

Application of the R0-R3 formulas using the ECToolbox software to calculate left ventricular ejection fraction in myocardial perfusion SPET and comparison with equilibrium radionuclide ventriculography. Normal cutoff values for a Chinese population

Wei Xia^{1,2*} MD, PhD,
Tong Zhu^{1*} PhD,
Jing Ni² MD,
Juhua Zhuang² MD,
Cuihua Hu² MD

1. College of Mechanical Engineering, Tongji University, Shanghai 200092, China

2. Department of Nuclear Medicine, Shanghai No. 7 People's Hospital, Shanghai 200137, China
 *Contributed equally to this work.

Keywords: ECToolbox software
 - Left ventricular ejection fraction
 - Myocardial perfusion SPET

Correspondence address:

Wei Xia, MD, PhD
 College of Mechanical Engineering,
 Tongji University, Shanghai
 200092, China
 E-mail: awingxia@hotmail.com

Received:

7 April 2013

Accepted revised:

12 May 2013

Abstract

The aim of this study was to compare the correlation and consistency of left ventricular ejection fraction (LVEF) obtained by ECG-gated myocardial perfusion SPET (GMPS) using the four formulas (R0-R3) in ECToolbox software and by equilibrium radionuclide ventriculography (ERNV), and determine the optimal diagnostic thresholds of the four formulas in a Chinese population. A hundred and three candidate donors (59 male and 44 female), including 38 patients with a history of myocardial infarction and 65 patients with suspected coronary heart disease, underwent both ^{99m}Tc-MIBI rest GMPS and technetium-99m red blood cells (^{99m}Tc-RBC) ERNV within a week. The LVEF values calculated by ECToolbox R0, R1, R2 and R3 were compared with those obtained by ERNV. Using LVEF \geq 50% obtained by ERNV as the gold standard, the optimal diagnostic thresholds of the four formulas (R0-R3) were assessed by receiver operating characteristic (ROC) curves. Results showed that the mean LVEF value of ERNV was 54.6 \pm 17.5%, and the mean LVEF value of the four formulas was 64.1 \pm 15.7%, 56.3 \pm 15.1%, 69.9 \pm 17.9% and 56.3 \pm 13.6%, respectively, showing a significantly strong correlation between the results obtained by the two methods ($r>0.85$, $P<0.001$). All mean LVEF values obtained by the four formulas were higher than the mean LVEF value obtained by ERNV, and there was very significant difference between R0 and R2 results and the ERNV result ($t=12.511$ and 18.652 , $P<0.001$). Furthermore, there was significant difference between R1 and R3 results and the ERNV result ($t=2.169$ and 2.570 , $P<0.05$). Using ERNV LVEF \geq 50% as the normal diagnostic value, the optimal diagnostic threshold of R0~R3 was 56.5%, 51.5%, 64.5% and 52.5%, respectively. There was a strong correlation between the LVEF values obtained by the four formulas in ECToolbox software and ERNV, but the numerical values of LVEF differed between the four formulas. In conclusion, A strong correlation was observed among R0, R1, R2 and R3 in the ECToolbox software when compared with ERNV and also between them for the assessment of LVEF. However, there were some differences in the numerical values of LVEF generated by the individual formulas, which must be taken into account in comparing clinical studies.

Hell J Nucl Med 2013; 16(2): 91-96

Epub ahead of print: 21 May 2013

Published on line: 20 July 2013

Introduction

Myocardial perfusion single photon emission tomography (SPET), (MPS) has been used increasingly as an important technique for the clinical diagnosis of cardiac function. Electrocardiography (ECG)-gated MPS (GMPS) is able to evaluate the left ventricular (LV) perfusion by a single imaging study, and analyze the LV function quantitatively by taking advantage of the software. ECToolbox software which is one of the most commonly used software for calculation of GMPS LV ejection fraction (LVEF) assumes that the LV is a 3D mixture of a semi-sphere and a cylinder to calculate thickening of the left ventricular wall according to the maximum myocardial radioactive counting at end-diastole and end-systole using Fourier analysis. Assuming the left ventricular wall thickness at end-diastole as 10mm, the outer radius of the internal and external membranes was calculated according to the thickening of the ventricular wall, based on which the borderline between the LV internal and external membranes was defined and parameters of LV function were calculated [1, 2].

