Assessment of Global and Regional Left Ventricular Function by Electrocardiographic Gated N-13 Ammonia Positron Emission Tomography in Patients With Coronary Artery Disease

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Background Electrocardiographic gated 13N-ammonia positron emission tomography (PET) enables simultaneous assessment of myocardial blood flow and left ventricular (LV) function. The aim of this study was to assess the accuracy of gated 13N-ammonia PET for evaluating global and regional LV function in patients with coronary artery disease (CAD) in comparison with conventional left ventriculography (LVG).

Methods and Results Fifty-four patients with CAD underwent gated 13N-ammonia PET and LVG. The LV end-diastolic and end-systolic volumes (LVEDV, LVESV) and ejection fraction (LVEF) by gated 13N-ammonia PET were calculated using Cedars-Sinai automated quantitative gated single photon emission computed tomography (QGS) and compared with those obtained by LVG. The regional wall motion (RWM) was visually scored, and compared with that on LVG. There were good correlations between the 2 methods for LVEF, LVEDV and LVESV (R=0.828, R=0.821 and R=0.874 respectively). The RWM assessed by gated 13N-ammonia PET also agreed well with that by LVG (complete agreement was 70.4%, κ=0.58).

Conclusions Gated 13N-ammonia PET combined with QGS works reasonably well for the assessment of both global and regional LV function in CAD patients, although additional calibration may be necessary. (Circ J 2005; 69: 177 – 182)

Key Words: Coronary artery disease; Gated-13N-ammonia positron emission tomography; Left ventricular function

The assessment of left ventricular (LV) function and volumes, together with myocardial perfusion, is important for prognostic stratification of patients with coronary artery disease (CAD)1-5. The electrocardiographic (ECG)-gated acquisition technique with perfusion tracers for single-photon emission computed tomography (SPECT) has been established to assess global and regional LV function, and several automated quantitative algorithms, such as the Cedars-Sinai quantitative gated SPECT (QGS), have been developed for this purpose.5-11 Several recent studies have applied these algorithms to positron emission tomography (PET)12-16 which has several advantages over SPECT in that it produces high-quality imaging and has the capability of quantitative analysis of perfusion or metabolism. Nitrogen-13-ammonia (13N-NH3) has been widely used for quantification of myocardial blood flow (MBF) in PET studies17-20. Although MBF and LV function should usually be closely related, they may disagree in some circumstances, such as myocardial stunning. Therefore, the integration of MBF and LV function is important for understanding of the pathophysiology of various disease conditions. In this regard, ECG-gated 13N-NH3 PET is attractive because it enables simultaneous assessment of MBF and LV function, but this promising technique has not been systematically validated in a large patient cohort. Furthermore, the feasibility of assessing regional function has not been previously addressed. The aim of this study was to evaluate the feasibility of ECG-gated 13N-NH3 PET to assess global and regional LV function in a relatively large cohort of patients with CAD in comparison with conventional left ventriculography (LVG) as the reference technique.

Methods

Study Population

The study group consisted of 54 consecutive patients (51 men, 3 women; age range: 30–85 years, mean age: 62.6±12.4 years) with CAD documented by coronary angiography. Of these 54 patients, 34 had a previous myocardial infarction. All patients underwent both LVG and gated 13N-NH3 PET at rest within 2 weeks of each other (mean duration 7.2 days). All patients had normal sinus rhythm, and...
none had any cardiac events or additional therapeutic intervention between the LVG and PET studies. All patients gave informed consent in accordance with the institutional Human Clinical Study Committee.

**PET Acquisition**

PET imaging was performed using a full-ring PET scanner (Advance, General Electric Medical System, Milwaukee, WI, USA). The characteristics of this scanner have been described previously.\(^1\) Transmission scans with rotating Ge-68 pin sources were performed for 15 min to check the position of the heart and to correct for the attenuation.\(^2\) Next, a 9-min dynamic acquisition was started at the same time of intravenous injection of 740 MBq of \(^{13}\)NH₃, and immediately after the dynamic scan, ECG-gated acquisition was started for 10 min with 8 frames/cardiac cycle. Images were reconstructed using a standard filtered back-projection algorithm with a Hanning filter with a cutoff frequency of 0.27 and a zoom of 1.57. The image data matrix was 128×128 with a pixel size of 2.73 mm and a slice thickness of 4.25 mm.

**PET Image Analysis**

The reconstructed image data were transferred to an eNTEGRA workstation (GE Medical System), and end-
diastolic volume (LVEDV), end-systolic volume (LVESV) and LV ejection fraction (EF) were automatically calculated by QGS. We applied QGS to the gated PET data without any changes or preprocessing, similar to the previous reports that applied QGS to gated fluorodeoxyglucose (FDG) PET, and the matrix size was still 128×128.

