

# Comparison of LVEF assessed by 2D echocardiography, gated blood pool SPECT, <sup>99m</sup>Tc tetrofosmin gated SPECT, and <sup>18</sup>F-FDG gated PET with ERNV in patients with CAD and severe LV dysfunction

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**Introduction** Left ventricular ejection fraction (LVEF) is the single most important predictor of prognosis in patients with coronary artery disease (CAD) and left ventricular (LV) dysfunction. Equilibrium radionuclide ventriculography (ERNV) is considered the most reliable technique for assessing LVEF. Most of these patients undergo two dimensional (2D) echocardiography and myocardial viability study using gated myocardial perfusion imaging (MPI) or gated <sup>18</sup>F-fluorodeoxyglucose (<sup>18</sup>F-FDG) PET. However, the accuracy of LVEF assessed by these methods is not clear. This study has been designed to assess the correlation and agreement between the LVEF measured by 2D echocardiography, gated blood pool single photon emission computed tomography (SPECT), <sup>99m</sup>Tc tetrofosmin gated SPECT, and <sup>18</sup>F-FDG gated PET with ERNV in CAD patients with severe LV dysfunction.

**Patients and methods** Patients with CAD and severe LV dysfunction [ejection fraction (EF) < 35 assessed by 2D echocardiography] were prospectively included in the study. These patients underwent ERNV along with gated blood pool SPECT, <sup>99m</sup>Tc tetrofosmin gated SPECT, and <sup>18</sup>F-FDG gated PET as per the standard protocol for myocardial viability assessment and LVEF calculation. Spearman's coefficient of correlation (*r*) was calculated for the different sets of values with significance level kept at a *P*-value less than 0.05. Bland–Altman plots were inspected to visually assess the between-agreement measurements from different methods.

**Results** Forty-one patients were prospectively included. LVEF calculated by various radionuclide methods showed good correlation with ERNV as follows: gated blood pool SPECT, *r* = 0.92; MPI gated SPECT, *r* = 0.85; and <sup>18</sup>F-FDG gated PET, *r* = 0.76. However, the correlation between 2D echocardiography and ERNV was poor (*r* = 0.520). The Bland–Altman plot for LVEF measured by all radionuclide

methods showed good agreement with ERNV. However, agreement between 2D echocardiography and ERNV is poor, as most of the values in this plot gave a negative difference for low EF and a positive difference for high EF. The mean difference between various techniques [2D echocardiography (a), gated blood pool SPECT (b), MPI gated SPECT (c), <sup>18</sup>F-FDG gated PET (d)] and ERNV (e) was as follows: (a) – (e), 3.3; (b) – (e), 5; (c) – (e), 1.1; and (d) – (e), 2.9. The best possible correlation and agreement was found between MPI gated SPECT and ERNV.

**Conclusion** This study showed good correlation and agreement between MPI gated SPECT and <sup>18</sup>F-FDG gated PET with ERNV for LVEF calculation in CAD patients with severe LV dysfunction. Thus, subjecting patients who undergo viability assessment by MPI gated SPECT or <sup>18</sup>F-FDG gated PET to a separate procedure like ERNV for LVEF assessment may not be warranted. As the gated blood pool SPECT also showed good correlation and agreement with ERNV for LVEF assessment in CAD patients with severe LV dysfunction, with better characteristics than ERNV, it can be routinely used whenever accurate LVEF assessment is needed. *Nucl Med Commun* 35:1156–1161 © 2014 Wolters Kluwer Health | Lippincott Williams & Wilkins.

*Nuclear Medicine Communications* 2014, 35:1156–1161

**Keywords:** CAD, ERNV, <sup>18</sup>F-FDG PET, gated blood pool SPECT, gated SPECT, LV dysfunction, LVEF

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Received 4 November 2013 Revised 9 July 2014 Accepted 19 July 2014

## Introduction

Heart failure is a major health problem affecting more than 20 million people worldwide. About 2% of adults and 6–10% over 65 years of age suffer from heart failure in developed countries [1]. The life-time risk of developing heart failure is approximately one in five at 40 years of age. Approximately 30–40% of heart failure patients

die within 1 year and 60–70% die within 5 years after the diagnosis of the disease [1]. Coronary artery disease (CAD) is the single most common cause of heart failure and is responsible for 60–75% of the total heart failure cases [1]. Heart failure due to CAD is associated with worse prognosis compared with other causes [2]. Left ventricular ejection fraction (LVEF) is the single most