The new edition (version 3.1) of ECToolbox provides four calculation formulas: R0, R1, R2 and R3. There are some differences between the LVEF values obtained by the four formulas. All these formulas have a normal data set against which the patient parameters are compared and gated results are obtained. As the database in these software programs is not based on a Chinese population, it is imperative to define normal limits using our patient population. However, there has not been a study reporting how to determine the

Table 1. The results of reproducibility obtained from five patients by repeated calculations of five observers using the four formulas

Patient	R0	CV	R1	CV	R2	CV	R3	CV	ERNV	CV
1	85.2±1.3	1.53	75.8±1.1	1.45	89.6±0.8	0.89	74.4±1.2	1.61	79.5±1.0	1.26
2	73.3±1.3	1.77	65.4±0.9	1.38	82.6±1.7	2.06	64.4±1.5	2.33	67.1±1.4	2.09
3	64.5±1.1	1.71	56.7±1.3	2.29	71.2±1.4	1.97	57.3±1.2	2.09	61.6±0.9	1.46
4	51.8±0.7	1.35	43.4±1.3	3.00	55.2±1.2	2.17	45.8±0.8	1.75	45.1±1.1	2.44
5	36.9±1.2	3.25	29.7±0.8	2.69	37.5±1.5	4.00	32.1±1.2	3.74	34.5±0.8	2.32

Table 2. LVEF values calculated by the four formulas in ECToolbox software using ERNV 50% as the dividing value of grouping

	<50%			≥50%		
	n	Mean±SD	Range	n	Mean±SD	Range
ERNV	66	35.3±9.0	21-49	66	65.5±10.1	50-89
R0	66	46.3±6.8	36-66	66	74.1±8.9	51-90
R1	66	39.2±6.5	29-58	66	65.9±8.6	44-84
R2	66	49.2±8.2	36-73	66	81.5±9.0	55-90
R3	66	41.2±5.8	32-58	66	65.3±7.8	45-82

Table 3. Paired analysis of the results (%) obtained by the four formulas and ERNV

	Mean value	SD	t
R0-ERNV	9.51	7.68	12.551**
R1-ERNV	1.65	7.74	2.169*
R2-ERNV	15.28	8.31	18.652**
R3-ERNV	2.04	8.07	2.570*

*P<0.05; **P<0.01

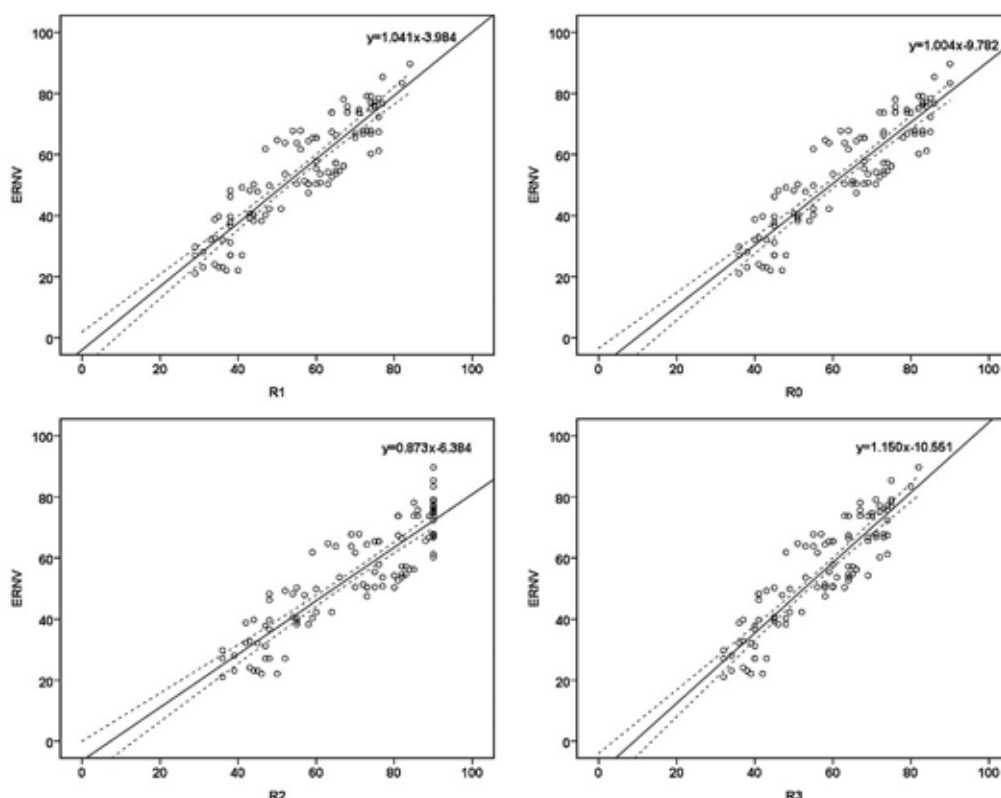
applicability of the four formulas. The report of Wang et al (2010) [3] compared R0, R1 and R2 only.

