^{201}Tl and ^{99m}Tc-MIBI Gated SPECT in Patients with Large Perfusion Defects and Left Ventricular Dysfunction: Comparison with Equilibrium Radionuclide Angiography

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Left ventricular ejection fraction (LVEF) is a major prognostic factor in coronary artery disease and may be computed by ^{99m}Tc-methoxyisobutyl isonitrile (MIBI) gated SPECT. However, ^{201}Tl remains widely used for assessing myocardial perfusion and viability. Therefore, we evaluated the feasibility and accuracy of both ^{99m}Tc-MIBI and ^{201}Tl gated SPECT in assessing LVEF in patients with myocardial infarction, large perfusion defects and left ventricular (LV) dysfunction. **Methods:** Fifty consecutive patients (43 men, 7 women; mean age 61 ± 17 y) with a history of myocardial infarction (anterior, 26; inferior, 18; lateral, 6) were studied. All patients underwent equilibrium radionuclide angiography (ERNA) and rest myocardial gated SPECT, either 1 h after the injection of 1110 MBq ^{99m}Tc-MIBI (n = 19, group 1) or 4 h after the injection of 185–203 MBq ^{201}Tl (n = 31, group 2) using a 90° dual-head camera. After filtered backprojection (Butterworth filter: order 5, cutoff 0.25 ^{99m}Tc or 0.20 ^{201}Tl), LVEF was calculated from reconstructed gated SPECT with a previously validated semiautomatic commercially available software quantitative gated SPECT (QGS). Perfusion defects were expressed as a percentage of the whole myocardium planimetered by bull's-eye polar map of composite nongated SPECT. **Results:** Gated SPECT image quality was considered suitable for LVEF measurement in all patients. Mean perfusion defects were 36% ± 18% (group 1), 33% ± 17% (group 2), 34% ± 17% (group 1 + group 2). LVEF was underestimated using gated SPECT compared with ERNA (34% ± 12% and 39% ± 12%, respectively; $P = 0.0001$). Correlations were high (group 1, $r = 0.88$; group 2, $r = 0.76$; group 1 + group 2, $r = 0.82$), and Bland-Altman plots showed a fair agreement between gated SPECT and ERNA. The difference between the two methods did not vary as LVEF, perfusion defect size or severity increased or when the mitral valve plane was involved in the defect. **Conclusion:** LVEF measurement is feasible using myocardial gated SPECT with the QGS method in patients with large perfusion defects and LV dysfunction. However, both ^{201}Tl and ^{99m}Tc-MIBI gated SPECT similarly and significantly underestimated LVEF in patients with LV dysfunction and large perfusion defects.

Key Words: gated SPECT; ejection fraction; thallium; methoxyisobutyl isonitrile

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Left ventricular ejection fraction (LVEF) and infarct size are major prognostic factors in patients with myocardial infarction (*1,2*). LVEF determination using equilibrium radionuclide angiography (ERNA) is highly reproducible and widely used in patients with heart failure. Low LVEF is associated with a poor long-term outcome (*1,3–5*). After myocardial infarction, ^{201}Tl allows the evaluation of hibernating myocardium and quantification of residual myocardial ischemia (*6–8*). Although ^{99m}Tc-labeled tracers such as methoxyisobutyl isonitrile (MIBI) have been reported as less accurate for myocardial viability assessment, they offer several advantages over ^{201}Tl. MIBI's short half-life allows greater amounts of radioactivity to be injected, and better image quality can be obtained because gamma cameras are optimized for the photopeak of ^{99m}Tc (*9,10*). Furthermore, LVEF may be measured using gated SPECT by finding left ventricular (LV) endocardial edges on SPECT slices along the whole LV volume. Therefore, ^{99m}Tc-MIBI is potentially useful in evaluating both myocardial perfusion and function using electrographically gated SPECT (*11–15*). However, the accuracy of LVEF determination in the setting of perfusion scan may be impaired in patients with large myocardial infarction, in which LVEF is a major prognostic factor.