The regional wall motion (RWM) was evaluated visually on a cinematic display of the reconstructed 3-dimensional LV. The LV was divided into 7 segments according to the LVG American Heart Association (AHA) classification: 5 segments in the right anterior oblique (RAO) and 2 segments in the left anterior oblique (LAO). Two experienced observers who were unaware of the result of LVG visually scored the RWM of each segment using a 4-point scale (1= normal, 2= mild hypokinesis, 3= severe hypokinesis and 4= akinesis or dyskinesis). The distribution of NH3 uptake in the LV was analyzed with a semi-quantitative polar map using a volumetric sampling algorithm, which has been developed at Technische Universität München, on the dynamic scan. In the polar maps, we measured regional NH3 uptake using the 7 segments model shown in Fig 1.

**Left Ventriculography**

All patients underwent biplane LVG using 40 ml of contrast agent through a 5F pigtail catheter. LVG was acquired at 40 frames/s in 30 degrees of the RAO and LAO, and recorded on 35mm cine film. Using a computer analysis system (Angiographic Ventricular Dynamics Version 5.4.1, Siemens, Germany), the end-systolic and end-diastolic outlines of the endocardial wall in the RAO were manually traced and calibrated by a 2-point scale, and the LVEDV, LVESV and LVEF were calculated by the single-plane area–length method. The RWM in the 7 segments as delineated by the AHA in the RAO and LAO were visually scored by 2 observers according to the same classification as described earlier for gated PET.

**Statistical Analysis**

The correlations of the LV volumes (LVEDV, LVESV) and LVEF between data obtained from gated PET using QGS and those from LVG were analyzed by linear regression analysis. The agreement between the 2 methods was assessed by Bland-Altman analysis. The mean values of LVEDV, LVESV and LVEF as calculated by gated PET were compared with the values obtained by LVG.

**Fig 3.** Comparison of left ventricular ejection fraction (LVEF), end-diastolic volume (LVEDV) and end-systolic volume (LVESV) between quantitative ECG-gated PET and contrast left ventriculography (LVG). Left panels (A–C) show scatter plots and liner regression analysis; right panels (D–F) show Bland-Altman plots. There were good correlations between the 2 methods for LVEF, LVEDV and LVESV. The mean differences on Bland-Altman analyses were 15.2±9.5% for LVEF, 2.0±27.4 ml for LVEDV and –14.3±20.0 ml for LVESV.
and LVEF were compared using paired Student's t-test. The agreement between the RWM scores from gated PET and LVG were evaluated by the Cohen \( \kappa \) statistic. One-way analysis of variance (ANOVA) was used to compare regional NH3 uptake in each visual RWM score as determined by gated PET and LVG. Statistical values were expressed as the mean value plus or minus 1 standard deviation (SD) and p<0.05 was considered to be significant.

**Results**

We could trace the endocardial border correctly by the fully automated analysis in all of the 54 patients, even those with a large perfusion defect. Fig 2 is a typical example of a patient with a previous myocardial infarction in the left anterior descending coronary artery territory.

**LV Volumes and LVEF**

The linear regression analyses of LVEDV, LVESV and LVEF between gated PET and LVG are shown in Fig 3A–C. The LVEF measured by gated PET significantly correlated with the values obtained by LVG (EF\_gated PET = 0.56 EF\_LVG + 1.99, R = 0.83, p<0.0001). The LVEDV and LVESV by gated PET also showed significant correlations with the LVG measurements (LVEDV\_gated PET = 0.96 LVEDV\_LVG + 1.77, R = 0.82, p<0.0001 and LVESV\_gated PET = 0.99 LVESV\_LVG + 1.49, R = 0.87, p<0.0001). The Bland-Altman analyses are shown in Fig 3D–F. The mean differences were 15.2±9.5% for LVEF, 2.0±7.4 ml for LVEDV and -14.3±20.0 ml for LVESV. There were significant linear regressions of y=0.43x–7.83, R=0.59, p=0.0001 for LVEF and y=-0.18x+20.11, R=0.27, p=0.047 for LVEDV on the Bland-Altman trend, and no significant trend for LVESV (y=-0.13x–7.56, R=0.24, p=0.08). The mean LVEF obtained by gated PET was significantly lower than that obtained by LVG (45±10% vs 61.1±16.3%, p<0.001) and the mean LVESV was significantly higher than that obtained by LVG (59.7± 41 ml vs 45.4±36.4 ml, p<0.001). There was no significant difference in the mean LVEDV values obtained by these 2 methods (102±47.8 ml vs 104.3±40.8 ml, NS). However, there was no significant difference in the mean LVESV values obtained by these 2 methods (102±47.8 ml vs 104.3±40.8 ml, NS). Comparisons of the mean LVEF, LVEDV, and LVESV values between gated PET and LVG for all subjects, and for the subgroups of myocardial infarction (n=34) and angina pectoris (n=20), are shown in Table 1. In all patients, the mean LVEF obtained by gated PET was significantly lower than that obtained by LVG (45±10% vs 61.1±16.3%, p<0.001) and the mean LVESV was significantly higher than that obtained by LVG (59.7± 41 ml vs 45.4±36.4 ml, p<0.001). However, there was no significant difference in the mean LVEDV values obtained by these 2 methods (102±47.8 ml vs 104.3±40.8 ml, NS). Comparisons of the mean LVEF, LVEDV, and LVESV values between gated PET and LVG