In this study, we compared the LVEF distribution obtained by the four formulas in ECToolbox software and the LVEF value obtained by equilibrium radionuclide ventriculography (ERNV), in an attempt to determine the most suitable LVEF thresholds calculated by the four formulas based on Chinese population.

Subjects and methods

Study population and ethics

Included in this study were 103 patients (59 male and 44 female) who underwent GMPS and ERNV between March 2012 and January 2013, who ranged in age from 37 to 84 years with a mean of 63.6±11.7 years.

**Figure 1.** Correlation analysis between LVEF values obtained by the four formulas and by ERNV.

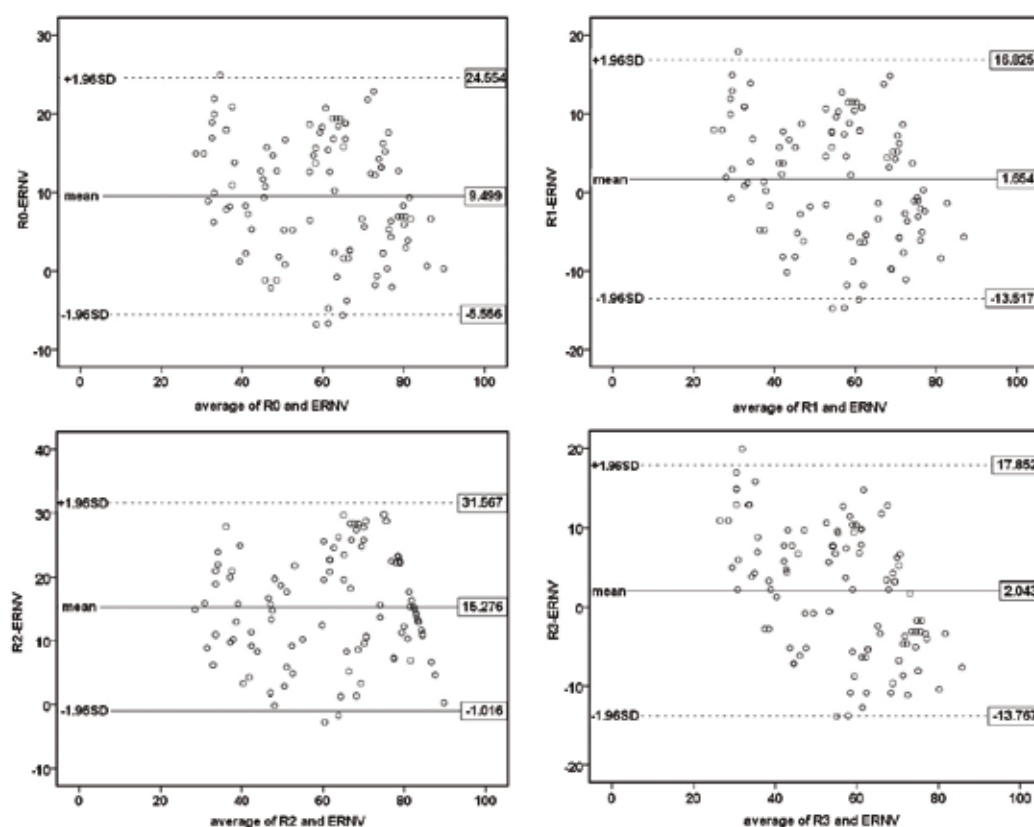


Figure 2. Bland-Altman plots showing the consistency between ECToolbox four formulas and ERNV.

