Gated blood pool tomography for the evaluation of global and regional left ventricular function in comparison to planar techniques and echocardiography

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Blood pool imaging; Echocardiography; Single photon emission computed tomography.

Background. **Multigated radionuclide ventriculography (MUGA) is a simple and reliable tool for the assessment of global systolic and diastolic function and in several studies it is still considered a standard for the assessment of left ventricular ejection fraction. However the evaluation of regional wall motion by MUGA is critical due to two-dimensional imaging and its clinical use is progressively declining in favor of echocardiography. Tomographic MUGA (T-MUGA) is not widely adopted in clinical practice. The aim of this study was to compare T-MUGA to planar MUGA (P-MUGA) for the assessment of global ejection fraction and to transthoracic echocardiography for the evaluation of regional wall motion.**

Methods. **A 16-segment model was adopted for the comparison with echo regional wall motion. For each one of the 16 segments the normal range of T-MUGA ejection fraction was quantified and a normal data file was defined; the average value -2.5 SD was used as the lower threshold to identify abnormal segments. In addition, amplitude images from Fourier analysis were quantified and considered abnormal according to three different thresholds (25, 50 and 75% of the maximum).**

Results. **In a study group of 33 consecutive patients the ejection fraction values of T-MUGA highly correlated with those of P-MUGA (r = 0.93). The regional ejection fraction (according to the normal database) and the amplitude analysis (50% threshold) allowed for the correct identification of 203/226 and 167/226 asynergic segments by echocardiography, and of 269/302 and 244/302 normal segments, respectively. Therefore sensitivity, specificity and overall accuracy to detect regional wall motion abnormalities were 90, 89, 89% and 74, 81, 79% for regional ejection fraction and amplitude analysis, respectively.**

Conclusions. **T-MUGA is a reliable tool for regional wall motion evaluation, well correlated with echocardiography, less subjective and able to provide quantitative data.**

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Introduction

Many non-invasive techniques have been developed for the evaluation of cardiac performance: among these, echocardiography, magnetic resonance ventriculography and multigated radionuclide ventriculography (MUGA) play an important clinical role. Concerning the radionuclide evaluation of biventricular function, MUGA is a simple and reliable tool for the assessment of global systolic and diastolic function and in several studies it is still considered a standard for the assessment of left ventricular ejection fraction (EF). However the evaluation of regional wall motion is suboptimal and, although acquired in multiple projections, the overlapping of different structures limits a reliable evaluation of several left ventricular segments, proximal septum especially and inferior and lateral wall basal portions. Tomographic techniques allow better evaluation of regional distribution of radiotracers. For this reason perfusional single photon emission computed tomography has almost completely replaced traditional planar scintigraphy in clinical practice and for the same reason the clinical use of MUGA is progressively declining in favor of echocardiography, which is now the technique most widely employed for the non-invasive assessment of cardiac performance. Several reports have emphasized the feasibility of tomographic MUGA (T-MUGA) for the de-

tection of left ventricular dysfunction[1-7]. The aim of our study was to evaluate the capability of T-MUGA of identifying left ventricular asynergies detected by two-dimensional echocardiography as well as of reproducing global EF measures as calculated by planar MUGA (P-MUGA). In order to achieve these results we developed a semiautomatic acquisition and processing method for the evaluation of global left ventricular function and regional wall motion. We defined the normal range of regional EF; furthermore a comparison between the ability of regional EF and amplitude images from Fourier analysis to detect regional asynergies was carried out.

Methods

Patient population. We evaluated two groups of subjects with good echocardiographic windows: Group 1 comprised 14 subjects (10 males, 4 females, mean age 46 ± 6 years), with normal two-dimensional echo study for both global and regional wall motion and normal EF by P-MUGA, low pre-test likelihood of coronary artery disease, no valvular regurgitation and no signs of idiopathic cardiomyopathy, who were identified as a control group to define normal ranges of regional EF by T-MUGA. Group 2 consisted of 33 patients (25 males, 8 females, mean age 47 ± 6 years) who had undergone an echo examination for functional assessment of previous myocardial infarction (12 patients) or congestive heart failure (8 patients); the remaining patients were evaluated on the basis of a non-specific request from their referring physicians. All patients were enrolled consecutively; patients with poor quality echo window were not evaluated in this study.

