Editorial

Nuclear Medicine Communications

Gated cardiac SPECT: can it be used for serial assessment of left ventricular function in oncology patients?

Penelope J. Thorley[a], Meg Bould[b] and Fahmid U. Chowdhury[b,c]

Nuclear Medicine Communications 2013, **34**:1137–1140

Departments of [a]Medical Physics, [b]Nuclear Medicine and [c]Clinical Radiology, Leeds Teaching Hospitals NHS Trust, Leeds, UK

Correspondence to Fahmid U. Chowdhury, MRCP (UK), FRCR, Department of Nuclear Medicine, St James's University Hospital, Bexley Wing, Level 1, Beckett Street, Leeds LS9 7TF, UK
Tel: +44 113 2068212; fax: +44 113 2068228;
e-mail: fahmid.chowdhury@leedsth.nhs.uk

Received 30 April 2013 **Accepted** 27 August 2013

Use of cardiotoxic chemotherapeutic drugs in oncology, both in clinical routine and in pharmacological research trials, requires regular monitoring of left ventricular ejection fraction (LVEF) [1]. It has been well recognized for over four decades that anthracycline chemotherapy can cause cumulative dose-dependent cardiac toxicity, which is mediated by direct and irreversible cellular damage to myocytes that can result in congestive heart failure and even cardiac death [2]. One of the most significant advances in medical oncology in recent years has been the routine use of the monoclonal antibody trastuzumab (Herceptin) in patients with HER2-receptor-positive early breast cancer [1,3–5]. Approximately 20% of all early breast cancer patients show overexpression of HER2 receptors, and the use of trastuzumab in the postsurgical (adjuvant) setting in these patients has been shown to reduce the risk of recurrence by 50% [4,5]. However, some early trials on the use of trastuzumab in patients with metastatic HER2-positive breast cancer, who had also received anthracycline and cyclophosphamide treatment, showed an unexpectedly high incidence of cardiac toxicity of up to 27% [3]. The pivotal HERA trial and related follow-up studies into adjuvant trastuzumab have subsequently shown that the incidence of symptomatic heart failure and asymptomatic reduction in LVEF (the long-term clinical significance of which remains unclear) is actually considerably lower, occurring in 1–2% and 7–10%, respectively [4–6]. It is also now recognized that cardiotoxicity associated with trastuzumab, in contradistinction to the cardiac effects of anthracycline chemotherapy, is idiosyncratic, not dose-dependent and reversible, in the majority of cases.

Currently, the most common indication for serial assessment of LVEF in the clinical setting is in early breast cancer patients undergoing trastuzumab therapy. This has previously been performed in an inconsistent and arbitrary manner based on trial protocols and results that were not directly comparable. The increasing recognition and greater understanding of trastuzumab-related cardiac toxicity has led to recommendations by the National Cancer Research Institute for the monitoring of LVEF in trastuzumab-treated patients with breast cancer [1]. These guidelines have simplified the algorithm for evaluation of cardiac function by recommending LVEF measurement at baseline before trastuzumab therapy and then at routine intervals of 4 and 8 months. The requirements for using the same monitoring modality (i.e. echocardiography or a radionuclide technique) and establishing institution-specific and modality-specific lower limits of normal (LLN) for LVEF have been re-emphasized. Trastuzumab can be initiated in patients with an LVEF greater than the LLN, and during monitoring the key nodal points for medical intervention (e.g. cardiology referral and commencement of cardioprotective therapy such as ACE inhibitors) and/or early re-evaluation (at 6–8 weeks) are (a) decrease in LVEF to less than 40% (considered to represent biologically important left ventricular systolic dysfunction), (b) decrease in LVEF below the LLN but LVEF remaining greater than 40% and (c) decrease in LVEF by 10 ejection fraction (EF) points or higher [1]. Therefore, any imaging test that can be shown to reproduce LVEF measurement effectively enough to identify these categories of patients can theoretically be used for serial monitoring of cardiac function during trastuzumab therapy.

Of the different methods that are available for serial assessment of LVEF, transthoracic echocardiography is recommended in patients who have clinical signs or symptoms of cardiac dysfunction at baseline, for example, abnormal ECG, as echocardiography provides additional structural and functional information, such as valvular function, pulmonary artery pressure and right ventricular function. Further, the technique does not involve any ionizing radiation. However, despite this, in the majority of asymptomatic patients the radionuclide technique of planar radionuclide ventriculography (RNV), often incorrectly referred to by nonimaging clinicians as 'MUGA', which nonspecifically stands for multiple gated acquisition, is frequently favoured over transthoracic echocardiography for its desirable technical qualities of availability, repeatability and reproducibility [7,8]. Since Strauss *et al.* [9] first described the technique of planar RNV in 1971, it has become the radionuclide method of choice for LVEF assessment, not only in the clinical routine but also in the clinical trial setting, wherein RNV (or 'MUGA') is often stipulated as the only permissible radionuclide test in research trial protocols.