important predictor of prognosis in patients with CAD and left ventricular (LV) dysfunction [3–5]. Traditionally, LVEF is being assessed by two dimensional (2D) echocardiography or equilibrium radionuclide ventriculography (ERNV) [6]. ERNV is considered the most reliable technique for assessing the LVEF because of its highest reproducibility [7]. Accurate assessment of LVEF in CAD patients is essential to prognosticate and demonstrate the functional improvement following revascularization. Most of these patients undergo viability assessment before revascularization by myocardial perfusion imaging (MPI) gated single photon emission computed tomography (SPECT) or  $^{18}\text{F}$ -fluorodeoxyglucose ( $^{18}\text{F}$ -FDG) gated PET, which also provide functional information like LVEF [8]. This information can be used to prognosticate and monitor the patient after revascularization. However, the accuracy of LVEF assessed by these methods is not clear. A new method for LVEF assessment using SPECT known as gated blood pool SPECT is being investigated for its accuracy [6]. It has a few advantages compared with ERNV – for example, the 3D nature of the tomographic data and nonoverlapping of chambers. The present study was designed to assess the correlation and agreement between the LVEF measured by 2D echocardiography, Gated blood pool SPECT, MPI gated SPECT, and  $^{18}\text{F}$ -FDG gated PET with ERNV in CAD patients with severe LV dysfunction (LVEF < 35 by echocardiography).

## Patients and methods

Patients with angiographically proven CAD and severe LV dysfunction [ejection fraction (EF) < 35 assessed by 2D echocardiography] were prospectively included in the study. They were also subjected to assessment of myocardial viability. Exclusion criteria included pregnancy, lactation, and refusal to give written informed consent. Patients with frequent ectopy, atrial fibrillation, or other significant arrhythmia were also excluded from the study. Written informed consent was taken from all patients before including them in the study. The departmental review committee also cleared the study protocol. All these patients underwent ERNV along with gated blood pool SPECT, MPI gated SPECT, and  $^{18}\text{F}$ -FDG gated PET as per the standard protocols. All these studies were performed within 15 days. None of these patients had undergone any intervention such as coronary stenting or coronary artery bypass grafting during this time period.

### 2D echocardiography

LVEF was measured by M-mode and Simpsons method in all patients using a Philips IE33 echocardiography machine (Philips Healthcare, Bothell, Seattle, Washington, USA).

### ERNV

After 20 min of oral administration of potassium perchlorate, 20 mCi of technetium-99m pertechnetate

( $^{99\text{m}}\text{TcO}^-_4$ ) was injected intravenously to label the red blood cells. Patients were positioned supine on the imaging table under a single-headed camera coupled with a low-energy general-purpose parallel-hole collimator (Millennium MPR; GE Healthcare, Milwaukee, Wisconsin, USA) in the best septal view [left anterior oblique (LAO) projection] with a caudal tilt for ERNV data acquisition. Data were acquired in frame mode with the cardiac cycle divided into 24 bins for an average of eight million counts, in a  $64 \times 64$  matrix, with a  $\pm 10\%$  R–R acceptance window, and a 20% energy window centered at 140 keV. The LVEF was calculated by the dual region of interest method. The background region of interest was placed adjacent to the free wall of the ventricles.

### Gated blood pool SPECT

Immediately after obtaining the planar views, gated blood pool SPECT was performed under a dual-headed SPECT/CT camera fitted with low-energy high-resolution parallel-hole collimators (Infinia Hawkeye-4; GE Healthcare), with the detectors in L-mode configuration. Acquisition parameters for gated blood pool SPECT consisted of 60 steps per  $180^\circ$ , at 20 s per step, 16 frames per cardiac cycle, in a  $64 \times 64$  matrix, in step and shoot mode, with zoom factor 1.3, an energy window of 20% centered at 140 keV, and an R–R acceptance window of  $\pm 10\%$ . Projection data were prefiltered using a Butterworth filter (cutoff frequency, 0.52 cycles/cm; order, 5) and reconstructed by filtered back projection using a ramp filter. The gated blood pool SPECT was processed by a single operator, using the fully automated algorithm (QBPS) [9,10]. The LVEF was calculated using the maximum diastolic and systolic dispersion of the LV.

### $^{99\text{m}}\text{Tc}$ tetrofosmin gated SPECT

All patients underwent a  $^{99\text{m}}\text{Tc}$  tetrofosmin gated SPECT using a double-headed gamma camera equipped with high-resolution collimators (Infinia Hawkeye; GE Healthcare). After a minimum of 4 h of fasting,  $^{99\text{m}}\text{Tc}$  tetrofosmin (7 mCi) was administered intravenously under resting conditions. About 45–60 min after radiotracer injection, a resting gated blood pool SPECT study was performed. Data were acquired in a  $64 \times 64$  matrix, in 32 projections, at 40 s/projection, and at eight frames per cycle, with a 20% window centered at a 140 keV photo peak of  $^{99\text{m}}\text{Tc}$ . Low-dose computed tomography (CT) was performed using a 2.5 mA tube current for attenuation correction. LVEF was calculated using an Emory cardiac tool box.

