbreviations see text)

Centering the images. The images in the eight time bins were then re-registered automatically upward or downward, so that the position of the valve plane was the same for all time bins [6]. The centre of the left ventricular cavity in the end-systolic time bin was then identified as the intersection of the diagonals of rectangles fitted around the left ventricle wall on short- and long-axis views. The coordinates of this point were used to measure all distances for each time bin.

Calculating the ejection fraction. The theoretical bases of the method used in this study have been previously described in detail [4]. For each time bin the myocardial wall was sampled in three-dimensional coordinates along radii originating in the centre of the left ventricular cavity (Fig. 1). The first moment of the count rate distribution along each radius was used to calculate the average position of the wall (Fig. 2). If the distribution of count rate densities along radius R is $C(R)$, the average position of the wall D is given:

$$D=\sum r\cdot C(r)\cdot dr \,/\, \sum C(r)\cdot dr. \quad (1)$$

The longitudinal angle of the radii originating in the centre of the cavity varied from 0° to 360° and the latitudinal angle from 0° (apex) to 135° in 32 steps. The sampling arc did not go beyond 135° to avoid sampling the left ventricular outflow tract where myocardium is absent. Along each radius, the average position of the wall (D) was calculated using Eq. 1. For each time bin, the sum of the cube of all D values was used as an estimate of the cavity volume (V'):

$$V'=\sum D^3. \quad (2)$$

The largest and the smallest V' values were considered to be the end-diastolic (ED) and the end-systolic (ES) estimates of the cavity volume and used to calculate LVEF:

$$\text{LVEF}=(V'_{ED}-V'_{ES}/V'_{ED})\times 100. \quad (3)$$

Quantification of myocardial perfusion defects

Myocardial perfusion defects were identified on the end-diastolic images and quantified on distance-weighted polar maps using the 20 patients with low likelihood of coronary artery disease as normal references. An index of the severity of perfusion defect was calculated as the sum of the differences between the normal mean minus 2 standard deviations polar map and the patient polar map.

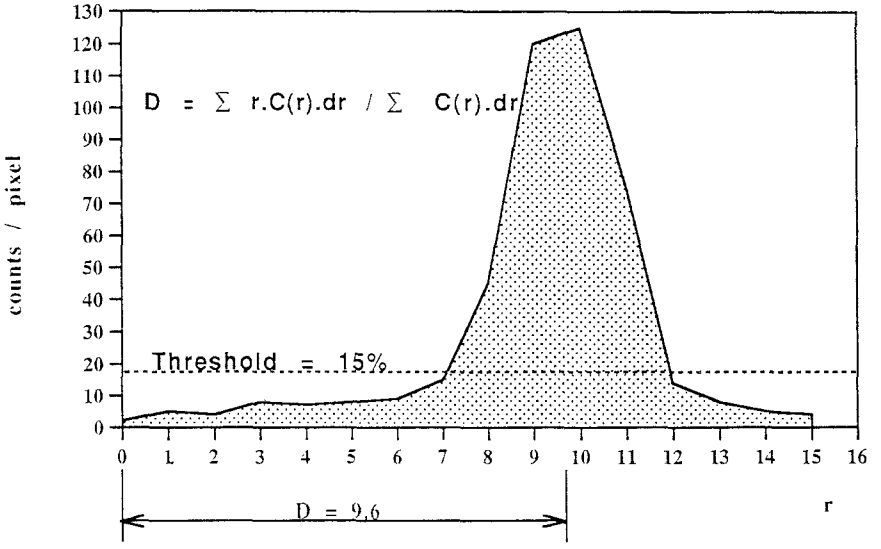

Fig. 2. Count rate distribution along a radius *O–R*. In this example, the distance *D* was calculated after applying a threshold of 15%. (For abbreviatons see text)

ERNA

ERNA was performed using in vivo labelled red blood cells obtained by the intravenous administration of stannous pyrophosphate followed 20 min later by 750 MBq of ^{99m}Tc-pertechnetate. Sixteen ECG gated frames were obtained in the left anterior oblique projection (best septal view) using a large field of view gamma camera (Orbiter 76, Siemens, Inc., Hoffman Estates, Ill.). Data were acquired in 64×64 format, zoom 2 (pixel size: 3.13. mm×3.13 mm) for at least 400 Kilo counts per frame. Images were transferred on a Sophy NXT (P) computer (Sopha Medical) and processed using a commercially available program used to calculate LVEF in daily practice (Sophy NXT, software revision 2.01).