All subjects were clinically stable and were imaged by P-MUGA and T-MUGA performed in the same sequence. Echocardiography was performed within 1 week from the radionuclide studies under the same therapeutic regimen. All studies were performed for clinical purposes and an informed written consent was obtained from all patients.

Planar MUGA acquisition and processing. Patients received an i.v. injection of unlabeled pyrophosphate and 20 min later were injected with 1100 MBq of 99mTc-pertechnetate.

P-MUGA was acquired in the best septal view. Acquisition was performed with a LFOV gamma-camera, using a high-resolution collimator (FWHM 7 mm). A 20% window centered on 140 Kev technetium photopeak and a 64 × 64 matrix with a zoom factor of 2 were used. Thirty-two ECG gated frames per cardiac cycle were acquired, using a phase mode acquisition. Beats exceeding 10% duration of the average cycle and the post-extrasystolic beats were rejected.

The acquisition was continued until 255 counts per pixel in one of the 32 frames of the cardiac area were achieved. The left ventricular EF was calculated on the best septal view by automated commercial software able to identify the left ventricular boundaries on the 32 frames and to plot the volume curve using a variable region of interest. The background activity was measured at end-systole using a semilunar area proximal to the cardiac apex. Left ventricular edges were inspected for accuracy by experienced observers and, if necessary, they were manually corrected.

Tomographic MUGA acquisition and processing. The same gamma-camera and collimator used for P-MUGA were employed for T-MUGA acquisition.

A 64 × 64 matrix, zoom 1.3 (pixel size 5 mm), and 60 steps of 25 s each over a 180° semielliptical orbit (RAO-LPO) were adopted. For each step 16 gated images were collected independent of the cycle length (phase mode acquisition) to avoid variation in count statistics in end-diastolic frames, due to sinus arrhythmia. A beat rejection program (> 10% R-R window) with normalization for rejected cycles was adopted; patients with more than 20% rejected beats were not included in this study.

One pixel thick transaxial sections were reconstructed, after correction for flood inhomogeneity and for center of rotation distortion, by filtered back projection (8 mm Wiener filter). From transaxial slices a gated mid-ventricular section oriented along the vertical long axis was reconstructed. A phase image of the vertical long axis derived from Fourier first transform analysis was then utilized to identify the valvular plane and subsequently three short-axis slices from the valvular plane to the apex and a mid-ventricular horizontal long-axis slice were identified by the operator and reconstructed. From this point the procedure was totally automatic including the following steps:

• the three short-axis slices were added together to obtain a gated single slice as thick as the entire left ventricle. This set of images was subsequently processed in an identical fashion as the P-MUGA using the same program to obtain the left ventricular volume curve (Fig. 1). As the tomographic reconstruction of the left ventricle should not contain the background of overlying structures, no background subtraction was applied;

• a second volume curve in which a background subtraction similar to that of P-MUGA was also obtained and compared to P-MUGA values;

• a second set of ventricular thick slices was obtained, but before adding the three slices a normalization process was performed in order to obtain the same maximum count pixel in each one of the three gated sequences. This procedure was theoretically justified according to the following consideration: the content of the left ventricle being homogeneous (radioactive blood) the maximum count density in slices with the same thickness should be the same unless the contribution of attenuation. Therefore normalization should compensate for the attenuation due to structures overlying the left ventricle.