### $^{18}\text{F}$ -FDG gated PET

Patients were advised to fast for at least 6 h before the  $^{18}\text{F}$ -FDG PET scan and baseline blood sugar was checked. About 45–60 min after 50–75 g of oral glucose loading, blood sugar was checked. If it was less than

140 mg/dl, 6–8 mCi of  $^{18}\text{F}$ -FDG was injected intravenously. If it was more than 140 mg/dl, regular insulin was injected intravenously according to blood glucose level (2, 3, and 5 U of regular insulin for 140–160, 160–180, and 180–200 mg/dl of blood glucose, respectively). About 45–60 min after  $^{18}\text{F}$ -FDG injection, myocardial  $^{18}\text{F}$ -FDG PET was performed using a hybrid PET/CT scanner (Discovery STE-16; GE Healthcare) in 3D mode. The myocardium was covered in one bed position (5 min per bed position) with ECG gating (eight frames/R–R cycle). Low-dose CT was acquired for the purpose of attenuation correction. LVEF was calculated using a vendor-provided software program.

### Statistical analysis

Version 17.0 of SPSS (SPSS Inc., Chicago, Illinois, USA) was used for statistical analysis. Spearman's coefficient of correlation ( $r$ ) was calculated for the different sets of values with significance level kept at  $P$ -value less than 0.05. Bland–Altman plots were inspected to visually assess the between-agreement measurements from different methods.

### Results

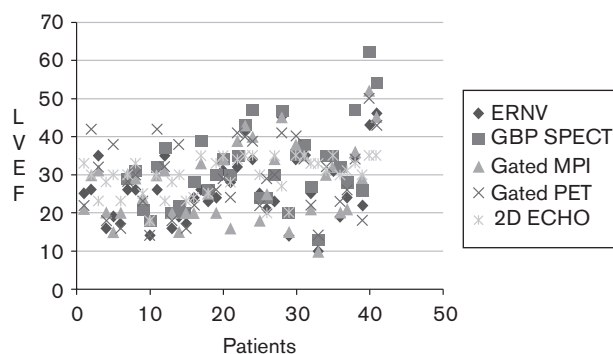
Forty-one patients (35 male and six female patients; mean age 57.5 years, range 36–76 years) with angiographically proven CAD and severe LV dysfunction (LVEF  $\leq 35\%$  assessed by echocardiography) were included in this study. Table 1 shows the demographic details of the patients. Data of individual patients have been listed in Fig. 1. All the patients underwent ERNV,  $^{99\text{m}}\text{Tc}$  tetrofosmin gated SPECT, and  $^{18}\text{F}$ -FDG gated PET, whereas only 35 patients underwent gated blood pool SPECT. The average EF values of ERNV, gated blood pool SPECT,  $^{99\text{m}}\text{Tc}$  tetrofosmin gated SPECT,  $^{18}\text{F}$ -FDG gated PET, and 2D echocardiography were 26.41 (range 10–46%), 31.97 (range 13–62%), 27.56

**Table 1 Demographic details**

Characteristics	Number of patients
Diabetes	17
Hypertension	18
Smokers	8
Alcoholic	15
NYHA dyspnea score	Grade I = 10 Grade II = 11 Grade III = 18 Grade IV = 02
Echocardiographic findings	Global hypokinesia = 9 LAD territory = 16 LAD and RCA = 7 LAD and LCx = 8 RCA and LCx = 1
Angiographic results	LAD = 10 LAD and RCA = 9 LAD and LCx = 11 RCA and LCx = 1 Triple vessel disease = 10

LAD, left anterior descending artery; Lcx, left circumflex artery; RCA, right coronary artery.

