Ventricular ejection fraction in patients with dilated cardiomyopathy calculated by gated blood pool SPET processing software: correlation with multigated acquisition and first pass radionuclide ventriculography

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Abstract

This study was performed to find out the left ventricular ejection fraction (LVEF) and right ventricular ejection fraction (RVEF) in patients with dilated cardiomyopathy (DCM) by using commercially available automated gated blood pool scintigraphy (GBPS) processing software and to correlate it with first pass radionuclide ventriculography (FPRNV) and planar multigated acquisition (MUGA). However, till date, no literature exists studying the application of GBPS and planar radionuclide ventriculography techniques in the setting of patients with DCM as a single cohort. *Forty-one patients having DCM* were prospectively included in the study. First pass RNV and MUGA were performed at rest after in-vivo labeling of red blood cells in all patients. Immediately after obtaining the planar views, GBPS was performed and LVEF and RVEF were calculated. *Our results showed* that the % LVEF values (mean±SD) calculated by MUGA, GBPS and echo cardiography were 31±11, 34±12 and 32±11, respectively. The % RVEF values (mean±SD) calculated by FPRNV and GBPS were 46±14 and 43±17, respectively. The LVEF values calculated by MUGA, GBPS and echcardiography showed very good correlation r=0.924 and r=0.844, respectively and for both P<0.0001. Bland–Altman plot showed overestimation for LVEF (and a tendency for overestimation of RVEF) values calculated by GBPS compared to MUGA. Values of RVEF calculated by GBPS and FPRNV also showed good correlation (*r*=0.88; P<0.0001). *In conclusion*, the automated GBPS for LVEF and RVEF calculation using GBPS SPET can be routinely applied in DCM patients. Given the practical difficulties with FPRNV like good bolus administration, quantitative blood pool SPET (QBPS) can be used to calculate RVEF. Similarly MUGA and GBPS can be used to calculate LVEF.

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Introduction

Congestive heart failure (CHF) is an increasing problem worldwide, with more than 20 million people affected. About one-third cases of CHF are due to dilated cardiomyopathy (DCM). Left ventricular (LV) and/or right ventricular (RV) systolic pump function gets impaired, leading to progressive cardiac dilatation. Symptoms of heart failure (HF) typically appear only after remodelling of the heart has been ongoing for months or even years. Although DCM may occur at any age, usually becomes apparent in the third or fourth decade, associated with systolic dysfunction [1]. Patients with DCM, particularly those above 55 years die within 4 years of the onset of symptoms. Spontaneous improvement or stabilization occurs in about one quarter of patients. As sudden cardiac death is a constant threat, it is always a wise to keep these patients in constant follow-up along with evaluation of LV and RV systolic function. Isolated right sided DCM is also a known entity. Patients with DCM also tend to suffer from RV DCM also. Since RVEF is an essential parameter in guiding the management of these patients, FPRNV is usually ordered to obtain RVEF. GBPS is a simple non-invasive investigation which offers such possibility. Both monitoring and tailoring of treatment in CHF patients is aided by precise measurements of left ventricular ejection fraction (LVEF) and right ventricular ejection fraction (RVEF). These parameters have also been shown to play an important role as prognostic factors [2-5]. Over the years, several imaging modalities have been developed which vary considerably regarding precision, ease of use, availability, and costs. Both LVEF and RVEF may be measured by cardiac magnetic resonance imaging (MRI), gated blood pool single photon emission computer tomography (GBPS), planar multigated radionuclide ventriculography (MUGA), or first-pass radionuclide ventriculography (FPRNV). Additionally, LVEF can be measured by radiographic contrast angiography and two or three dimentional echocardiography (Echo). However, not much literature exist discussing the clinical utility of an ''all-in-one'' method providing left and right ventricular parameters to monitor CHF in such patients. Gated BPS offers this advantage because it is easily performed and clearly differentiates LV from RV [6-8]. A good correlation has been

reported for LV and RV parameters between GBPS and MRI [6, 7]. Numerous studies have also described a good correlation between GBPS, MUGA and FPRNV for measurement of LVEF [8-10]. Recently, fully automated software programs for GBPS processing have been developed and are now commercially available. Using these programs, excellent correlation and accuracy of LVEF measured by MUGA, MRI and a bi-ventricular dynamic physical phantom was documented [10-14]. Good correlation was also found for RV parameters compared with MRI and FPRNV [13-15].