The new generation of multidetector gamma cameras allows the increase of count statistics without prolonging the total acquisition time by using two heads instead of one over the 180° acquisition orbit. Therefore, it is theoretically possible to perform gated SPECT with ^{201}Tl without excessive acquisition duration (*16,17*), thus allowing the simultaneous evaluation of viability and LVEF in patients with myocardial infarction.

The aim of this study was to evaluate the feasibility and accuracy of LVEF measurement with ^{201}T1 or ^{99m}Tc-MIBI gated SPECT compared with ERNA in a particular subset of high-risk patients presenting with large perfusion defects and low ejection fraction.

MATERIALS AND METHODS

Subjects

Fifty consecutive patients (43 men, 7 women; mean age 61 ± 17 y) were prospectively studied between January 1997 and December

1997 in two Departments of Nuclear Medicine (Rouen University Hospital, Rouen, France, and Bichat University Hospital, Paris, France). Patients were included according to the following criteria: sinus rhythm, history of Q-wave myocardial infarction (anterior, 26; inferior, 18; lateral, 6), documented LV dysfunction and planimetered perfusion defect size over 20% of the whole myocardium evaluated on bull's-eye polar map of previous rest perfusion scan. Patients were referred for evaluation of both LV function and myocardial viability according to the clinical practice of our institutions. The exclusion criteria were acute myocardial infarction or unstable angina in the last 3 wk, to avoid the phenomenon of myocardial stunning, and atrial fibrillation or atrial flutter. History of myocardial revascularization or nonsustained ventricular arrhythmias were not considered to be exclusion criteria.

Nineteen patients underwent rest ^{99m}Tc-MIBI gated SPECT (group 1) and 31 patients underwent rest ^{201}Tl gated SPECT (group 2).

Myocardial Gated SPECT

Myocardial gated SPECT was performed either 1 h after a rest injection of 1110 MBq ^{99m}Tc-MIBI (group 1) or 4 h after a rest injection of 185–203 MBq ^{201}Tl chloride (group 2). Acquisitions were performed using a 90° dual-head camera (DST; SMVi, Buc, France) equipped with low-energy high-resolution parallel-hole collimators. Acquisition parameters were as follows: no acquisition zoom; 32 projections over a 180° orbit; 60 s per projection for ^{99m}Tc-MIBI or 120 s per projection for ^{201}Tl; and 64 × 64 matrix (word mode). Images were gated at 8 frames per cycle using an R-wave trigger with an acceptance window set at 100%. Energy discrimination was provided by a 20% window centered on 140 keV for ^{99m}Tc-MIBI and by two 20% windows centered on 70 keV and 167 keV for ^{201}Tl.

Gated SPECT images were reconstructed after low-pass prefiltering (Butterworth order, 5; cutoff frequencies, 0.25 cycle per pixel for ^{99m}Tc-MIBI and 0.20 cycle per pixel for ^{201}Tl) and ramp-filtered backprojection. No attenuation correction was performed. Perfusion images were obtained from gated SPECT by adding the reconstructed data in one composite image.

Quality Control

Count statistics in the total acquisition and in the myocardial area were calculated from gated SPECT using a standard software (NXT 2.0 0.1; SMVi). For myocardial count statistics, a 16 × 64 rectangular region of interest (ROI) was drawn. It was centered on the myocardial area on the first projection and was fixed on all the following projections (i.e., 256 projections for gated scans). Then, a curve representing the activity along each projection was generated, and myocardial counts were calculated as the area under this curve. While the myocardial ROI was being centered, attention was given to avoid the hepatic and splanchnic regions (*18,19*).

Quantification of Perfusion Defect

Bull's-eye polar maps were obtained from nongated SPECT. According to previous studies (*7,20*), the defect size was delineated by a 60% level isocontour and was quantified as a percentage of the whole LV surface planimetered on bull's-eye polar map.