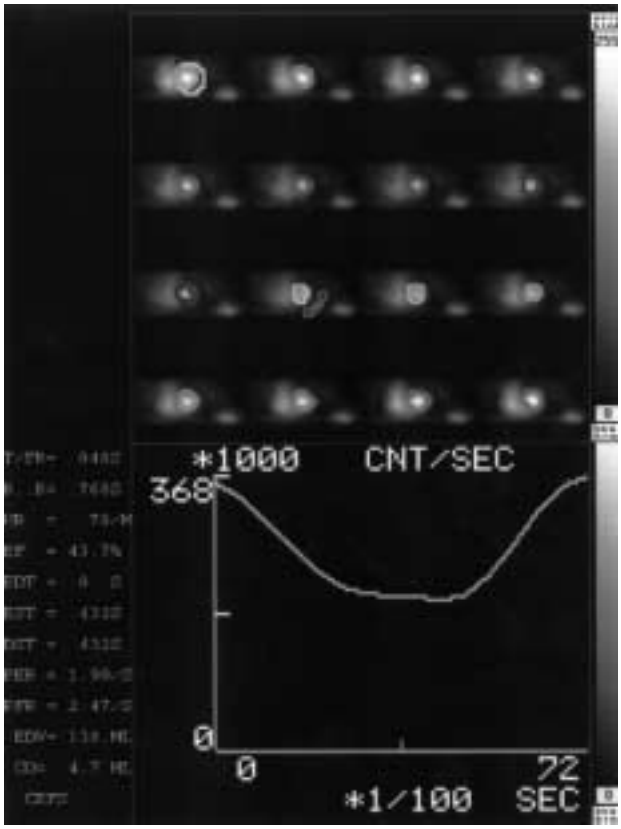


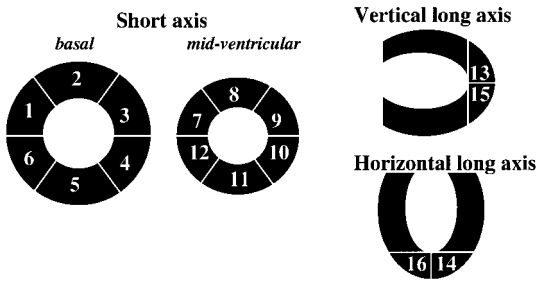
Figure 1. *A report of the automatic analysis for the assessment of global left ventricular function by tomographic MUGA. The short-axis slices are summed to obtain single slices corresponding to the thickness of the left ventricle. A standard procedure is then applied to calculate global ejection fraction, volumes, ejection and filling rates. CO = cardiac output; DST = diastolic time; EDV = end-diastolic volume; EDT = end-diastolic time; EST = end-systolic time; EF = ejection fraction; HR = heart rate; PER = peak ejection rate; PFR = peak filling rate.*

Therefore, four volume curves were obtained and compared to that of P-MUGA: a non-normalized left ventricular volume curve with no background subtraction (T1-MUGA); a normalized left ventricular volume curve with no background subtraction (T2-MUGA); a non-normalized left ventricular volume curve with background subtraction (T3-MUGA), and a normalized left ventricular volume curve with background subtraction (T4-MUGA).

Regional wall motion analysis by tomographic MUGA. A 16-segment model was used to evaluate regional wall motion (Fig. 2). The long-axis slices were used to evaluate apical wall motion (anterior segment 13, inferior segment 15, septal segment 14, and lateral segment 16); basal and mid-ventricular slices were used to evaluate anterior, high septal, low septal, inferior low lateral, and high lateral wall motion (segments 1-12).

For each one of the 16 segments the regional left ventricular volume curve was obtained and filtered by Chebyshew 12 order fitting. No background subtraction was performed. The regional EF was then calculated and compared to the normal database (average -2.5 SD) obtained in the control group (Fig. 2). Figure 3 shows a report of regional EF analysis.

From the same tomographic slices we obtained an amplitude image by Fourier first transform analysis; the amplitude of contraction was quantified using four



Segm.	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
EF (%)	48	64	77	72	61	50	53	60	71	73	67	63	69	72	74	81
Sd (%)	7	8	9	8	8	7	7	8	8	9	8	8	8	8	9	9

Figure 2. *Sixteen-segment left ventricular model adopted for regional wall motion analysis. Normal values and standard deviation of regional ejection fraction (EF) for each one of the 16 segments are reported in the table.*