Table 4. Thresholds of ECToolbox four formulas

	AUC value	SD	Threshold	Sensitivity (%)	Specificity (%)
R0	0.990	0.007	56.5	97.0	94.6
R1	0.990	0.007	51.5	95.5	97.3
R2	0.990	0.007	64.5	95.5	97.3
R3	0.990	0.007	52.5	95.5	97.3

The 103 patients included 38 patients with a history of myocardial infarction and 65 patients with suspected coronary heart disease. All patients underwent GMPS and ERNV within a week. Patients who developed acute myocardial infarction or unstable angina pectoris within the last three weeks, or received coronary artery revascularization or had valvular reflux within the previous 30 days were excluded from the study. The local Ethics Committee approved the study and all patients gave their informed consent.

^{99m}Tc-MIBI GMPS

Rest GMPS was performed 60min after the intravenous (i.v.) injection of ^{99m}Tc-MIBI 740MBq. Images were collected using Infinia Hawkeye SPET/CT (matrix 64X64) low-energy high-resolution collimator (GE, US), and by GMPS simultaneously. With the probe rotating 180°, a postural picture was taken per 3°. Each cardiac cycle was divided into 8 frames of equal duration, and each posture lasted 20sec. Images were reconstructed by the ordered subset expectation maximization (OSEM) method. Tomographic images were reconstructed by Butterworth. The cutoff frequency was 0.4, and the steepness factor was 10.

^{99m}Tc-RBC ERNV

Equilibrium radionuclide ventriculography was performed

20min after the i.v. injection of stannous pyrophosphate until it was equilibriumally mixed with the subsequent i.v. injection of the eluent of 740MBq ^{99m}TcO₄⁻. Images were acquired in a 64X64 matrix of 32 gated frames using Infinia Hawkeye SPET/CT low-energy high-resolution collimator (GE, US). The data from the ERNV were acquired and stored in ECG-gated frame mode. Studies with rejected beats greater than 10% of the total were excluded from the analysis.

Image treatment and analysis

The collected images were treated and analyzed on Xeleris workstation (version 3.0). Gated myocardial perfusion SPET LVEF image treatment was performed by the four formulas (R0-R3) in ECToolbox software (version 3.1). The ERNV LVEF image treatment was performed using the blood pool analysis system provided by Xeleris workstation. Left ventricular ejection fraction of ≥50% obtained by ERNV was regarded as the normal reference.

Reproducibility test

Five GMPS and ERNV images were selected randomly and treated by the same doctor who was blind to the experiment, for five times, to analyze consistency.