The severity of perfusion defect was qualitatively analyzed by two experienced observers on reconstructed tomographic slices. Regional myocardial uptake was scored on a 13-segment division of the LV using a four-point grading system: 3 = normal uptake, 2 = equivocal, 1 = moderate and 0 = severe reduction of uptake. Discrepancies were resolved by consensus. Defect scores were calculated as the sum of each segment grade divided by the total number of segments (i.e., 13 in this model).

Gated SPECT Ejection Fraction Measurement

Gated SPECT reconstruction was automatic, but reorientation into three orthogonal views was manually performed in all cases.

LVEF was calculated from gated SPECT using previously validated and commercially available automated software (quantitative gated SPECT [QGS]; Cedars-Sinai Medical Center, Los Angeles, CA) (*11*) implemented on a Unix workstation (IBM RS6000, Vision 4.1 0.0; SMVi). This software uses gated reconstructed short-axis images to estimate endocardial and epicardial volumes for all intervals of the cardiac cycle. LVEF is then automatically derived from the end-diastolic and end-systolic volumes. The software allows manual correction of LV reconstruction limits in case of operator discrepancy, especially in regions with severe perfusion defects or when the mitral valve plane is involved in the defect. Automatic determination of LV volumes by QGS, including the selection of LV base and apex, was successful in all but 3 patients. In these 3 patients, there was an operator disagreement with the software determination of valve plane. This point was manually corrected.

Equilibrium Radionuclide Angiography

ERNA was performed in all patients; it was performed within the same week of ^{99m}Tc-MIBI gated SPECT in group 1 and was performed immediately after ^{201}Tl gated SPECT in group 2. Based on an in vivo red blood cell labeling technique or human serum albumin, 740–925 MBq ^{99m}Tc was intravenously injected. Studies were acquired in the left anterior oblique coronary artery 45° with a caudal tilt to optimize ventricular separation, with a large-field-of-view monodetector gamma camera equipped with an all-purpose parallel-hole collimator. A zoom factor of 2 was applied to acquire 64 × 64 matrices with 16 frames per cardiac cycle and 350 K counts per frame. A 30% energy window centered on 140 keV was used. Images from group 1 and group 2 were processed using previously validated software (ECCAP, F83; SMVi).

Statistical Analysis

Comparisons between ERNA and gated SPECT ejection fractions were performed with a Student paired t test. Comparisons between groups 1 and 2 were performed with an unpaired t test. Correlations between ERNA and gated SPECT ejection fractions were evaluated using simple linear regression. The effect of tracer (^{99m}Tc-MIBI or ^{201}Tl) on the latter correlation was tested using covariance analysis. Agreement between ERNA and gated SPECT ejection fractions was assessed by the Bland-Altman method (*21*). Data are expressed as mean value ± 1 SD, and a P value ≤ 0.05 was considered statistically significant.

RESULTS

Radionuclide Angiography and Perfusion Defect

Intraobserver and interobserver reproducibilities were optimal for ERNA LVEF. Correlations were 0.99 and 0.98, respectively, for ejection fraction measurement from the same acquisition. Mean ERNA LVEF was 38 ± 12 in the entire population, without a significant difference between group 1 and group 2 (38 ± 15 and 39 ± 11, respectively; not significant) (Table 1).

The interobserver and intraobserver agreements for perfusion assessment were high (κ = 0.87 and 0.82, respectively).

TABLE 1
Image Quality, Extent of Perfusion Defect, Perfusion Defect Scores, Equilibrium Radionuclide and Gated SPECT LVEF

	^{99m}Tc-MIBI (group 1)	^{201}Tl (group 2)	^{201}Tl + ^{99m}Tc-MIBI (groups 1 + 2)
ERNA LVEF (%)	38 ± 15	39 ± 11	38 ± 12
Perfusion defect (%)	36 ± 18	33 ± 17	34 ± 17
Perfusion defect scores	2.43 ± 0.47*	2.05 ± 0.48	2.10 ± 0.5
Total counts	17 ± 8.67†	10.91 ± 2.85	13.5 ± 6.7
Myocardial ROI	4.60 ± 1.87‡	2.81 ± 0.74	3.6 ± 1.6
Gated SPECT LVEF (%)	31 ± 13§	35 ± 11‖	34 ± 12#
ERNA − gated SPECT (%)	6.2 ± 7	3.7 ± 7.4	4.7 ± 7.3