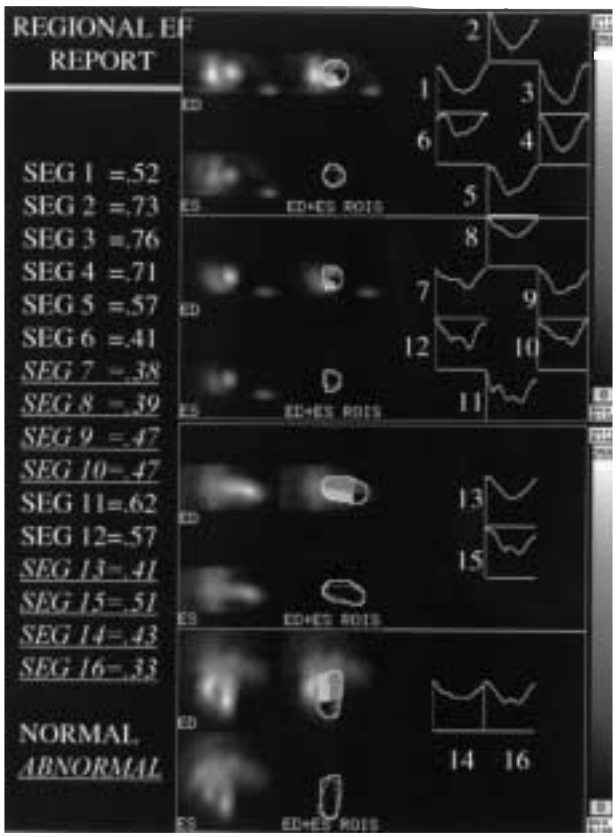


Figure 3. *Regional wall motion analysis obtained by evaluation of regional ejection fraction (EF).* Top: *basal and mid-ventricular slices.* Bottom: *evaluation of apical regional wall motion.* On the left: *regional EF values on segmental basis.* In italics *and* underlined *the segments with regional EF below the normal range.*

different threshold values (< 50, ≥ 50, < 75, and ≥ 75% of the maximum); sensitivity and specificity were tested according to the different grade of abnormality.

Comparison with echo regional wall motion. The analysis of regional wall motion by two-dimensional echocardiography had been described in a previous paper by our group[19]. Briefly, a 16-segment model was adopted and for each segment regional wall motion was graded according to a 5 grade score (0 = normal, 1 = mild hypokinesia, 2 = severe hypokinesia, 3 = akinesia, 4 = dyskinesia). Grade scores 0-1 were considered normal and > 1 abnormal.

Abnormal regional EF values obtained in the patient group (< 2.5 SD) were compared to echo regional wall motion to determine test sensitivity, and normal values to evaluate test specificity. Test sensitivity and specificity to detect regional wall motion abnormalities were also evaluated for each one of the three grades (< 50, ≥ 50, < 75, ≥ 75% of the maximum) of the regional amplitude abnormalities from Fourier analysis.

Test reproducibility. In order to verify the reproducibility of EF measurements a second tomographic acquisition was repeated in 15 subjects. After 10-15 min relaxing time the patient was repositioned under the gamma-camera and T-MUGA acquisition restarted. Both global and regional function were compared in the two studies. Processing was performed by a second observer. Being processing almost completely automatic no intraobserver reproducibility was tested.

Statistical analysis. Simple linear regression analysis was used to compare global EF between P-MUGA and T-MUGA. Variability about the regression line was expressed as standard error. Group values for samples were expressed as mean + SD. Comparison of paired EF values between P-MUGA and T-MUGA was made by paired Student's t-test. Differences were considered statistically significant when p value was < 0.05.

Results

Comparison between planar and tomographic ejection fraction. The following correlations were found for global EF evaluation:

• P-MUGA vs T1-MUGA: r = 0.94, r^2 = 0.88, SE 7.2, slope 0.95, intercept 1.15 (Fig. 4);
• P-MUGA vs T2-MUGA: r = 0.93, r^2 = 0.87, SE 7.6, slope 0.97, intercept -0.6 (Fig. 5);
• P-MUGA vs T3-MUGA: r = 0.96, r^2 = 0.92, SE 6.1, slope 1.05, intercept 1.14 (Fig. 6);
• P-MUGA vs T4-MUGA: r = 0.95, r^2 = 0.92, SE 6.3, slope 1.06, intercept 0.95 (Fig. 7).