The aim of the present study was to assess the clinical utility of a commercially available automated GBPS processing software (QBS, Cedars-Sinai Medical Centre, Los Angeles, USA), introduced by Kriekinge et al. (1999), in the setting of patients having DCM and correlate their EF measurements derived from GBPS with MUGA and FPRNV as well as two-dimensional echocardiography in DCM patients [12]. Till date, no literature exists that studied the application of GBPS and planar radionuclide ventriculography techniques in the setting of patients with DCM as a single cohort.

Subjects and methods

Forty-four patients suffering from DCM were prospectively included in the study for assessment of cardiac function. We performed FPRNV and MUGA at rest after in-vivo labeling of red blood cells RBC and 2-D echo within a week before the radionuclide study. The patients were asymptomatic to severe symptoms (NYHA Class I to NYHA Class IV). Most of the patients were on beta blockers, ACE inhibitors. The inclusion and exclusion criteria were as following:

Inclusion criteria: 1. Left ventricular ejection fraction (LVEF) ≤ 40% at presentation. Absence of past history of myocardial infarction or coronary artery disease. 2. Absence of secondary cause of left ventricular dysfunction including primary valvular heart disease, ventricular outflow tract obstruction, and coronary artery anomalies. 3. Coronary angiography was carried out in all patients more than 35 years of age and in young individuals if clinically indicated.

Exclusion criteria: Patients with concomitant disease like; infection, autoimmune disease, cancer, as well as patients with coronary artery disease (CAD) and with advanced chronic renal failure (CRF), were excluded.

First-pass radionuclide ventriculography studies were performed at rest by in-vivo RBC labeling. An 18-gauge indwelling intravenous catheter with a 3-way stopcock was established via the right antecubital vein. Standard electrocardiogram (ECG) leads were then placed. After 20min, patients were positioned supine on the imaging table under a Millennium MPR single head camera (GE Healthcare, Milwaukee, USA), equipped with a low energy general purpose parallel hole collimator in approximately 25° RAO projection and 0.5mL of 740MBq technetium-99m pertechnetate ($^{99m}TcO^-_4$) was injected, followed by a rapid injection of 20mL normal saline. Acquisition parameters included, zoom factor 1.33, 64x64 matrix and a 30% energy window centred on 140keV. A total of 1200 frames at 30ms/frame for 36sec duration were acquired, simultaneously with R-wave trigger information and ±10% R-R acceptance window. Only those studies with the full width at half maximum (FWHM) of the bolus transit in the superior vena cava less than or equal to three seconds were included for analysis. Initial RV region of interest (ROI) was drawn and the time-activity curves generated. Start and stop of the RV phase and first identifiable beats were defined and the ROI were modified through iterative steps by the computer software. Sinus beats with end-diastolic counts above 50% of the maximum end-diastolic count, were included for calculation of RVEF. Borders of the RV end-diastolic regions were determined from the phase images and the end-systolic difference images. The phase images were used to identify valve planes. The end-systolic regions were drawn from the end-systolic images. First pass RVEF was calculated by the dual ROI method.

Planar multigated radionuclide ventriculography. After the FP acquisition, patients were positioned under the same gamma camera with the collimator set in best septal view (LAO projection) with a caudal tilt for MUGA data acquisition. Data were acquired in frame mode with the cardiac cycle divided into 24 bins for an average of 8 million counts, in a 64x64 matrix, with a ±10% R-R acceptance window and a 20% energy window centred at 140keV. The LVEF was calculated by the dual ROI method. The background ROI was placed adjacent to the free wall of the ventricles.