*P = 0.01 vs. ^{201}Tl.
†P = 0.0002 and ‡P < 0.0001 vs. ^{201}Tl.
§P = 0.001, ‖P = 0.01 and #P = 0.0001 vs. ERNA LVEF.
LVEF = left ventricular ejection fraction; MIBI = methoxyisobutyl isonitrile; ERNA = equilibrium radionuclide angiography; ROI = region of interest.

As demonstrated on bull's-eye polar maps, mean perfusion defects were severe and comparable in both groups, as were perfusion defect scores (Table 1).

Gated SPECT Image Quality

In all patients, image quality was suitable for myocardial gated SPECT reconstruction. The presence of significant splanchnic or hepatobilary uptake did not alter the reconstructed image quality. As shown in Table 1, the mean ^{201}Tl-to-^{99m}Tc-MIBI count activity ratio was 64% in the total gated acquisition and 61% in the myocardial ROI.

Gated SPECT Left Ventricular Ejection Fraction

Reproducibilities were calculated as the correlation of two LVEF measurements using gated SPECT, including reconstruction and reorientation of the acquisitions. The intraobserver and interobserver correlations were 0.98 and 0.97, respectively. Correlations were high between ERNA and gated SPECT in the overall population ($y = 4.911 + 0.75\,x$, $r = 0.82$, SEE = 7.8%) and in group 1 and group 2 (Fig. 1). Covariance analysis showed that the correlation between ERNA and gated SPECT ejection fraction was not significantly different with ^{201}Tl and ^{99m}Tc-MIBI ($F = 0.003$, df = 47, $P = 0.95$).

However, gated SPECT significantly underestimated LVEF compared with ERNA in both groups (Table 1). The mean difference between ERNA and gated SPECT was 4.7% ± 7.3% (95% confidence interval: 0%–9.41%; SEE = 1.056%). There was no significant variation of this underestimation whether the mitral valve plane was involved in the perfusion defect (mitral valve involved, 4% ± 7.9%; mitral valve not involved, 5% ± 6.7%). Moreover, the LVEF underestimation with gated SPECT was not correlated either to the defect size evaluated by polar map or to the severity of hypoperfusion on the basis of perfusion defect score ($y = 0.066 + 1.653\,x$, $r = 0.077$, not significant). The potential effect of dyskinesia was tested in the 30 first patients. Fifteen of 30 patients demonstrated an LV dyskinesia (50%) on ERNA. There was no significant variation of LVEF underestimation whether a dyskinesia was observed on ERNA (ERNA gated SPECT LVEF in patients with dyskinesia, 2% ± 9.4%; in patients without dyskinesia, 4.5% ± 6.6%, not significant).

Bland-Altman analysis demonstrated a fair agreement between the two methods in the whole population (Fig. 2). No increasing underestimation with the gated SPECT method was found as the mean ejection fraction increased. In the entire population, the limits of agreement for the mean difference between the two methods were −9.92 and +19.336, respectively, for mean − 2 SD and mean + 2 SD.

DISCUSSION

This study examined the feasibility, reproducibility and accuracy of ^{201}Tl and ^{99m}Tc-MIBI gated SPECT in assessing LVEF in patients with large perfusion defects and LV dysfunction.

A high correlation was found between gated SPECT and ERNA, despite significant perfusion defects. This correlation was independent of the perfusion tracer. However, both ^{201}Tl and ^{99m}Tc-MIBI gated SPECT significantly underestimated ejection fraction compared with ERNA in this population. Although the correlation was good, Bland-Altman plots showed sizeable limits of agreement between the two methods.