The mean left ventricular EF for the different groups were: P-MUGA 42 ± 20%, T1-MUGA 43 ± 20%, T2-MUGA 41 ± 21%, T3-MUGA 47 ± 22%, and T4-MUGA 47 ± 22%. No significant differences were observed between P-MUGA EF and T1, T2-MUGA EF at paired Student's t-test (p = NS). Conversely, significant differences were found between P-MUGA EF and T3-MUGA EF (p < 0.003) and between P-MUGA EF and T4-MUGA EF (p < 0.003).

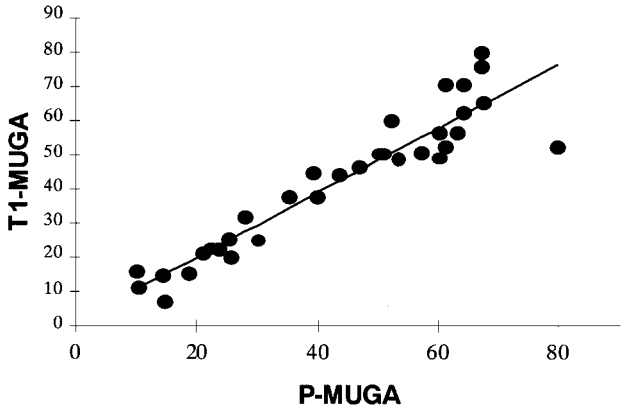


Figure 4. *Linear regression between T1-multigated radionuclide angiography (T1-MUGA) and planar MUGA (P-MUGA) ejection fraction values.*

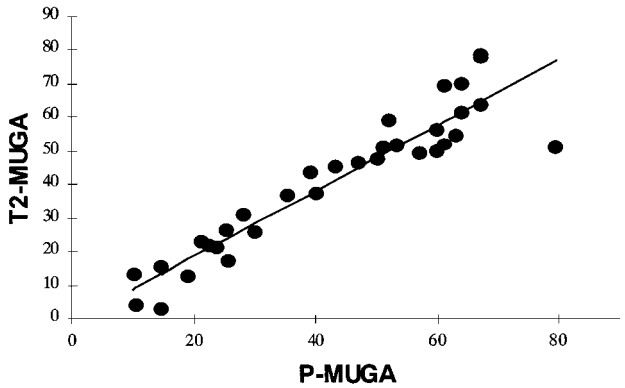


Figure 5. *Linear regression between T2-MUGA and P-MUGA ejection fraction values. Abbreviations as in figure 4.*

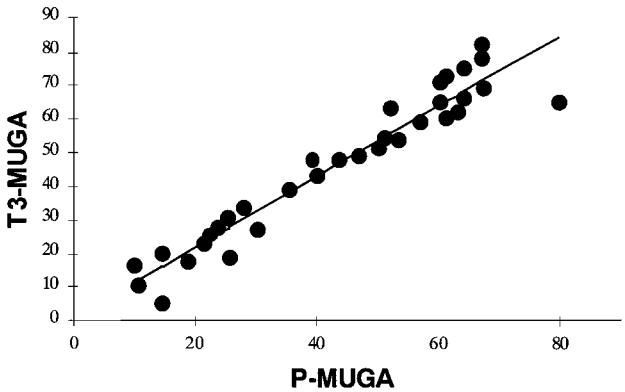


Figure 6. *Linear regression between T3-MUGA and P-MUGA ejection fraction values. Abbreviations as in figure 4.*

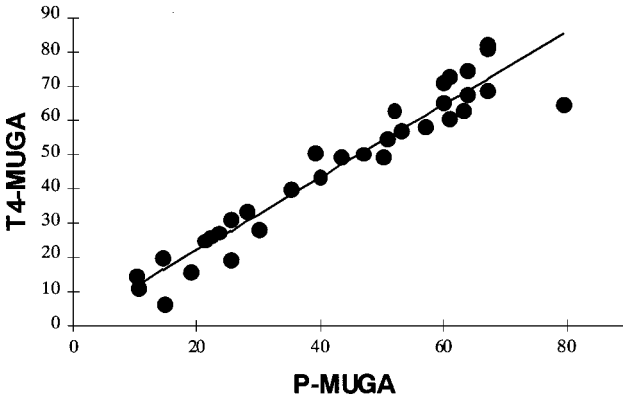


Figure 7. *Linear regression between T4-MUGA and P-MUGA ejection fraction values. Abbreviations as in figure 4.*