Analysis of data

The operator-dependent variability in LVEF using gated SPET myocardial perfusion images was determined by comparing the measurements obtained either by two independent observers (interobserver reproducibility) or by two measurements separated by an interval of 2 months (intraobserver reproducibility) in the 30 patients with known or suspected coronary artery disease. Systematic error in respect of LVEF and the degree of agreement between measurements were assessed using Bland-Altman plots [8]. The standard deviation of the summed positive and negative differences between successive measurements was used as the index of operator-dependent variability.

Comparison of LVEF on gated SPET myocardial perfusion and on ERNA was done by linear regression analysis, determination of the standard error of the estimates (SEE) and analysis of the Bland-Altman plot. Paired *t*-test was applied to the data to determine whether LVEFs were significantly different.

Errors due to thresholding and centering gated SPET myocardial perfusion images were also evaluated. LVEFs obtained after applying increasing levels of threshold (up to 40% of the maximal activity in the gated study) were compared in ten patients with the LVEFs measured with ERNA. The variability due to centering gated data was taken to be the mean±SD of the absolute difference between measurements made by two independent observers using the same preprocessed, masked and thresholded data sets.

Statistical significance was defined as $P<0.05$.

Results

The method was successful in all patients, including those with severe perfusion abnormalities, and over a wide range of LVEF values. LVEF averaged 65.5%±5.5% for the 20 patients with a low likelihood of CAD, and ranged from 12% to 88% for the 30 patients with known or suspected CAD.

Intra- and interobserver reproducibility

The linear regression coefficient between two measurements performed by the same observer at an interval of 2 months was 0.97 ($LVEF_{MEAS\ 1}$=0.78+0.97 $LVEF_{MEAS\ 2}$) (Fig. 3a). The Bland-Altman plot (Fig. 3b), which expresses the difference between the two measurements as a function of the mean value, demonstrated no relation between this difference and the LVEF value. The standard deviation of differences between the two measurements was 4.5%. The absolute difference averaged 3.2%.

The linear regression coefficient between measurements performed by two independent observers was 0.97 ($LVEF_{OBS\ 1}$=3.55+0.88 $LVEF_{OBS\ 2}$) (Fig. 4a). The Bland-Altman plot showed a good reproducibility even in patients with low LVEF values. The standard deviation of the differences between the two observers was 4.7% (Fig. 4b). The absolute difference averaged 3.5%.

Comparison with ERNA

The linear regression coefficient between the LVEF determined on gated SPET perfusion images and LVEF determined by ERNA was 0.93, with the $LVEF_{GSPET}$ =1.05+0.92 $LVEF_{ERNA}$ and an SEE of 7.06% (Fig. 5a).

The Bland-Altman plot, showing the difference in ejection fraction as a function of the averaged ejection fraction measured between $LVEF_{ERNA}$ and $LVEF_{G\text{-}SPET}$, demonstrated that no apparent trend existed over a wide

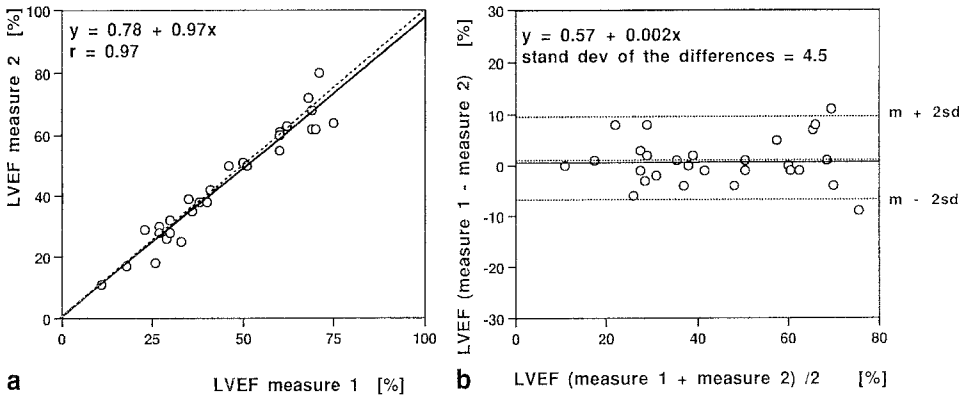

Fig. 3a, b. Intraobserver reproducibility of LVEF determined from gated SPET myocardial perfusion images in 30 patients with known or suspected CAD. **a** Linear regression analysis; **b** Bland-Altman plot

