Equilibrium radionuclide angiography: Present and future

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This editorial refers to the article published by Sachpekidis et al¹ titled 'Equilibrium radionuclide angiography (ERNA): intra- and interobserver repeatability and reproducibility in the assessment of cardiac systolic and diastolic function' on the *Journal of Nuclear Cardiology*. The objective of this study was to assess the intra- and interobserver agreement in assessing the systolic and diastolic function with ERNA. The authors analyzed thirty-two adults underwent baseline and repeat ERNA. An experienced and a trainee operator analyzed the data by assigning regions of interest manually, fully automatically, and semi-automatically. The Bland–Altman statistic was used to assess the repeatability (two different assessments of a single acquisition) and reproducibility (assessments of two different acquisitions). According to the obtained results, the Authors concluded that: 'A good repeatability but a moderate reproducibility was found in the assessment of the left ventricular ejection fraction (LVEF). Less good were the findings in the assessment of diastolic function. The results also depended on the software tool'.

This article provides interesting information about the intra- and interobserver repeatability and reproducibility in the assessment of cardiac systolic and diastolic function. Despite the fact that in the conclusions of this study the authors say that ERNA has a moderate reproducibility in the assessment of the LVEF; ERNA continues to be one of the best imaging techniques for the analysis of ventricular function. The analysis of the variability in the measurements of a technique is complex and not only depends on of the intra- and interobserver variability, but of other variabilities that are not generally taken into account, such as the day-to-day variability of the phenomenon studied, the variability of the pathology, age, gender, etc. In addition to this research study, it has a very heterogeneous population (men = 20, women = 12, heart failure = 13, cardiotoxic chemotherapy = 12, different degree of systolic dysfunction) in a small (n = 31) number of patients. Table 1 shows the reproducibility, and inter- and intra-observer variations of ERNA according to different acquisition methodology to evaluate left and right ventricular function.^{1–7} ERNA has a high reproducibility, very low inter- or intra-observer variability, and high precision; it has been shown to be accurate when compared to other modalities and has strong early data that demonstrated efficacy in guiding the safety of treatment regimens, and it continues to be widely used for routine clinical monitoring.⁸ This information is consistent with the comments of Sachpekidis et al.⁹ in a previous review. Haarmark et al¹⁰ evaluated 463 subjects without diabetes, previous potentially cardiotoxic chemotherapy, known cardiovascular or pulmonary disease, by means of Cadmium Zinc Telluride (CZT) SPECT camera. They conclude that there are age-related changes in cardiac dimensions with age depending on gender, although with only

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Table 1. Reproducibility, inter- and intra-observer variations of equilibrium radionuclide angiography

Author	Year	N	Population	Acquisition methodology	Reproducibility, inter- and intraobserver variations
Sachpekidis et al ¹	2019	32	Heart failure (n = 13), diabetes mellitus (n = 7), potentially cardiotoxic chemotherapy (n = 12)	Manual Planar-ERNA Automated Planar-ERNA (for experienced physician and experienced trainee)	Lin's concordance correlation coefficient: Experienced physician Intraobserver repeatability, automated method: LVEF, 0.99 PFR, 1 TPF, 0.99 1/3 FF, 0.99 RVEF (manual method), 0.96 Intraobserver reproducibility, automated method: LVEF, 0.91 PFR, 0.16 TPF, 0.11 1/3 FF, 0.65 RVEF (manual method), 0.83 (for experienced trainee see manuscript) Intra-class correlation coefficient: Reliability between t-ERNA and MDCT for: LVEDV, 0.900 LVESV, 0.911 LVEF, 0.765 RVEDV, 0.728 RVEDV, 0.875 RVEF, 0.781
Lairez et al ²	2018	24	Patients with left ventricular assist devices	2D-Trans thoracic echocardiography Planar- and Tomographic-ERNA Multidetector Computed Tomography	Intra-class correlation coefficient: MRI, interobserver reproducibility, 0.96 ERNA, interobserver reproducibility, 0.94 Linear correlation: LVEF, Planar vs CZT, $r^2 = 0.84$ LVEF, CZT vs Nal-SPECT, $r^2 = 0.95$ LVEF, Nal-SPECT vs Planar, $r^2 = 0.48$ LVEDV, CZT vs Nal-SPECT, $r^2 = 0.75$ LVESV, CZT vs Nal-SPECT, $r^2 = 0.79$ Coefficients of variance intraobserver-variation: LVEF, Planar Nal, mean between observers = 3.4 LVEF, SPECT-Nal, mean between observers = 3.6 LVEF, CZT-SPECT-Nal, mean between observers = 2.4 LVESV, SPECT-Nal, mean between observers = 11.5 LVESV, CZT-SPECT, mean between observers = 3.5 LVEDV, SPECT-Nal, mean between observers = 16.3 LVEDV, CZT-SPECT, mean between observers = 3.2 Coefficients of variance interobserver-variation: LVEF, Planar Nal, mean between observers = 4.85 LVEF, SPECT-Nal, mean between observers = 5.2 LVEF, CZT-SPECT-Nal, mean between observers = 3.05 LVESV, SPECT-Nal, mean between observers = 15.1 LVESV, CZT-SPECT, mean between observers = 5.15 LVEDV, SPECT-Nal, mean between observers = 8.65 LVEDV, CZT-SPECT, mean between observers = 3.95
Kotha et al ³	2018	124	Patients referred for assessment of ICD implantation	ERNA Cardiac MRI	
Jensen et al ⁴	2014	82	Patients with BMI < 35 referred for assessment of LVEF were included	ERNA: 3 different camera types: Planar 2D camera with a Nal crystal (Planar Nal) Dedicated cardiac SPECT camera with Nal crystals (tomographic Nal) Dedicated cardiac SPECT camera using the CZT detector system (tomographic CZT)	