**Fig. 1**



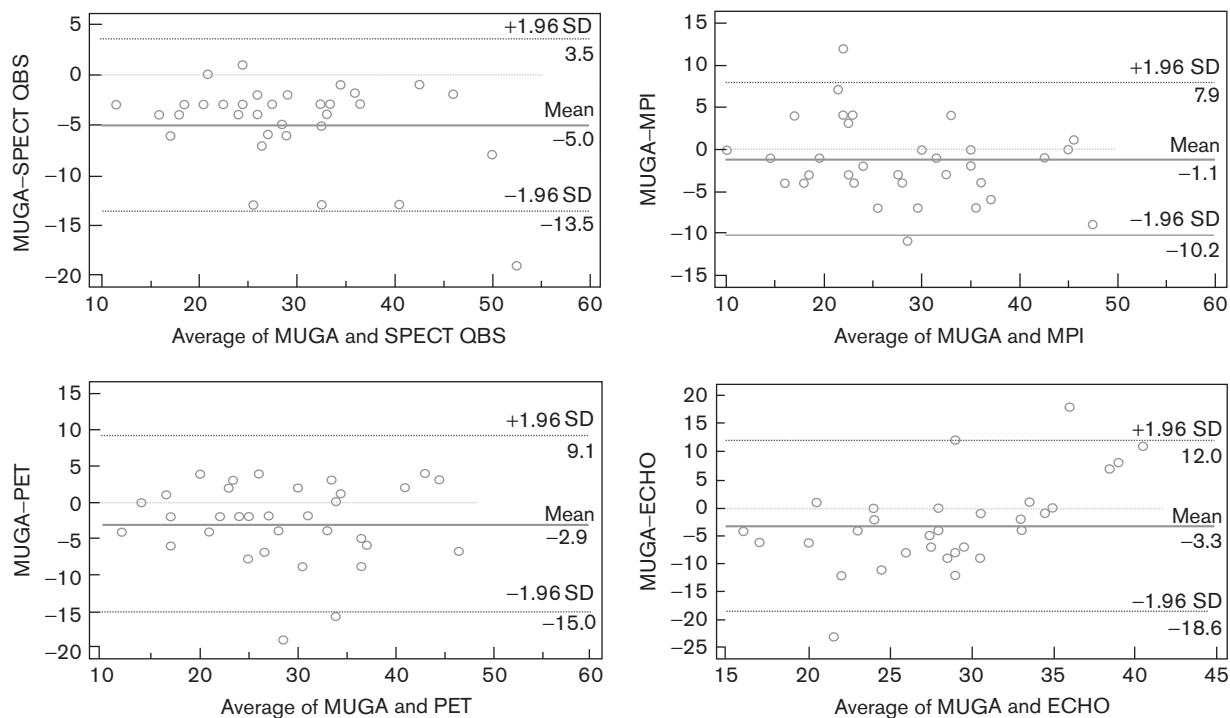
Values of LVEF of individual patients determined by different methods are shown (individual patients in the  $x$ -axis and LVEF in the  $y$ -axis). 2D, two dimensional; ERNV, equilibrium radionuclide ventriculography; GBP, gated blood pool; LVEF, left ventricular ejection fraction; MPI, myocardial perfusion imaging; SPECT, single photon emission computed tomography.

(range 10–52%), 29.34 (range 13–50%), and 29.73 (range 18–35%), respectively. LVEF calculated by various radionuclide methods showed good correlation with ERNV as follows: gated blood pool SPECT, Spearman's correlation coefficient  $r=0.92$ ;  $^{99\text{m}}\text{Tc}$  tetrofosmin gated SPECT,  $r=0.85$ ; and  $^{18}\text{F}$ -FDG gated PET,  $r=0.76$ . However, the correlation between the 2D echocardiography and ERNV was poor ( $r=0.520$ ). The Bland–Altman plot for LVEF measured by all three radionuclide methods showed good agreement with ERNV (Fig. 2). However, agreement between 2D echocardiography and ERNV was poor as most of the values in this plot gave a negative difference for low EF and a positive difference for high EF because of the underestimation of lower EF values and overestimation of higher EF values with 2D echocardiography. The mean difference between various techniques [2D echocardiography (a), gated blood pool SPECT (b), MPI gated SPECT (c),  $^{18}\text{F}$ -FDG gated PET (d)] and ERNV (e) were as follows: (a) – (e), 3.3; (b) – (e), 5; (c) – (e), 1.1; and (d) – (e), 2.9.

### Discussion

Accurate assessment of LVEF in CAD patients with severe LV dysfunction before revascularization is very important for assessing the outcome following the intervention. The routinely performed 2D echocardiography is relatively subjective in nature. Most of these patients undergo viability assessment by MPI or  $^{18}\text{F}$ -FDG PET, which provide additional gating information like LVEF. The accuracy of these techniques in assessing LVEF is not clear. Among radionuclide techniques, ERNV is considered the most reliable technique as it has the least variability and operator interference. However, it has a few disadvantages – for example, overlap of the cardiac chambers and 2D nature [6]. Gated blood pool

Fig. 2



Bland-Altman plot of the left ventricular ejection fraction values calculated using four different techniques in comparison with ERNV. The mean difference was the least with MPI (1.1) and the maximum with gated blood pool (5). Good agreement is noted between ERNV and the other three radionuclide methods, with no changing trend in the estimation of EF with increasing or decreasing values. However, agreement between 2D echocardiography and ERNV is poor as most of the values in this plot give a negative difference for low EF and a positive difference for high EF. 2D, two dimensional; EF, ejection fraction; ERNV, equilibrium radionuclide ventriculography; MPI, myocardial perfusion imaging; SPECT, single photon emission computed tomography. MUGA, multigated acquisition; QBS, quantitative blood pool SPECT.