**Regional Wall Motion**

The agreement of LV RWM scores between gated PET and LVG is shown in Table 2. From a total of 378 segments, 266 (70.4%, \( \kappa \) value =0.58) showed complete agreement between gated PET and LVG, including 140 normal segments, 55 segments with mild hypokinesia, 44 segments with severe hypokinesia, and 30 segments with akinesia–dyskinesis. No segments showed a disagreement between the 2 methods by 2 or more points. The relationship between the RWM scores obtained by gated PET or LVG and the regional NH3 uptake is shown in Fig 4. In the gated PET the mean NH3 uptake on each score was: normal –81.5±5.8% of peak count (%); mild hypokinesia –79.3±7.5%; severe hypokinesia –71.5±8.2%; akinesia/dyskinesis –53.3±17.3%; and in the LVG they were: 81.7±5.6%; mild hypokinesia –79.1±4.7%; severe hypokinesia –73.1±10.6%; akinesia/dyskinesis –55.8±17.9%. In neither gated PET nor LVG was there a significant difference in the NH3 uptake between normal and mild hypokinesia, but there were significant differences among the other RWM scores.

**Discussion**

To our knowledge this is the first study to assess global and regional LV function using ECG gated NH3 PET in a relatively large patient cohort. There were good correlations between the 2 methods for LVEF (R=0.83), LVEDV (R=0.82) and LVESV (R=0.87), although gated PET significantly underestimated LVEF and overestimated LVESV as compared with LVG. The RWM assessed by gated-PET also agreed well with LVG (complete agreement=70.4%, \( \kappa \)=0.58).

**Global Function**

In this study, the LVEF and LV volumes estimated from NH3 gated PET using QGS correlated significantly with those obtained by single-plane LVG. However, gated PET underestimated LVEF and overestimated LVESV as compared with LVG. This tendency was found in both the myocardial infarction group and the angina group, and it

**Table 1** Comparison of Mean LVEF, EDV and ESV Obtained by Gated PET and LVG in All Patients, as Well as in the Myocardial Infarction Group (MI) or Angina Group (AP)

<table>
<thead>
<tr>
<th></th>
<th>Gated PET</th>
<th>LVG</th>
<th>p-value</th>
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<tbody>
<tr>
<td>All patients (n=54)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EDV (ml)</td>
<td>102.0±47.9</td>
<td>104.3±40.8</td>
<td>NS</td>
</tr>
<tr>
<td>ESV (ml)</td>
<td>59.7±41.0</td>
<td>45.4±36.4</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>45.0±10.0</td>
<td>61.2±16.8</td>
<td>&lt;0.0001</td>
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<tr>
<td>MI (n=34)</td>
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<tr>
<td>EDV (ml)</td>
<td>116.0±53.0</td>
<td>114.9±44.9</td>
<td>NS</td>
</tr>
<tr>
<td>ESV (ml)</td>
<td>72.5±45.8</td>
<td>58.5±39.7</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>41.0±10.0</td>
<td>54.0±15.4</td>
<td>&lt;0.0001</td>
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<tr>
<td>AP (n=20)</td>
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<tr>
<td>EDV (ml)</td>
<td>77.0±22.9</td>
<td>85.0±24.6</td>
<td>NS</td>
</tr>
<tr>
<td>ESV (ml)</td>
<td>37.3±19.2</td>
<td>22.8±11.5</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>53.0±7.3</td>
<td>73.4±8.8</td>
<td>&lt;0.0001</td>
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EDV, end-diastolic volume; ESV, end-systolic volume; LVEF, left ventricular ejection fraction; LVG, left ventriculography; PET, positron emission tomography.

**Table 2** Agreement Between the Assessment of Left Ventricular Regional Wall Motion by Gated PET and LVG

<table>
<thead>
<tr>
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<th>Gated PET</th>
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<tbody>
<tr>
<td>LVG</td>
<td></td>
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<tr>
<td>1</td>
<td>140</td>
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<tr>
<td>2</td>
<td>40</td>
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<td>3</td>
<td>3</td>
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<td>4</td>
<td>0</td>
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Complete agreement was 70.4%, \( \kappa \) =0.58.