Table 1. continued

Author	Year	N	Population	Acquisition methodology	Reproducibility, inter- and intraobserver variations
Daou et al ⁵	2006	10	Chronic coronary artery disease	SPECT ERNA with SPECT-QBS SPECT ERNA with SPECT-35% Planar ERNA	LVEF: The repeatability coefficient with SPECT-35% was slightly lower than that with planar ERNA. Both were substantially lower than that with SPECT-QBS. The within subject coefficient of variation for SPECT-QBS was estimated to be 3.835 times higher than that for planar ERNA and 6.322 times higher than that for SPECT-35% Linear regression analysis LVEF, $r = 0.99$ LVESV, $r = 0.99$ LVEDV, $r = 0.99$ RVEF, $r = 0.99$ RVESV, $r = 0.99$ RVEDV, $r = 0.99$
Clements et al ⁶	2006	35	Heterogeneous population	EBCT SPECT ERNA	
Van Reet et al ⁷	1984	93	Within 48 hours and at 10 days after acute myocardial infarction	Two-dimensional echocardiography Planar ERNA	Linear regression analysis LVEF, $r = 0.82$ (and did not change from the first 48 hours to 10 days after infarction)

BMI, body mass index; CZT, cadmium-zinc-telluride; EBCT, electron beam computed tomography; ERNA, equilibrium radionuclide angiography; ICD, implantable cardioverter defibrillators; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; MRI, magnetic resonance imaging; PFR, peak filling rate; RVEDV, right ventricular end-diastolic volume; RVEF, right ventricular ejection fraction; RVESV, right ventricular end-systolic volume; TPF, time to peak filling; 1/3 FF, first third filling fraction

Figure 1. Relationship between the number of tomographic equilibrium radionuclide angiography (ERNA) and SPECT myocardial perfusion imaging (MPI) studies over a 10-year period at the Nuclear Cardiology Department of Vall d'Hebron Hospital, Barcelona, Spain.

limited influence on left ventricular ejection fraction or right ventricular ejection fraction. There is a decrease in ventricular volumes and a slight increase in left ventricular ejection fraction in women with advancing age.

There are many different nuclear techniques¹¹ for measuring ventricular function including ERNA referred to also as gated bloodpool scan or multigated angiography (MUGA), first-pass radionuclide ventriculography, gated single-photon computed tomography (SPECT) with myocardial perfusion imaging, SPECT ERNA, gated PET MPI, gated PET ¹⁸F-FDG, and gated first-pass ¹⁸F-FDG PET.^{11,12} Is true that studies of quantitative echocardiography, cardiac magnetic resonance and cardiac computed tomography, to assess ventricular function, are becoming more frequent. Although this does not mean that these imaging techniques will replace ERNA as they do not have a better ventricular functional assessment; ERNA continues to be widely used for routine clinical monitoring.⁸