Gated blood pool SPET. Immediately after obtaining the planar views, GBPS was performed with Infinia Hawkeye-4 camera (GE Healthcare, Milwaukee, USA), fitted with low-energy high resolution parallel-hole collimators, with the detectors in L-mode configuration. Acquisition parameters for GBPS consisted of 60 steps per 180°, 20s per step, 16 frames per cardiac cycle, 64x64 matrix, step and shoot mode, zoom factor 1.3, an energy window of 20% centered on 140keV, and a R–R acceptance window of ±10%. Projection data were pre-filtered by using a Butterworth filter (cut-off frequency, 0.52 cycles per centimetre; order, 5) and reconstructed by filtered back projection by using ramp filter. The GBPS was processed by a single operator, using the fully automated QBS algorithm (QBPS) as described elsewhere [12, 15]. In case of implausible identification of ventricle borders, the QBS software allows to manually adjust LV and RV ROI by shifting an ellipsoid over the LV. However, this happened only in 3 patients and the data were discarded to allow uniformity in automatic identification of ventricular borders. The LVEF was calculated using the maximum diastolic and systolic dispersion of the LV. For RVEF calculation, the dispersion of the RV according to the LV phases was used without further adjustment of LV and RV ROI. All measurements from GBPS, MUGA, FPRNV and Echo recordings were performed offline by experts, blinded to the results of complementary readings.

Data analysis. Results are presented as mean±standard deviation (SD), unless stated otherwise. Version 7.0 of SPSS was used for statistical analysis. The variables were distributed normally as observed by the Kolmogorov test. The different imaging modalities were compared using paired t-test. Pearson's coefficient of correlation (*r*) was calculated for the different sets of values. The level of statistical significance was set at less than 5%. Bland–Altman plots, analysed by Medcalc software were inspected to visually assess the association between measurements from different methods.

Results

Of the 44 patients, ventricle borders were manually identified in 3 patients as automatic delineation was difficult; hence their data were discarded to allow uniformity. Of the remaining 41 patients were 24 male, age of 44±14 years in whom ventricular borders were identified by computer controlled

automatic method and were eligible for data analysis. The % LVEF values (mean±SD) calculated by MUGA, QBPS and Echo were 31±11, 34±12 and 32±11 respectively. The % RVEF values (mean±SD) calculated by FP-RNV and QBPS were 46±14 and 43±17 respectively. The LVEF and RVEF values as calculated by different methods are also depicted in Table 1.

Table 1. *Comparison of the mean values of LVEF and RVEF calculated by different methods*

Parameters	Planar mean±SD	QBPS mean±SD	ECHO mean±SD
LVEF %	31±11	34±12	32±11
RVEF %	46±14	43±17	N/A

Planar – MUGA for LVEF and FP=RNV for RVEF

The LVEF values calculated from QBPS showed very good correlation with MUGA (r = 0.924) and Echo (r=0.844; all P<0.0001). Bland–Altman plot showed overestimation for LVEF values calculated by QBPS when compared to MUGA; the mean difference was also statistically different (Fig. 1). However, there was no significant difference in the estimation of LVEF by QBPS and Echo (Table 2). Limits for agreement were - 6.4 to +11.9 for LVEF by QBPS and MUGA, respectively.

Values of RVEF calculated by FPRNV and QBPS also showed good correlation (r=0.88; P<0.0001). Bland-Altman plot for RVEF values showed a tendency for an overestimation of higher RVEF values and underestimation of lower RVEF values with QBPS compared to FP-RNV (Fig 1). Limits for agreement were -18.5 to +12.9 for RVEF by QBPS and FPRNV. The QBPS delivered statistically significant lower values compared to FP-RNA (Table 2).