Image Quality

Electrocardiographic gating of perfusion SPECT offers the possibility of measuring LVEF. Segmentation of myocardial perfusion tomograms into 8 or 16 frames per cardiac cycle requires high-quality scans. Moreover, this quality

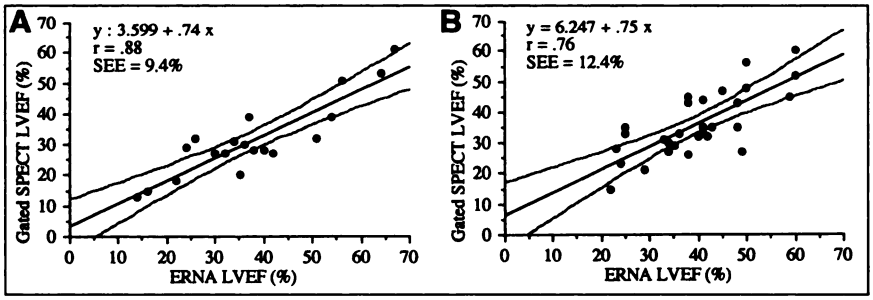

FIGURE 1. (A) Correlation between gated SPECT and ERNA LVEF in group 1 (^{99m}Tc-MIBI). (B) Correlation between gated SPECT and ERNA LVEF in group 2 (^{201}Tl).

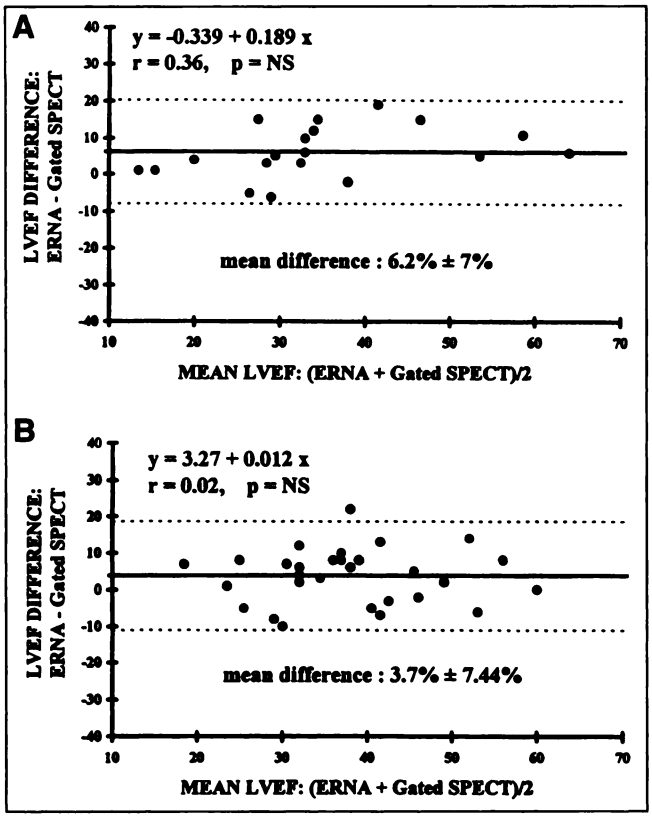

FIGURE 2. (A) Gated SPECT versus ERNA in group 1 (^{99m}Tc-MIBI). (B) Gated SPECT versus ERNA in group 2 (^{201}Tl). NS = not significant.

may be impaired in patients with myocardial infarction. The development of ^{99m}Tc-labeled perfusion agents allows the injection of greater amounts of radioactivity. Nevertheless, ^{201}Tl still has a higher percentage of extraction by the myocardium (*9,10*). For these reasons, we found high count densities of ^{201}Tl in the myocardium as the acquisition time increased to 120 s per projection and the injected dose increased to 185–203 MBq. Under these conditions, ^{201}Tl allowed the evaluation of LVEF, despite count statistics that were less favorable than with ^{99m}Tc-MIBI. In contrast, the injected dose of ^{201}Tl was not significantly higher than the routine dose administrated in our clinical practice, including thallium reinjection (129 MBq + 45 MBq).