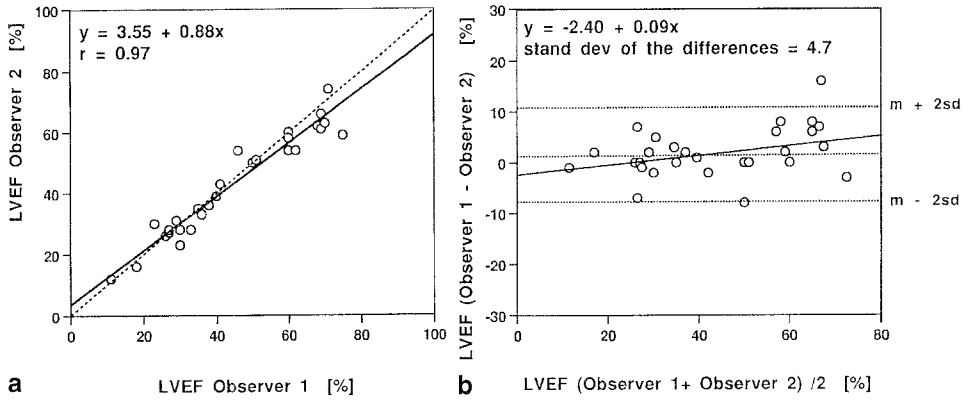

Fig. 4a, b. Interobserver reproducibility of LVEF determined from gated SPET myocardial perfusion images in 30 patients with known or suspected CAD. **a** Linear regression analysis; **b** Bland-Altman plot

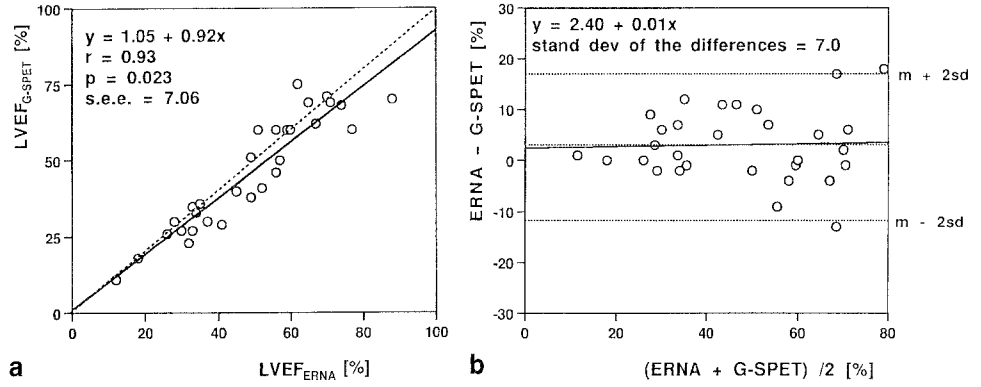

Fig. 5. a Comparison of LVEF determined from gated SPET myocardial perfusion images and from ERNA in 30 patients with known or suspected CAD. **b** Bland-Altman plot

range of ejection fractions. The standard deviation of the differences between LVEF determined from gated SPET perfusion images and from ERNA was 3.1% (Fig. 5b). Interestingly, these differences were similar for all degrees of perfusion defect severity (Fig. 6).

Effect of centering

The linear regression coefficient between measurements performed by two independent observers using the same preprocessed, masked and thresholded data sets was 0.97 ($LVEF_{OBS\ 1}$=3.83+0.90 $LVEF_{OBS\ 2}$). The standard deviation of the differences was 4.9%.

Effect of thresholding

The average count density measured at the basis of the left ventricle to determine the percent threshold averaged 9.37%±3.65% (range 4%–20%) of the maximal myocardial activity in the gated study. The influence of thresholding on the LVEF measurement was evaluated in ten representative patients using LVEF measured with ERNA as a reference. The largest differences between the two methods were observed when no threshold was applied on the gated SPET studies. On the other hand, increasing levels of threshold from 5% up to 40% had only a modest influence on the LVEF values (Fig. 7). The minimal differences between the two methods were observed for a 20% threshold. The correlation between