T-MUGA (2nd)		T-MUGA (1st) Normal	T-MUGA (1st) Abnormal
	Normal	118	18
	Abnormal	14	90

A

T-MUGA (2nd)		T-MUGA (1st) Normal	T-MUGA (1st) Abnormal
	Normal	134	8
	Abnormal	9	89

B

Figure 8. *Reproducibility of regional wall motion evaluation by regional ejection fraction* (A) *and amplitude analysis* (B) *in two consecutive acquisitions.*

Comparison between echo and tomographic MUGA regional wall motion. In Group 2 patients, echo regional wall motion analysis revealed a normal contraction pattern in 302 (57%) segments and abnormalities in 226 (43%), respectively.

Regional ejection fraction. The normal ranges of regional EF in each one of the 16 segments are reported in figure 2. Lower values were observed in basal regions in comparison to distal regions as well as in septal segments in comparison to lateral ones. Two hundred sixty-nine segments out of 302 with a 0-1 echo score had regional T-MUGA EF values within the normal range and were correctly classified as normal; conversely, 203 out of 226 segments with an abnormal echo score had a regional EF below the normal range. Therefore sensitivity, specificity, positive and negative predictive values and overall accuracy of T-MUGA regional EF to detect regional wall motion abnormalities were, respectively, 90, 89, 86, 92 and 89%. A T-MUGA report for evaluation of regional EF is shown in figure 3.

Amplitude images. The ability of amplitude images to detect regional asynergies according to the predefined abnormality thresholds (< 50, ≥ 50, < 75, and ≥ 75% of the maximum) was the following: sensitivity 98, 74 and 40%, respectively, and specificity 51, 81 and 96%, respectively. Therefore the best compromise between sensitivity and specificity was found with a ≥ 50 and < 75% threshold (74% sensitivity, 81% specificity, 75% positive predictive value, 81% negative predictive value, and 79% overall accuracy).

Test reproducibility. The correlation between two EF measurements obtained in two acquisition sessions was the following: T-MUGA (first) vs T-MUGA (second) $r = 0.986$, $r^2 = 0.94$, SE 3.1, slope 1.01, intercept 0.11.

The concordance between regional wall motion analysis by regional EF measurements and amplitude analysis are reported in figure 8. A global agreement of 87 and 93% was observed between the measures by regional EF and amplitude analysis, respectively.

Discussion

T-MUGA is a real three-dimensional, count-based tool for evaluating left ventricular performance; thus, for this reason, it seems to be a promising technological procedure for the evaluation of both global and regional function.

T-MUGA was first introduced by Corbett et al.[1], Moore et al.[2], Tamaki et al.[3], and Maublant et al.[4] in the early '80s and it has been validated in few successive studies[5-7]. Its routine clinical usage has not reached a wide application, perhaps for two main reasons: 1) time consuming acquisition and processing procedures, only recently overcome with multiple detector gamma-cameras, powerful computers and dedicated processing software[8], and 2) improvement in technology of echocardiography, widely available in every cardiology department. The easy feasibility and the high spatial resolution of echocardiography makes it the first choice method for the evaluation of regional wall motion. Nevertheless accuracy and reproducibility of echo determination of global left ventricular EF appear to be suboptimal and for this reason planar gated blood pool ventriculography continues to maintain a limited but specific role when accurate and precise measurements of left ventricular EF are required: 1) evaluation of the effects of different therapeutic regimens on left ventricular performance[9,10], and 2) monitoring of EF in patients on antiblastic treatment for cancer[11-16].

Global ejection fraction evaluation. Our study demonstrates that global left ventricular EF measured by T-MUGA compares favorably with that measured by P-MUGA.