At present, conventional planar ERNA has recently gained less favor due to the growing concern of radiation exposure (740 MBq; 5.18 mSV) to patients.^{13,14} As Giubbini et al¹¹ explain, planar imaging is limited by the overlap of different cardiac structures affecting the calculation of LVEF, especially in the presence of mitral regurgitation, the valvular function cannot be explored, and the volumes of heart chambers are only roughly

determined. Though, when compared to planar image acquisition, SPECT ERNA acquired with high-sensitivity CZT cameras can be done with lower radiation dose, faster image acquisition time, and improved reproducibility.^{4,8,11,15} Several studies have been published indicating that tomographic MUGA as a potential replacement for the planar MUGA.^{4,5,16,17} In addition, there may be a tendency to decrease the number of ERNA. For example, Beller¹⁸ commented in an editorial that, at the University of Virginia, a total of 3302 SPECT studies, and 347 MUGA studies, were performed in 2006. By 2017, the number of SPECT and MUGA procedures had decreased to 2021 and 103, respectively. However, this decrease in SPECT MPI was attenuated by the performance of 365 PET MPI studies in 2017. Similar results we obtained in our Nuclear Cardiology Department from Universitari Vall d'Hebron Hospital, Barcelona, Spain. A total of 16,943 SPECT studies, and 7815 SPECT ERNA studies were performed between 2008 and 2018. In Figure 1, we observed a reduction in the number of ERNA studies between 2008 and 2011, and between 2013 and 2018. This evolution of the image occurs because the new imaging techniques allow other parameters to be assessed simultaneously and with less or without irradiation, but not because they are significantly better than ERNA in evaluating ventricular function.

Table 2. Ventricular function validation using equilibrium radionuclide angiography

	Year	N	Population	Validation	Reference standards	Results
Ben Bouallègue et al ²⁸	2019	24	Oncologic patients	Gated first-pass ¹⁸ F-FDG cardiac PET	ERNA	LVEF, CCC = 0.81 PET reproducibility, CoV = 2 ± 1%, ICC = 0.97 ERNA reproducibility, CoV = 3 ± 2%, ICC = 0.92
Liu et al ¹³	2019	20	Subjects	Low-dose gated bloodpool SPECT	ERNA	LVEF, linear correlation, $r^2 = 0.68$ to 0.83 EDV, linear correlation, $r^2 = 0.55$ to 0.67 ESV, linear correlation, $r^2 = 0.85$ to 0.88 PFR, linear correlation, $r^2 = 0.49$ to 0.69 100% projections times, LVEF, $r^2 = 0.87$ 30% projections times, LVEF, $r^2 = 0.85$
Tissot et al ²⁹	2019	73	Cardiomyopathy (n = 23) chemotherapy monitoring (n = 50)	CZT-SPECT with 100% and 30% projections times.	ERNA	
Pelletier-Galarneau et al ³⁰	2018	60	Ischemic cardiomyopathy (n = 32) Dilated cardiomyopathy (n = 12) Without cardiomyopathy (n = 16)	IQ-SPECT system cMRI	ERNA	LVEF, Pearson correlation coefficients between planar and QBPS LVEF measurements were 0.70, and 0.83 with QBS and MHI, respectively Correlation coefficients between cMRI and GBPS LVEF were 0.52 and 0.65 with QBS and MHI, respectively EDV, correlation coefficients between cMRI and GBPS EDV were 0.80 with both QBS and MHI ESV, correlation coefficients between cMRI and GBPS ESV were 0.73 and 0.80 with for QBS and MHI, respectively
Chen et al ³¹	2016	48	Heterogeneous population	CZT-SPECT	ERNA (Nal-planar) cMRI TD	LVEF, CZT-SPECT, correlation, $r = 0.93$ LVEF, CZT-repro, correlation, $r = 0.93$ RVEF, cMRI reference: BP-SPECT, $r = 0.42$ QBS, $r = 0.30$ TOMPOOL, $r = 0.42$ RVEDV, cMRI reference: BP-SPECT, $r = 0.69$ QBS, $r = 0.77$ TOMPOOL, $r = 0.81$ RCO, TD reference: BP-SPECT, $r = 0.73$ QBS, $r = 0.72$ TOMPOOL, $r = 0.85$
Dercle et al ³²	2015	48	Heterogeneous population Dilated non-ischemic (n = 17)	Gated blood pool SPECT: BP-SPECT QBS TOMPOOL		Correlation of LVEF between: ERNA and gated blood pool SPECT, $r = 0.92$ ERNA and MPI gated SPECT, $r = 0.85$ ERNA and F-FDG gated PET, $r = 0.76$ ERNA and 2D echocardiography, $r = 0.52$ EF, linear correlation, $r = 0.94$ EDV, linear correlation, $r = 0.86$ PFR, linear correlation, $r = 0.91$
Raja et al ³³	2014	41	Coronary artery disease with LVEF < 35%	Gated blood pool SPECT MPI gated SPECT F-FDG gated PET 2D echocardiography	ERNA	
Wells et al ³⁴	2013	48	Heterogeneous population	Dedicated cardiac SPECT camera	Gated blood-pool imaging	