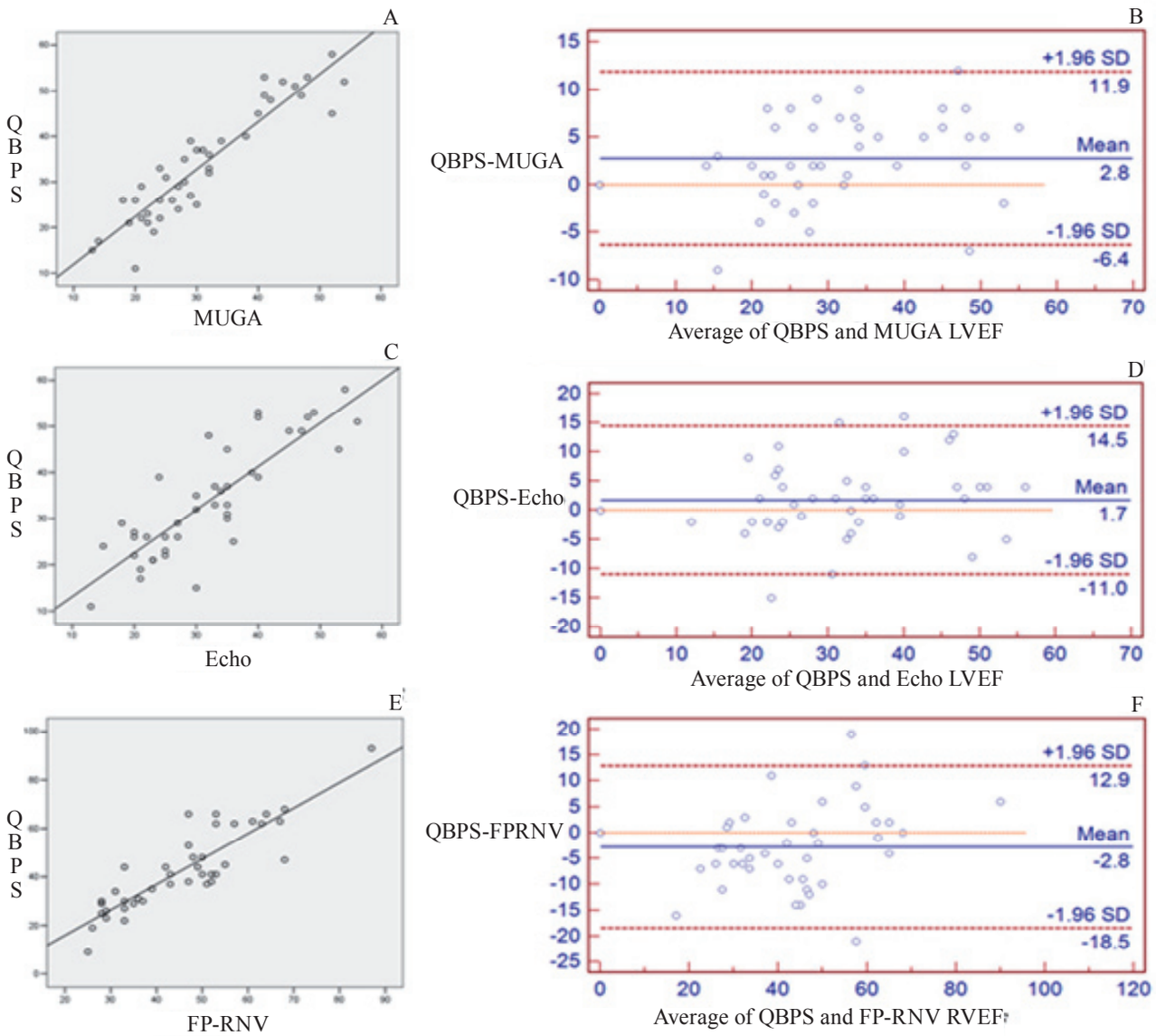

Figure 1. Showing linear regression (**A**) and Bland Altman plots (**B**) for the LVEF values as calculated by QBPS and MUGA, linear regression (**C**) and Bland Altman Plot (**D**) for the LVEF values of patients by QBPS and Echo, linear regression (**E**) and Bland Altman Plots (**F**) for the RVEF values as calculated by QBPS and FPRNV. A good correlation between QBPS and MUGA (r=0.924, P<0.0001), QBPS and echocardiography (r=0.844; P<0.0001). Bland–Altman plot showed overestimation for QBPS-LVEF values compared to MUGA and Echo; and overestimation of higher RVEF and underestimation of lower RVEF values by QBPS compared to FPRNV.