Among the different calculation algorithms proposed in our study we observed that the normalization process, adopted to reduce the effect of left ventricular self-attenuation, minimally affects EF values. This result may be explained by the nature of tomographic acquisition itself in which projections oriented in both a perpendicular and a parallel position to the left ventricular long axis contribute to generate the count content of the left ventricle and, therefore, the attenuation of each left ventricular voxel is the average value of attenuation factors obtained over the semicircular orbit and not, as in planar imaging, in a single direction in the left anterior oblique view. Moreover, it is worth noting that looking at the linear regression between planar and tomographic EF, 10 out of 15 patients with a left ventricular EF < 40% by P-MUGA show higher values by T-MUGA, whereas only 8 out of 18 patients with an EF > 40% have T-MUGA EF values higher than those of P-MUGA. This observation seems to confirm the hypothesis that T-MUGA acquisition partially compensates for the attenuation in count loss which predominantly affects poorly contracting and dilated ventricles[16].

If background subtraction procedures similar to that applied to planar imaging are adopted, a significant increase in T-MUGA EF average values is determined in comparison to P-MUGA (50 vs 46%, $p < 0.003$). Conversely a better correlation and lower standard error on linear regression analysis are observed. Taking into account that a systematic underestimation of EF has been documented in several studies comparing P-MUGA to other modalities including first-pass radionuclide ventriculography, contrast ventriculography and magnetic resonance ventriculography[17], we might conclude that the background subtraction procedure may help to approximate the real EF values. We have not evaluated ventricular volumes as the aim of this paper was to compare EF and regional wall motion between P-MUGA and echocardiography, respectively, and both these two techniques cannot be considered reliable tools for volume calculation. However it is our impression that T-MUGA gives reliable volume values which fit well the cardiovascular state of the patient; our impression has also been supported by a recent paper by Chin et al.[18], who observed a strict correlation of right and left ventricular volumes obtained by T-MUGA and magnetic resonance.

Regional wall motion evaluation. To our knowledge this is the first paper comparing regional wall motion analysis of T-MUGA to echocardiography in a consecutive cohort of patients. We evaluated two methods in order to analyze and quantify regional wall motion: analysis of regional EF and of contraction amplitude with Fourier first transform analysis. The first method, previously described by Cerqueira et al.[7] offers the advantage of a real quantification of regional left ventricular function. Left ventricular abnormalities were detected in comparison to a normal database and seemed to highly correlate with left ventricular asynergies detected by echocardiography. Differently from Cerqueira et al.[7] we did not use a left ventricular realignment according to a floating axis system, which would have corrected for left ventricular movements and torsion during systole. This choice was determined for two main reasons: a) this procedure cannot be easily automated, and b) this kind of correction is not usually performed in echo studies which were used as a reference standard for regional wall motion evaluation. Both sensitivity and specificity of T-MUGA EF were found to be very high in comparison to echocardiography[19]. The semiquantitative analysis of amplitude images was less satisfactory in terms of sensitivity; this is not surprising because the amplitude image is a relative evaluation in comparison to the best contracting segment and in the presence of diffuse left ventricular dysfunction an underestimation of left ventricular asynergies may occur.

The reproducibility of T-MUGA seems to be very high, due to automatic processing. We checked the reproducibility of our results performing two different acquisitions and processing procedures, without reinjecting the patient for obvious ethical reasons. In our hands T-MUGA seems to be a very reproducible tool in both global and regional evaluation of left ventricular contraction. In this particular evaluation amplitude image appears to be slightly more reproducible than regional EF.

Study limitations. Limitations to this study must be acknowledged. First, this study has validated T-MUGA at rest, without considering the possibility of stress imaging. The global acquisition time that is required to obtain high quality studies is too long for exercise or pharmacological stress imaging. The reliability of a short acquisition time (3-5 min) which may be adopted for pharmacological stress imaging was not tested in this study. Second, although T-MUGA is more accurate than P-MUGA in evaluating regional wall motion, it does not permit a reliable evaluation of valvular function.

Conclusion. T-MUGA is at least as reliable as P-MUGA for left ventricular EF determination and at least as accurate as echocardiography for regional wall motion abnormality detection. It can reliably replace P-MUGA for rest studies. Its high reproducibility might make it the method of choice for the evaluation of left ventricular remodeling, the effect of treatment, and characterization and follow-up of cardiac failure.

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