LVG, left ventriculography; PET, positron emission tomography.
means the extent of the perfusion defect did not influence the underestimation of LVEF or overestimation of LVESV. There was a small, but significant inverse linear relationship on the Bland-Altman trend for LVEDV, and it might mean that the gated PET underestimated LVEF in patients with a small LV cavity and overestimated it in patients with a dilated LV cavity. Furthermore, the Bland-Altman analysis demonstrated a significant positive linear relationship for LVEF, suggesting greater underestimation of LVEF obtained by the gated PET in patients with a higher range of LVEF.

It is known that LVG overestimates the LV volumes because the infusion of contrast material increases the preload and results in hypercontractility of the LV wall according to the Frank-Starling mechanism. A previous report indicated that the LV volumes calculated from cineangiograms by means of the area–length method overestimated the true volumes determined on the postmortem LV cast. Yoshikawa et al and Nichols et al reported that LVEF and LVEDV estimated by gated SPECT using QGS were significantly lower than those obtained by contrast angiographic measurements. They consider the most likely reason to be that the endocardial drawing by LVG sometimes includes more outflow tract than in gated SPECT. Willemsen et al compared the LVEF estimated from gated FDG PET using QGS with equilibrium radionuclide angiography (RNA) and reported that there was a slight trend toward underestimating LVEF with gated FDG PET. They suggested that when QGS is applied to gated PET data, additional calibration is required because QGS was developed for the SPECT system. Okazawa et al compared the LVEF estimated from 13N-NH3 gated PET using Perfusion and Function Assessment by Myocardial SPECT (pFAST) with gated blood-pool imaging (GBP) C15O PET. They also found that the LVEF obtained by gated PET was slightly underestimated as compared with the LVEF by GBP PET in patients with perfusion defects. They also measured LVEF from LVG for 20 patients, and the mean LVEF obtained by gated PET with pFAST was significantly underestimated as compared with LVG (46% vs 54%, p<0.001). Schaefer et al compared the LV volumes and LVEF estimated from gated FDG PET using QGS with cine magnetic resonance imaging (cMRI) in 30 patients and showed a highly significant correlation of LVEF between gated FDG PET and cMRI, but also reported that gated FDG PET significantly underestimated LVEF as compared with cMRI.

Regional Wall Motion

In addition to global LV function, an assessment of regional LV function plays an important role in diagnosing and determining the severity of CAD. This study demonstrated that there was a significant correlation of visual RWM scores between 13N-NH3 gated PET and biplane LVG, even in regions with hypoperfused myocardium. In this study, the complete agreement ratio of wall motion scores was 70.4%, which was higher than the results of Hattori et al (58%) who compared FDG gated PET and LVG in 26 patients using another 3-dimensional (D) algorithm. Conversely, our results were slightly lower than the results of Schaefer et al (complete agreement ratio=76%, α=0.58) who compared FDG gated PET and cMRI.

The regional NH3 uptake was significantly related to the RWM scores in both gated PET and LVG. Hence, RWM is closely related to myocardial perfusion, although we did not measure regional MBF directly in this study.

Study Limitations

First, conventional LVG is a 2-D technique, so it can only give rough estimations of LV volumes and LVEF. It would be better to compare 13N-NH3 gated PET with a 3-D method such as MRI instead of LVG. Second, the measurement of LV volumes obtained by LVG was based on a single plane in the RAO projection. A previous study reported that the LV volumes and mass from single-plane LVG in the RAO are useful but less precise than those obtained using the biplane method. Third, we performed ECG-gated acquisition using 8 frames/cardiac cycle. As reported earlier, the 8 frame gating slightly underestimates LVEF as compared with the 16 frame gating although the image quality in each frame is better in the 8 frame. Finally, we did not estimate the quantitative RWM analysis as % wall thickening (%WT). Several studies have shown that the %WT is an important parameter in assessment of myocardial viability. We used QGS because this algorithm...
is widely used around the world and many reports have been validating this algorithm for evaluating LV function in gated SPECT5–8,30–32 and also in gated PET12,15,16. We would like to apply the other algorithms such as pFAST10 or Emory Cardiac Toolbox (ECT)11 for 13N-NH3 gated PET to measure LVEF and LV volumes and compare them with QGS.

Conclusion

ECG gated 13N-NH3 PET using QGS is feasible for the assessment of both global and regional LV function in patients with CAD, although additional calibration may be necessary before the results can be directly compared with those obtained by other techniques (eg, a formula that converts QGS measurements to those by LVG as shown in this study). We believe that ECG gated 13N-NH3 PET can be a part of the clinical routine flow PET study, because it provides information about cardiac function as well as MBF, without additionally burdening the patient in terms of scanning time and cost.

References