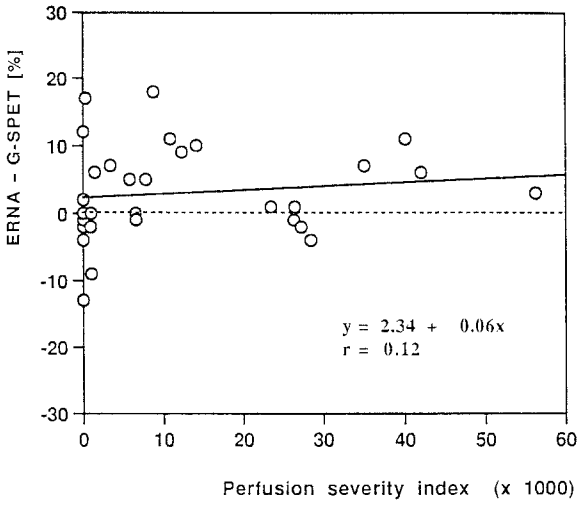

Fig. 6. Difference between $LVEF_{ERNA}$ and $LVEF_{G\text{-}SPET}$, as a function of the severity of perfusion defects

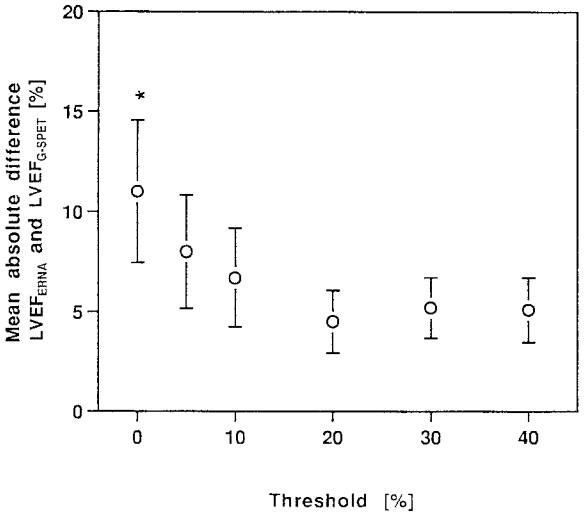

Fig. 7. Mean absolute difference between $LVEF_{ERNA}$ and $LVEF_{G\text{-}SPET}$ (±SEM) as a function of increasing levels of threshold. Data were obtained in a group of ten patients

$LVEF_{G\text{-}SPET}$ and $LVEF_{ERNA}$, however, was not influenced when the threshold was fixed at 20% for all patients.

Discussion

LVEF computed on gated SPET perfusion studies using simple statistical parameters correlates closely with LVEF obtained with ERNA. This correlation remains excellent over a wide range of LVEF values, even for patients with myocardial infarction associated with extensive and severe perfusion defects. The method runs with minimal operator intervention, and guarantees a very high intra- and interobserver reproducibility.

Several attempts have been made to derive LVEF from gated SPET perfusion studies. DePuey et al. [1] developed a method whereby LVEF was derived from end-diastolic and end-systolic endocardial borders that were outlined manually on gated mid-ventricular vertical long-axis and horizontal long-axis slices. Volumes were estimated using an elliptical version of the Simpson's rules. Although the method predicted with reasonable accuracy LVEF calculated from ERNA, intra- and inter-observer reproducibility was suboptimal (r=0.75). The major source of imprecision was the drawing of endocardial borders in patients with infarcts and associated extensive, severe perfusion defects. A modification of the method was proposed in which the endocardial border was determined semi-automatically after digital matrix inversion to improve edge detection [2]. The method correlated well with bi-plane contrast ventriculography (r=0.93) and with first-pass radionuclide angiocardiography (r=0.87). However, in patients with severe perfusion defects, the edge detection algorithm utilized a manually drawn region of interest as the outer border of the segment. For practical processing considerations these methods utilized only a bi-planar portion of the full three-dimensional tomographic data set. As a consequence, dysfunctional areas occurring in segments located predominantly out of the horizontal and vertical plane might be undersampled. Nuyts et al. [9] proposed a three-dimensional model for quantitative analysis of myocardial perfusion SPET. Although the model could be used to calculate cavity volume it has not yet been applied to gated studies. Faber et al. [5] described a three-dimensional surface detector algorithm that identified sets of endocardial and/or epicardial points from gated SPET radionuclide ventriculography and from sestamibi images. The method has not yet been validated clinically and it is not known how the algorithm behaves in patients with severe perfusion defects. Germano et al. [3] also described a technique for three-dimensional edge detection of gated perfusion images using an asymmetrical gaussian fit of the myocardial count distribution profile. Preliminary results indicated a high correlation (r=0.91) with first-pass determined LVEF over a wide range of LVEF values.