SPECT can determine the LV function more accurately because overlap of the cardiac chambers can be avoided. Furthermore, the 3D nature of the tomographic data lends itself naturally to a space-based rather than count-based analysis when geometric assumptions for volume estimation are needed [6]. The accuracy of this method needs to be investigated. To our knowledge, this is the first prospective study comparing LVEF assessed by five modalities such as 2D echocardiography, gated blood pool SPECT,  $^{99m}\text{Tc}$  tetrofosmin gated SPECT, and  $^{18}\text{F}$ -FDG gated PET and ERNV in the same patients.

The performance and determination of global systolic LV function by gated MPI is affected by various factors such as the severity and extent of myocardial perfusion defect, presence of increased extracardiac activity, LV size, sex, dose of radioactivity injected, and signal-to-noise ratio [11–14]. However, many studies have shown good correlation between LV function measurements using ERNV and gated MPI with good interobserver and intraobserver variability [7,15–20]. A few studies have analyzed the accuracy of LVEF assessed by  $^{18}\text{F}$ -FDG PET [21–26]. Some of these studies have compared  $^{18}\text{F}$ -FDG PET with MRI and shown good correlation between the two [21,23,26]. In our study also gated MPI

and  $^{18}\text{F}$ -FDG PET showed good correlation and agreement with ERNV for LVEF assessment in CAD patients with severe LV dysfunction.

In contrast to the widespread use of gated SPECT in myocardial perfusion scintigraphy [27], gated blood pool SPECT has not yet become routine for cardiac gated blood pool studies. A few studies have shown good correlation between LVEF measured by gated blood pool SPECT and ERNV in various patient groups [6,28–31]. As this study has shown good correlation and agreement between gated blood pool SPECT and ERNV, gated blood pool SPECT can be used to evaluate the LVEF, which might give better results compared with ERNV because of better separation of cardiac chambers. It is also superior for visual analysis of regional wall motion abnormalities because of the 3D nature of the tomographic data. In addition, it avoids the practical difficulties of first pass radionuclide ventriculography – for example, good bolus administration – by providing right ventricular functional information such as right ventricular ejection fraction in the same study [6].

On Bland-Altman analysis, the LVEF values calculated using three different radionuclide techniques showed

significant positive correlation with ERNV. Overall, the three radionuclide methods showed overestimation of the LVEF compared with ERNV. The mean difference was the least with MPI (1.1) and the maximum with gated blood pool (5). There was no changing trend in the estimation of EF with increasing or decreasing values. However, agreement between 2D echocardiography and ERNV was poor as most of the values in this plot gave a negative difference for low EF and a positive difference for high EF. Even though the gated blood pool SPECT showed best correlation ( $r=0.92$ ) among all the techniques, the highest overestimation compared with ERNV was also found with this technique (mean difference, 5). MPI gated SPECT gave the best combination of good agreement (least mean difference of 1.1) and correlation (second best correlation coefficient of  $r=0.85$ ) among all.

### Limitations

As our study compared these modalities only in patients with severe LV dysfunction (LVEF < 35%), the accuracy of these modalities in patients with mild to moderate LV dysfunction or in normal subjects needs to be determined. The accuracy of gated blood pool SPECT in other groups of patients, such as patients with dilated cardiomyopathy, patients receiving doxorubicin therapy, and patients with nonischemic LV dysfunction, also has to be evaluated.

### Conclusion

This study has shown good correlation and agreement between MPI gated SPECT and  $^{18}\text{F}$ -FDG gated PET with ERNV for LVEF calculation in CAD patients with severe LV dysfunction. Therefore, subjecting those patients, who undergo viability assessment by MPI gated SPECT or  $^{18}\text{F}$ -FDG gated PET, to a separate procedure like ERNV for LVEF assessment may not be warranted. As the gated blood pool SPECT also shows good correlation and agreement with ERNV for LVEF assessment in CAD patients with severe LV dysfunction, with better characteristics than ERNV, it can be routinely used whenever an accurate LVEF assessment is needed.

### Acknowledgements

#### Conflicts of interest

There are no conflicts of interest.

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