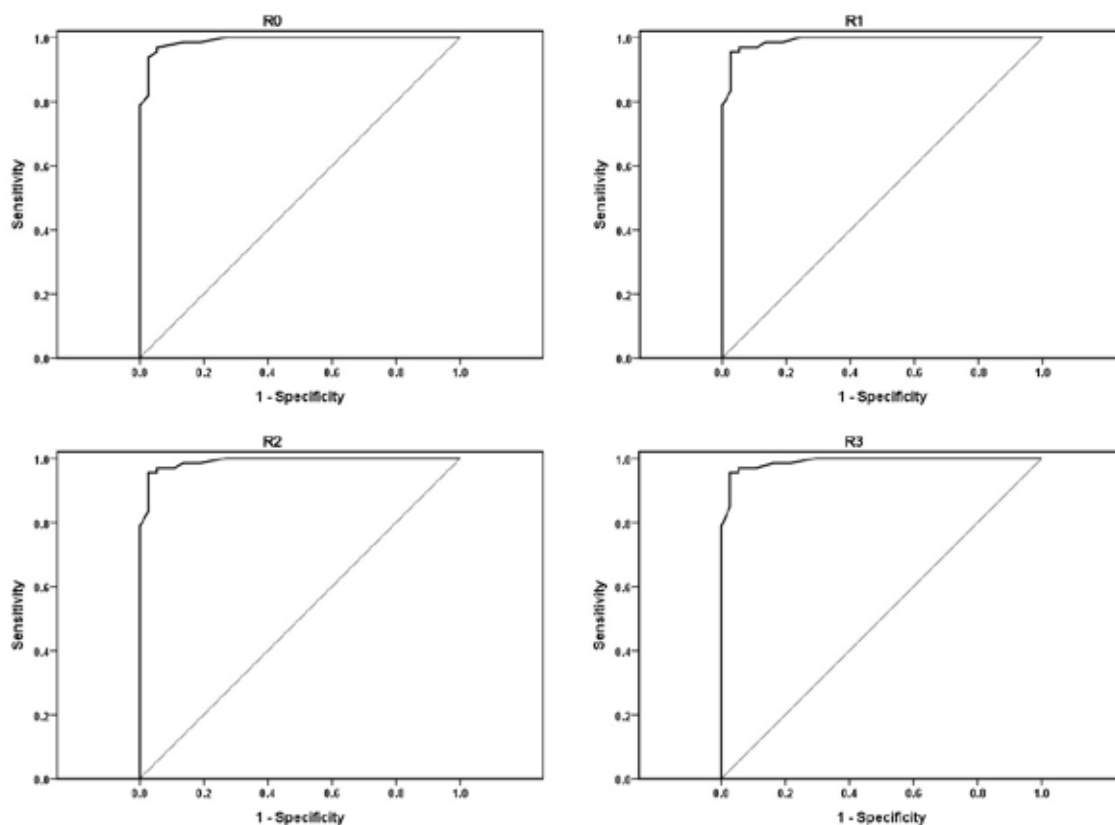


Figure 3. ROC curves obtained by ECToolbox four formulas using ERNV LVEF 50% as the threshold.

Statistical analysis

Statistical analysis was performed using SPSS 18.0. All data are expressed as $\bar{x} \pm s$. Consistency of the observer was examined by coefficient of variation. Correlation analysis was verified by Pearson test. Consistency of image analyses was verified by Bland-Altman method. R0~R3 LVEF dividing values were obtained by ROC curves with reference to ERNV LVEF $\geq 50\%$.

Results

Reproducibility of ECToolbox software

The LVEF values repeatedly obtained by the observer showed good reproducibility with a CV <5% (Table 1).

LVEF results of ERNV

The mean LVEF value of the 103 patients calculated by ERNV was $54.6 \pm 17.5\%$ (median: 55%, range: 21%-89%), and the mean LVEF value calculated by R0, R1, R2 and R3 was $64.1 \pm 15.7\%$ (median: 67%, range: 36%-90%), $56.3 \pm 15.1\%$ (median: 59%, range: 29%-84%), $69.9 \pm 17.9\%$ (median: 75%, range: 36%-90%), and $56.7 \pm 13.6\%$ (median: 59%, range: 2%-82%), respectively.

Of the 103 patients, ERNV LVEF value was <50% in 37 patients, and $\geq 50\%$ in 66 patients. LVEF values calculated by the four formulas in ECToolbox software are shown in Table 2.

Comparison of LVEF values between ECToolbox and ERNV

Correlation analysis showed good correlation between LVEF values obtained by the four formulas and those obtained by ERNV (R0-ERNV: $r=0.899$, $P<0.001$; R1-ERNV:

$r=0.898$, $P<0.001$; R2-ERNV: $r=0.890$, $P<0.001$; R3-ERNV: $r=0.895$, $P<0.001$) (Fig. 1). Paired t test showed that there were some differences between the mean LVEF values obtained by R0~R3 and the mean LVEF value obtained by ERNV (Table 3). There was very significant difference between the results obtained by R0 and R2 and those obtained by ERNV ($t=12.511$ and 18.652 , $P<0.001$), and there was significant difference between the results obtained by R1 and R3 and those obtained by ERNV ($t=2.169$ and 2.570 , $P<0.05$). Bland-Altman plots showed the 95% CI range of LVEF difference obtained by the four formulas was similar to that obtained by ERNV, but the difference in the mean value of LVEF obtained by R1 and R3 and that obtained by ERNV was near zero (Fig. 2).

Assessment on LVEF thresholds obtained by the four formulas and ERNV

Using ERNV LVEF $\geq 50\%$ as the gold standard, the optimal threshold of R0~R3 was 56.5%, 51.5%, 64.5% and 52.5% respectively as shown by the ROC curves. Analysis of the area under the curve (AUC) of LVEF obtained by each formula showed that the mean AUC was 0.99 (Table 4, Fig. 3).

Comparison of ECToolbox four formulas

The result of two-two correlation analysis of the LVEF values obtained by R0~R3 showed a good correlation between the results of the four formulas (all $r>0.99$). Further paired t test showed that there was significant difference between R1 and R3 ($t=2.281$, $P=0.025<0.05$), and there was very significant difference between the other formulas (R1: $t=106.024$, $P<0.001$; R0-R2: $t=19.9160$, $P<0.001$; R0-R3: $t=33.530$, $P<0.001$; R1-R2: $t=39.936$, $P<0.001$; R2-R3: $t=28.267$, $P<0.001$).