Table 2. *Paired t-test for LVEF and RVEF as assessed by different methods*

Parameters	Mean difference	'P' value
QBPS-MUGA LVEF	2.829	.0001
QBPS-ECHO LVEF	1.780	.090
QBPS-FPRNV RVEF	-2.829	.031

Discussion

Ejection fraction measurement of both ventricles is essential in the management of patients with DCM. Till date, very few studies have described the clinical utility of the QBPS for the evaluation of LV and RV function [10-18]. We measured LV and RV parameters from a single GBPS study and compared that with the results from MUGA, FP-RNV and Echo, considering MUGA as the reference standard for LVEF and FP-RNV for RVEF.

Till date, there is no published data using the QBPS for evaluating patients with DCM, as a single cohort. Others have reported good correlation between LVEF calculated from QBPS and MUGA in 50 patients with permanent pacemaker and an Echo LVEF $\leq$40% [16]. The success rate of the automated algorithm with 70% was relatively poor in that study whereas others delivered a higher success rate of 81% [17], or explained the low automatic contour finding rate by pacemaker induced ventricular dyssynchrony, while the QBS algorithm was not able to automatically resolve this problem [16]. Others found that the QBS algorithm was not flexible enough in differentiating the base of the LV from the left atrium which is relevant in CHF patients with mitral regurgitation [17]. However, in our study no such problems were encountered. In the present study, good correlation of the single LVEF values was found between QBPS and other modalities. This is in accordance with previous studies describing both good correlation and high reproducibility of LVEF measurements assessed by QBPS with other methods [8, 11-13].

Moreover in patients with normal LVEF values, the published results for QBPS compared to MUGA are inconsistent [11, 13, 17]. Others found significantly lower LVEF values from QBPS compared to MUGA in a retrospective analysis of 422 patients [13, 17], or that normal limits for QBPS were significantly lower than for MRI [13] and concluded that separate normal limits for QBPS calculations are needed for correct interpretation of measurements. On the contrast, others reported significantly higher LVEF values calculated from QBPS compared to MUGA, assuming atrial overlap in MUGA [11]. Both studies investigated heterogenous patient populations including patients after heart transplantation or chemotherapy, and patients with primary arterial hypertension, coronary artery disease and previous myocardial infarction but only a small number of heart failure patients with compromised LV function. Despite potential advantages, GBPS processed using the QBS algorithm results in a less repeatable measurement of LVEF than MUGA. The repeatability of LV EDV measurements from GBPS is poor. This happens probably because of the ventricular dyssynchrony due to remodelling.

However, our study included a single cohort of patients having DCM, in which we measured LVEF by different methods and found that QBPS tended to overestimate the LVEF values compared to MUGA. This could be explained by the 16-frame and L-mode acquisition in our study, as most other studies have used only 8-frame acquisition. Higher correlation of RVEF between FP-RNA and GBPS when using 16 frames than when using 8 frames had been demonstrated in a cohort of patients where most of the patients had normal LV function [19]. An underestimation of LV values of 8-frame studies compared to 16-frame studies has been demonstrated using gated myocardial perfusion single photon emission tomography (SPET) [20] while others could not find statistically significant differences in LVEF volumes for QBPS comparing 8 and 16 frame studies in a heterogenous collective of 66 patients [21].