Comparison with Equilibrium Radionuclide Angiography

Overall accuracy of gated SPECT for LVEF assessment has previously been studied and has led to high correlations ranging from 0.83 to 0.97 (*11–13,17,22–24*). However, gated SPECT significantly understimated LVEF in this particular population of patients with large myocardial infarction and LV dysfunction. The discrepancies between ERNA and gated SPECT LVEF values included several parameters.

Because the gated SPECT cycle is composed of 8 time segments and the ERNA cycle is composed of 16 time segments, end systole could be better resolved in the ERNA than in the gated SPECT cycle. This temporal undersampling may induce a truncation of the end systole and lead to a reduction of LVEF. This phenomenon was confirmed by Germano et al. (*11*), who demonstrated a 3.71% average reduction in LVEF by using 8-interval versus 16-interval gating. Moreover, one would expect this reduction to increase as LVEF increases, because the relative truncation is proportional to the rate and amplitude of the time-volume curve. Because we only studied patients in a small range of low ejection fractions, we were not able to confirm this phenomenon. Williams and Taillon (*22*), in a larger range of ejection fractions, noted a greater underestimation of LVEF in high normal values.

Another possible explanation is that, in regions with myocardial scar, the thinner the myocardium is the more it is subject to the partial volume effect phenomenon. A poor agreement between gated SPECT and MRI in assessing wall thickening was previously found in segments with severely reduced perfusion (*25,26*). This phenomenon may lead to overestimation of end-systolic volumes and therefore to underestimation of ejection fraction.

Finally, the extent and severity of perfusion defect as well as the presence of a dyskinesia could potentially interfere with LVEF measurement. However, this was not confirmed in this study due to either our selected population or a powerful effect of temporal undersampling. However, this latter hypothesis remains to be proven when comparing 8- versus 16-interval acquisition.

In addition to this underestimation of LVEF, the limits of agreement between gated SPECT and ERNA were quite large, as shown by Bland-Altman analysis. Similar results were found in previous studies (*12,22*). The accuracy of ERNA is confirmed by its ability to demonstrate LVEF variations <5% during stress or after drug administration (*3,27,28*). When precise measurements are needed, particularly in prognosis evaluation, these limits of agreement may compromise the accuracy of gated SPECT. However, in routine studies, this agreement is similar to that previously reported with echocardiography (*29,30*).

Recent studies focused on the use of ^{201}Tl for myocardial gated SPECT. Germano et al. (*16*) found a high correlation between rest ^{201}Tl and postexercise ^{99m}Tc-sestamibi gated SPECT. Using a different software configuration, Maunoury et al. (*17*) found similar correlations. To our knowledge, no previous studies have compared thallium gated SPECT with ERNA. Furthermore, we only explored patients with severely impaired perfusion and LV dysfunction. Using ^{201}Tl, our results were slightly lower than previously reported with ^{99m}Tc-sestamibi (*11–13,22,23*), but the correlation with ERNA did not depend on the perfusion tracer.

Clinical Implications

Both LVEF and myocardial viability evaluation are technically feasible and clinically relevant in patients with myocardial infarction (*2,7,8,31*). Basically, the use of ^{201}Tl as the preferred tracer of myocardial viability is not detrimen-

tal to radionuclide angiographic LVEF measurement. In regard to the injected dose and acquisition time, ^{201}Tl gated SPECT could be useful in evaluating LVEF.

CONCLUSION

LVEF measurement was feasible in the setting of perfusion gated SPECT using the Cedars-Sinai method, even in patients with large myocardial infarction and LV dysfunction. The correlation with ERNA was slightly but not significantly better with ^{99m}Tc-MIBI than with ^{201}Tl. Moreover, in this selected population, gated SPECT significantly underestimated ejection fraction compared with ERNA. Although the agreement between gated SPECT and ERNA appear sufficient for routine evaluation of LVEF, ERNA should be preferred when precise measurements are required.

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