Discussion

The aims of this study were: a) to correlate the LVEF obtained on rest-gated SPET using four formulas in ECToolbox software with LVEF obtained on ERNV at rest, which is considered the reference standard for the calculation of LVEF; b) to intercompare the LVEFs obtained by different formulas and c) to set a cutoff value for LVEF obtained using different formulas in our patient population.

The initial study of Faber et al (1999) [4] showed that the success rate of ECToolbox automatically mapping out the LV internal and external membranes was 96%, showing a good correlation with the MR phenomenon and first-pass RNA. Later studies reported that LV parameters calculated by ECToolbox had a good correlation with the MRI result [5-7], and with the result of cardiac blood pool imaging as well [8-10]. As ECToolbox assumes the thickness of the LV wall at end-diastole as 10mm, error may occur when there is a LV wall tumor or myocardial hypertrophy causing thickening or thinning of the ventricular wall. Other studies have found that ECToolbox usually over-rates LVEF as compared with heart MRI or cardiac blood pool imaging [5, 8]. Similarly, in our study we noted the LVEF values obtained by all formulas of ECToolbox software were higher than that obtained by ERNV.

All these LVEF calculations were based on the original R0 formula, but version 3.1 ECToolbox software has three more R1~R3 formulas for verification. Of the four formulas in ECToolbox software, R0 is the original formula established on the basis of the heart model; R1~R3 are progression equations of R0; R1 and R3 are obtained on the basis of comparison of LVEF values as calculated by ECToolbox and Cedars Sinai Quantitative Gated SPET (QGS) programs, of which R1 is calibrated according to QGS images of the 8 frames of each cardiac cycle, and R3 is calibrated according to QGS images of the 16 frames of each cardiac cycle, where the equation for LVEF calculation is: $y=0.96x-0.53$ and $y=0.885x+0.0173$, respectively. R2 is the result of comparison between ECToolbox and GMPS images, where the equation is $y=1.22x-0.072$. It was found in clinical practice that there were relatively large differences in LVEF values calculated by the four formulas. Wang et al (2010) [3] assessed the LVEF measured by three of the four formulas in ECToolbox software in correlation with ERNV in 64 patients with ischaemic heart disease or hypertension. They showed that there was good correlation between the LVEF values measured by the three formulas and those measured by ERNV ($P<0.05$). They also found that the three formulas overestimated LVEF in varying degrees, and the LVEF values of R1 and ERNV revealed no significant differences ($P<0.05$), whereas R0 and R2 yielded significantly higher values compared with ERNV ($P>0.05$). However, this report did not study the R3 formula and moreover, did not analyse the normal cutoff values of LVEF of R0, R1 and R2.

Few studies [8, 11] have compared the LVEF values of cardiac software programs with ERNV. Ballal et al (2012) [8] reported a strong correlation of ECToolbox, QGS, 4D-MSPECT and Myometrix software programs with ERNV for the assessment of LVEF. In the above study, there were some differences in the objective values and the normal cutoff values of LVEF generated by individual software, for clinical studies. Similar findings were suggested by other researchers [11], who found that the LVEF values obtained by the ECToolbox

or QGS were significant correlation with gated cardiac blood pool scan (GCBPS), they are significantly different and not interchangeable with gated cardiac blood pool scan (GCBPS) results. In our study good correlation between LVEF values obtained by the ECToolbox software and by ERNV was also found. The authors compared only LVEF values obtained from the different software, however, they were not concerned about the four formulas of the same software ECToolbox.

The higher LVEF values calculated by the four R0-R3 formulas than by ERNV, that we found in this study could be explained by differences in the operation of software algorithms. The mean value of LVEF obtained by R1 was closest to that obtained by ERNV as others have also reported [3]. Ours was the only study that compared the mean LVEF of all four R0-R3 formulas with those of the ERNV.

In the present study, we also found that the width of Bland-Altman limits of LVEF for all four formulas was similar with that of ERNV indicating that the LVEF values for the four formulas seemed to similarly disperse around the ERNV values.