Computations of RV are generally more challenging than LV calculations, because of the relatively more eccentric shape of the RV even in normal subjects and the difficulty of adequately identifying the pulmonary outflow tract [12]. In our study, mean RVEF calculated from GBPS-QBS was in the same range compared to FP-RVEF (43% vs. 46%) which is in line with data from others [17]. Correlation among RVEF values was good (r=0.88). Others also found a good correlation (r=0.68) between QBPS-RVEF and FP-RVEF in 64 patients with chronic post-embolic pulmonary hypertension [15]. However, this study excluded 25% of patients because of unsuccessful FPRNV (fractioned or diffuse bolus transit), while in the present study only 7% had to be excluded because automatic delineation was difficult; hence their data were discarded to allow uniformity. Others found a week correlation (r=0.33) among RVEF values. However, strong correlation between RVEF assessed with a different automated QBPS algorithm and MRI (r=0.85) was already reported by Nichols et al., who investigated 28 patients with primary arterial hypertension or Tetrology of Fallot [13].

Our study has also yielded good correlation between FP-RNA and 16-frame QBS for RVEF values. In the present study, the success rate of the automated QBPS was in a similar range compared to LVEF measurements. However, automated contour finding results were hampered by difficulties to separate the valve plane area from the right atrium as described above for the left ventricle. The current version of the QBPS software does not allow to draw separate contours around the RV and unsatisfactory results of the automated QBPS algorithm were discarded (3 patients). Considering the lesser number of data with unsatisfactory automated QBS results being excluded, we think this would have not affected the good correlation in our study.

In our study, Bland-Altman plot for RVEF values showed a tendency for an overestimation of RVEF values when compared with GBPS which is in line with others; however, underestimation of lower RVEF values was also observed. In the study others [18] also, QBS underestimated actual normal RVEF. This finding is in accordance with our study. The underlying cause is that QBS rely too heavily on modelling the RV by surface gradients. Overestimation of higher RVEF values doesn't have much clinical significance. However, underestimation of actual normal RVEF values carries clinical significance in patients with DCM. Since, these patients might be subjected to further investigations and therapies adding to the cost of management. Hence, care should be taken while reporting lower RVEF with GBPS.

Most of the studies comparing GBPS with FP-RNA have used two detectors in 180° configuration for acquisition. However, we used L-mode configuration for GBPS. This gives better three-dimensional representation of the cardiac chambers and hence a better calculation of the functional parameters.

The automated QBS algorithm for LVEF and RVEF calculation using GBPS is feasible for clinical routine diagnostic in DCM patients. Further studies with larger cohorts having DCM and a good number of controls for establishing the normal range of ejection fraction values by GBPS will be needed in the future.

In conclusion, given the practical difficulties with FPRNV like good bolus administration, QBPS can be warranted to calculate RVEF, as a good correlation is shown between the two techniques, in DCM patients. There was a good correlation between MUGA and GBPS for LVEF measurements.

The authors declare that they have no conflicts of interest.