The method used in this study differs from previously described methods in several respects. First, in contradistinction to other methods, sampling is truly three-dimensional. Sampling is radial not only within planes but also between planes. Since wall motion is not restricted to motion within the planes, and more 10 towards the apex, comparison of regions at different times of the cardiac cycle becomes uncertain when using algorithms which are radial in planes but Cartesian between planes. Second, the position of the myocardial wall is defined by statistical analysis of the distribution of count rate densities,and not by edge detection. The average position of the wall is given by the first moment of the count rate distribution along radii originating in the centre of the cavity. The algorithm operates well, even at extremely low count rates, provided that only left ventricular myocardial structures have significant non-zero count rate density values. This was achieved by masking out the right ventricular free wall and the non-cardiac structures,

and by thresholding. Threshold level was determined by measuring the average count density in a small region of interest located at the base of the left ventricular cavity. Threshold varied from 4% to 20% of the maximal myocardial activity in the gated SPET study. Applying higher threshold levels (up to 40% of the maximal activity) had only a modest influence on LVEF measurements. Accordingly, a fixed threshold could be used for all patients provided that even underperfused myocardial segments maintain non-zero values. Using a fixed 20% threshold for all patients had no significant influence on the correlation between $LVEF_{ERNA}$ and $LVEF_{G\text{-}SPET}$ using variable thresholds.

LVEFs measured with gated SPET myocardial perfusion studies correlated closely with ERNA-determined LVEFs. A small but systematic difference was observed: LVEFs measured with gated SPET perfusion were, on average, 3.1% lower (mean absolute difference) than the LVEFs measured with ERNA. This difference was not related to the ejection fraction value or to the presence or the severity of myocardial perfusion defects. The difference may have been due to several factors. First, we used eight-interval gating SPET while ERNA was acquired with 16 intervals. The reduction in the number of time intervals is equivalent to a smoothing of the time-activity curve. Germano et al. [3] found that compacting 16-interval gated SPET data into eight intervals led to lower ejection fractions: the reduction averaged 3.7% (absolute difference) and was essentially constant over a wide range of ejection fractions. The use of 12- or 16-interval gated SPET perfusion data would have taken a much longer time since the counts generated by the injected dose must be distributed over a larger number of image sets. This may influence the statistical quality of the images in a negative way. Secondly, the first moment of the count rate distribution identifies the mid point of the myocardial thickness and not the endocardial border. This might tend to cause a slight overestimation of the left ventricular volumes compared to ERNA and hence a slight underestimation of the LVEF values. Other factors included the planar nature of ERNA, background correction and delineation of regions of interest.

Conclusion

We have validated a method to calculate global LVEF from gated SPET myocardial perfusion studies. The algorithm operates in the three-dimenstional space, requires minimal operator interventions and produces results in good agreement with ERNA over a wide range of ejection fraction values. Because of its high intra- and interobserver reproducibility, even in patients with severe perfusion defects, the method could be used in following patients after myocardial infarction, providing diagnostic and prognostic information complementary to myocardial perfusion studies.

References

1. DePuey EG, Nichols K, Dobrinsky C. Left ventricular ejection fraction assessed from gated technetium-99m-sestamibi SPECT. *J Nucl Med* 1993; 34: 1871–1876.
2. Williams KA, Taillom LA. Left ventricular function in patients with coronary artery disease assessed by gated tomographic myocardial perfusion images. Comparison with assessment by contrast ventriculography and first-pass radionuclide angiography. *J Am Coll Cardiol* 1996; 27: 173–181.
3. Germano G, Kiat H, Kavanagh PB, et al. Automatic quantification of ejection fraction from gated myocardial perfusion SPECT. *J Nucl Med* 1995; 36: 2138–2147.
4. Kouris K, Abdel-Dayem HM, Taha B, et al. Left ventricular ejection fraction and volumes calculated from dual gated SPECT myocardial imaging with ^{99m}Tc-MIBI. *Nucl Med Commun* 1992; 13: 648–655.
5. Faber TL, Akers MS, Peshock RM, Corbett JR. Three-dimensional motion and perfusion quantification in gated single-photon emission computed tomograms. *J Nucl Med* 1991; 32: 2311–2317.
6. Goris ML, Thompson C, Malone LJ, Franken PR. Modelling the integration of myocardial regional perfusion and function. *Nucl Med Commun* 1994; 15: 9–20.
7. Diamond GA, Forrester JS. Analysis of probability as an aid in the clinical diagnosis of coronary artery disease. *N Engl J Med* 1979; 300: 1350–1358.
8. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet* 1986; I: 307–310.
9. Nuyts J, Mortelmans L, Suetens P, Oosterlinck A, De Roo M. Model-based quantification of myocardial perfusion images from SPECT. *J Nucl Med* 1989; 30: 1992–2001.