Table 2 continued

Year	N	Population	Validation	Reference standards	Results
2000	62	Patients with an earlier myocardial infarction and severe perfusion defects	Gated SPECT-Tc-99m	ERNA	EDV, correlation, $r = 0.882$ ESV, correlation, $r = 0.954$

Chua et al²⁵

Ccc, concordance; cMRI, cardiac magnetic resonance imaging; CoV, coefficient of variation; CZT, cadmium-zinc-telluride; EDV, end-diastolic volume; EF, ejection fraction; ERNA, equilibrium radionuclide angiography; ESD, end-systolic volume; GBPS, gated blood pool SPECT; ICC, intra-class correlation; MHI, software (Montreal Heart Institute, Montreal, Canada); PFR, peak filling rate; QBS, software (Cedars-Sinai Medical Center, Los Angeles, USA); RCO, right cardiac output; RVEDV, right ventricular end-diastolic volume; RVEF, right ventricular ejection fraction; TD, Catheter measurements from thermodilution. Three algorithms to evaluated right ventricle function on Gated blood pool SPECT: BP-SPECT, QBS, TOMPOOL

Currently, ERNA is used to: (A) quantify left ventricular and right stroke volumes and ejection fractions in patients with moderate to severe tricuspid regurgitation,¹⁹ (B) obtain measures of dyssynchrony to predict outcomes in heart failure patients,²⁰⁻²³ (C) assess left ventricular function and mechanical dyssynchrony in patients with right ventricular outflow tract pacing and right ventricular apical pacing,²⁴ (D) study the accuracy of automated LVEF measurements in the presence of large perfusion defects in a myocardial infarction, in which the estimation of endocardial borders might be expected to be difficult because of reduced or absent counts, requiring some degree of extrapolation with a geometric model,^{25,26} (E) evaluate left and right ventricular volumes and function in patients with left ventricular assist devices,² (F) analyze the left and right ventricular function after surgical repair of Tetralogy of Fallot,²⁷ (G) validate (Table 2) the ventricular function assessment by other imaging techniques,^{13,25,28-34} and (H) analyze left and right ventricular function before lung transplant (Figure 2).

Furthermore, in oncologic patients treated with chemotherapy, ERNA is a good imaging technique to detect systolic dysfunction through left and right ventricular ejection fraction analysis. Small changes in LVEF may be important in clinical decision-making,^{8,11} and added to low inter- and intra-observer variability of ERNA, it is ideal for cardiac monitoring cardiac conditions.⁸ Thus, ERNA serves to guide therapy of oncologic patients.⁸ In addition, the measures of diastolic left ventricular dysfunction by means of ERNA can precede systolic dysfunction in chemotherapies and provide a more sensitive and specific predictor of long-term chemotherapy-induced heart failure.³⁵

The occurrence of right ventricular dysfunction is a well-known indicator of poor prognosis in patients with chronic cardiopulmonary disease.³⁶ Selimovic et al³⁶ performed a retrospective analysis of lung transplant candidates (n = 152) who had undergone ERNA, to determine baseline and exercise right ventricular ejection fraction. The authors concluded that in lung transplant candidates, right ventricular function during exercise is a stronger predictor of outcome than right ventricular function at rest. Right ventricular ejection fraction during exercise assessed by ERNA could be incorporated into priority-based allocation algorithms for lung transplant.

CONCLUSION

In conclusion, ERNA continues to be a valid method for the analysis, validation and monitoring of left and right ventricular systolic and diastolic function in several clinical settings. It is a reference standard for

Figure 2. Example of left (A) and right (B) ventricular function assessment before lung transplant, from Nuclear Cardiology Department of Vall d'Hebron Hospital. *ED*, time to diastole; *ES*, time to systole; *LVEF*, left ventricular ejection fraction; *PER*, peak ejection rate; *PFR*, peak filling rate; *PEP*, end of pre-ejection period; *RFT*, recovery filling time; *RVEF*, right ventricular ejection fraction.

the evaluation of ventricular function as well as cardiac magnetic resonance; and tomographic ERNA probably has advantages and the potential to replace planar ERNA. Finally, we recognize the effort, enthusiasm and the complex statistical analysis of Sachpekidis, and the rest of the authors in the preparation of this research work.¹

Disclosure

The authors have no conflict of interest and nothing to disclose.

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