Bibliography

1. Joshua Wynne, Eugene Braunwald. Cardiomyopathy and myocarditis. In: Fauci, Braunwald, Kasper, Hauser, Longo, Jameson et al (Eds). *Harrison's Principles of Internal Medicine*.17th edn. New York: Mc Graw Hill; 2008: pp.1481.
2. de Groote P, Millaire A, Foucher-Hossein C et al. Right ventricular ejection fraction is an independent predictor of survival in patients with moderate heart failure. *J Am Coll Cardiol* 1998; 32: 948-54.
3. Gradman A, Deedwania P, Cody R et al. Predictors of total mortality and sudden death in mild to moderate heart failure. Captopril-Digoxin Study Group. *J Am Coll Cardiol* 1989; 14: 564-70.
4. Di Salvo TG, Mathier M, Semigran MJ, Dec GW. Preserved right ventricular ejection fraction predicts exercise capacity and survival in advanced heart failure. *J Am Coll Cardiol* 1995; 25: 1143-53.
5. Parameshwar J, Keegan J, Sparrow J et al. Predictors of prognosis in severe chronic heart failure. *Am Heart J* 1992; 123: 421-6.
6. Chin BB, Bloomgarden DC, Xia W et al. Right and left ventricular volume and ejection fraction by tomographic gated blood-pool scintigraphy. *J Nucl Med* 1997; 38: 942-8.
7. Nichols K, Saouaf R, Ababneh AA et al. Validation of SPECT equilibrium radionuclide angiographic right ventricular parameters by cardiac magnetic resonance imaging. *J Nucl Cardiol* 2002; 9: 153-60.
8. Calnon DA, Kastner RJ, Smith WH et al. Validation of a new counts-based gated single photon emission computed tomography method for quantifying left ventricular systolic function: comparison with equilibrium radionuclide angiography. *J Nucl Cardiol* 1997; 4: 464-71.
9. Groch MW, DePuey EG, Belzberg AC et al. Planar imaging versus gated blood-pool SPECT for the assessment of ventricular performance: a multicenter study. *J Nucl Med* 2001; 42: 1773-9.
10. Daou D, Harel F, Helal BO et al. Electrocardiographically gated blood-pool SPECT and left ventricular function: comparative value of 3 methods for ejection fraction and volume estimation. *J Nucl Med* 2001; 42:1043-9.
11. Daou D, Coaguila C, Benada A et al. The value of a completely automatic ECG gated blood pool SPECT processing method for the estimation of global systolic left ventricular function. *Nucl Med Commun* 2004; 25: 271-6.
12. Van Kriekinge SD, Berman DS, Germano G. Automatic quantification of left ventricular ejection fraction from gated blood pool SPECT. *J Nucl Cardiol* 1999; 6: 498-506.
13. Nichols K, Humayun N, De Bondt P et al. Model dependence of gated blood pool SPECT ventricular function measurements. *J Nucl Cardiol* 2004; 11: 282-92.
14. De Bondt P, Nichols K, Vandenberghe S et al. Validation of gated blood-pool SPECT cardiac measurements tested using a biventricular dynamic physical phantom. *J Nucl Med* 2003; 44: 967-72.
15. Daou D, Van Kriekinge SD, Coaguila C et al. Automatic quantification of right ventricular function with gated blood pool SPECT. *J Nucl Cardiol* 2004; 11: 293-304.
16. Wright GA, Thackray S, Howey S, Cleland JG. Left Ventricular Ejection Fraction and Volumes from Gated Blood Pool SPECT: Comparison with Planar Gated Blood-Pool Imaging and Assessment of Repeatability in Patients with Heart Failure. *J Nucl Med* 2003; 44: 494-8.
17. Hacker M, Hoyer X, Kupzyk S et al. Clinical validation of the gated blood pool SPECT QBS processing software in congestive heart failure patients: correlation with MUGA, first-pass RNV and 2D-echocardiography. *Int J Cardiovasc Imaging* 2006; 22: 407-16.
18. De Bondt P, Nichols KJ, De Winter O et al. Comparison among tomographic radionuclide ventriculography algorithms for computing left and right ventricular normal limits. *J Nucl Cardiol* 2006; 13: 675-84.
19. Kim SJ, Kim IJ, Kim YS et al. Automatic quantification of right ventricular volumes and right ventricular ejection fraction with gated blood pool SPECT: Comparison of 8- and 16-frame gated blood pool SPECT with first-pass radionuclide angiography. *J Nucl Cardiol* 2005; 12: 553-9.
20. Germano G, Kiat H, Kavanagh PB et al. Automatic quantification of ejection fraction from gated myocardial perfusion SPECT. *J Nucl Med* 1995; 36: 2138-47.
21. Kim SJ, Kim IJ, Kim YS, Kim YK. Gated blood pool SPECT for measurement of left ventricular volumes and left ventricular ejection fraction: comparison of 8 and 16 frame gated blood pool SPECT. *Int J Cardiovasc Imaging* 2005; 21: 261-6.