The cutoff values derived by the ROC analysis were 56.5, 51.5, 64.5 and 52.5% for R0, R1, R2 and R3, respectively. The area under the curve (AUC) value for each formula was high and not different between algorithms, indicating high sensitivity and specificity of each of the formulas. Correlation analysis showed a strong correlation between the LVEF values calculated by the four formulas, which is consistent with the fact that R1, R2 and R3 all come from the regression equation of R0. However, two by two correlation analysis of these four formulas showed that there was significant difference in LVEF values, indicating that the values calculated by the four formulas should not be used randomly. The same formula should be used in the follow-up of the same patient. The differences in the objective values of LVEF generated by the individual formulas can be explained by the different regression coefficient used in the linear equations for each formula. In addition, whether or not the LVEF is normal should not be judged by its 50% value only; rather, a different threshold should be selected when a different formula is used. We can conclude that similar results can be obtained from each formula, keeping in mind the different threshold values. To the best of our knowledge this study is the first to derive the normal cutoff values in a Chinese population for all these four formulas.

In conclusion, we found a high degree of correlation between all four formulas R0-R3 of the ECToolbox and equilibrium radionuclide ventriculography. We also found a good correlation when software packages were compared with each other. However, there were some differences in the objective values of left ventricular ejection fraction (LVEF) generated by individual formulas, which must be taken into account for clinical studies and use only the same formula in the same patient for comparison. The normal cutoff values for the derived LVEF were 56.5, 51.5, 64.5 and 52.5% for R0, R1, R2 and R3, respectively, as measured for the first time in a Chinese population. These cutoff values can be taken into account when reporting LVEF by the different formulas in clinical practice.

Acknowledgement

We thank Prof. Zhi-bin Yuan for helpful discussions and suggestions in this study.

The authors declare that they have no conflicts of interest.

Bibliography

1. Garcia EV, Santana CA, Faber TL et al. Comparison of the diagnostic performance for detection for coronary artery disease (CAD) of their program (QPS) with that of the Emory Cardiac Toolbox (ECToolbox) for automated quantification of myocardial perfusion. *J Nucl Cardiol* 2008; 15: 476-8.
2. Kakhki VR, Zakavi SR, Sadeqhi R et al. Comparison of two software in gated myocardial perfusion single photon emission tomography, for the measurement of left ventricular volumes and ejection fraction, in patients with and without perfusion defects. *Hell J Nucl Med* 2007; 10: 19-23.
3. Wang TS, Zhao JH, Xing Y. Application of ECToolbox software in evaluation of left ventricular ejection fraction. *Chin J Med Imaging Technol* 2010; 26: 330-2.
4. Faber TL, Cooke CD, Folks RD et al. Left ventricular function and perfusion from gated perfusion images: an integrated method. *J Nucl Med* 1999; 40: 650-9.
5. Wang F, Zhang J, Fang W et al. Evaluation of left ventricular volumes and ejection fraction by gated SPET and cardiac MRI in patients with dilated cardiomyopathy. *Eur J Nucl Med Mol Imaging* 2009; 36: 1611-21.
6. Guterberlet M, Mehs S, Froelich M et al. Determination of ventricular volumes in coronary artery disease: comparison of two gated SPET analysis tools with MRI. *Nuklearmedizin* 2006; 45: 63-73.
7. Tsuboi K, Fuse H, Sasaki M. Evaluation of left ventricular volumes and ejection fraction by gated myocardial perfusion SPECT versus cardiac MRI. *Nihon Hoshasen Gijutsu Gakkai Zasshi* 2011; 67: 1304-13.
8. Ballal S, Patel CD, Singla S et al. Comparison of software programs for the assessment of left ventricular ejection fraction using ^{99m}Tc -tetrofosmin-gated SPECT/CT: correlation with equilibrium radionuclide ventriculography in the Indian population. *Nucl Med Commun* 2012; 33: 1160-8.
9. Kiratli PO, Bozkurt MF. Assessment of cardiac parameters using gated myocardial perfusion and echocardiography in children. *Cardiol Young* 2009; 19: 53-9.
10. Harisankar CN, Mittal BR, Kamaleshwaran KK et al. Reliability of left ventricular ejection fraction calculated with gated myocardial perfusion single photon emission computed tomography in patients with extensive perfusion defect. *Nucl Med Commun* 2011; 32: 503-7.
11. Yap KS, Cherk M, Van Every B et al. Comparison of contemporaneous left ventricular ejection fraction (LVEF) obtained from planar gated cardiac blood pool scans (GCBPS) and Tl-201 gated myocardial perfusion scans (MPS) using a novel solid state dedicated cardiac camera. *J Nucl Cardiol* 2013; in press, doi:10.1007/s12350-013-9693-3.



Grandma Moses (USA): *The medical physician* (1950). Gallery St. Etienne, New York