0143-3636 © 2013 Wolters Kluwer Health | Lippincott Williams & Wilkins DOI: 10.1097/MNM.0000000000000000

RNV requires two separate intravenous injections (a stannous agent followed by ^{99m}Tc-pertechnetate). Patients may need to be scanned for up to 20–30 min to acquire sufficient counts, and the effective dose (ED) for the examination is in the 'intermediate risk' category at 6–8 mSv [10]. Processing is often by a manual method of drawing regions of interest, and, although good interobserver and intraobserver reproducibility can be achieved with training to follow specified protocols, the method is liable to subjectivity. Semiautomatic and automatic methods of region of interest delineation (with user intervention if required) are also available, and these may improve reproducibility. RNV also suffers from difficulties in separation of the left ventricle and from background subtraction problems, which are inherent disadvantages of a planar methodology.

Within this context, it is of practical importance to remember that gated single-photon emission computed tomography (SPECT) is now routinely performed for all myocardial perfusion scintigraphy studies and that this technique can give an accurate, reproducible and repeatable LVEF from a single injection of ^{99m}Tc-methoxyisobutylisontrile or tetrofosmin (Myoview). There have also been technical advances in cardiac SPECT technology in recent years, including cameras equipped with multipinhole collimation, new solid-state detectors (e.g. cadmium–zinc–telluride detectors) and resolution recovery, which have substantially reduced imaging time and/or injected activity, such that a gated acquisition can now be completed in less than 5 min with an ED of 3 mSv [10]. Of course, the latest gamma camera technology may not be universally available, but even by using conventional dual-head cameras gated SPECT can be completed within 15 min. This can be highly convenient for both the patient and the clinical workflow in dedicated nuclear cardiology departments, while reducing the ED by more than 50%. These are extremely important considerations for the patient who has to undergo serial testing over a long period of time. The costs of myocardial perfusion scintigraphy may superficially appear to be greater than those of RNV, but such financial calculations are often arbitrary and depend heavily on local factors such as clinical workload rather than just pharmaceutical cost; for example, performing a few rest-only gated SPECT studies in the course of routine 2-day stress–rest studies in a dedicated nuclear cardiology department (when up to 15 individual patient doses can be extracted from a single vial of tetrofosmin) is actually less costly than RNV. As a three-dimensional technique, gated SPECT also eliminates background subtraction issues, and automated processing algorithms can reduce the subjective reproducibility issues presented by human processing of RNV [11]. It should be pointed out, of course, that automatic processing of gated SPECT data may require user intervention if edge detection fails because of poor perfusion of the left ventricle or the presence of overlying extracardiac activity. Moreover, similar to RNV, LVEF values may be affected by arrhythmias.

Thus, from a pragmatic and practical viewpoint, the question has to be asked: can gated SPECT be used as an alternative to planar RNV for serial LVEF assessment in oncology patients? The practical arguments are compelling, especially in a dedicated nuclear cardiology department, but one of the key issues in this clinical context is reproducibility of LVEF measurements. Gated SPECT is a widely used technique in clinical practice for providing both functional and perfusion information from a single study [12,13]. LVEF, left ventricular wall motion and ventricular volumes calculated using Cedars-Sinai Quantitative Gated SPECT (QGS) software [11] have been widely validated by comparison with other methods used to calculate LVEF and volumes, including RNV [14], echocardiography [15] and MRI [16,17]. Nakajima *et al.* [18] showed excellent interinstitution reproducibility using QGS on a standard data set of gated SPECT projections even when different workstations were utilized. A recent large study involving 514 patients with suspected or known coronary artery disease compared gated SPECT and radionuclide angiography [19]. Using 16 frames for both techniques they found a high level of agreement in LVEF measurements both in patients with normal perfusion (58 ± 9 and 57 ± 8%, respectively) and in those with abnormal perfusion (48 ± 10 and 48 ± 11%, respectively). It is important to note that using eight frames for gated SPECT rather than 16 frames as used for RNV will give a reduction in absolute LVEF value of around 4% but will have no effect on repeatability [13]. Serial measurement of LVEF using conventional SPECT imaging has been shown to have good reproducibility of 5–7 EF units [20–22]. A recent study examining the reproducibility of gated SPECT using the newer technology of cadmium–zinc–telluride detectors showed differences between successive scans of 13 EF units in 50 patients, provided manual optimization of the valve plane and ventricular wall was used. This compared with 11 EF units in a different set of 52 patients who underwent planar RNV. A large EF range was used for both studies [23].

It is generally fair to say that planar RNV is a well-validated technique for measuring LVEF, and reproducibility between separate studies is generally accepted to be in the range of ± 10 EF units [19]. RNV is often quoted as being highly reproducible and repeatable, but there are actually few published data [24,25], and patient numbers are often low in those studies that have been published. This has led to several authors recently questioning the previously unassailable position of RNV as the only validated radionuclide technique for serial assessment of LVEF [26]. Heidendal *et al.* [27] reviewed the literature on the reproducibility of LVEF measurements from RNV. They found that comparing studies was difficult because of the different ways in which variability was expressed but concluded that overall reproducibility can be expected to be around 10 EF units.

Pfisterer *et al.* [28] states a difference of 8 EF units in an individual patient to be significant for planar RNV from data acquired on 16 patients 15 days apart. Hecht *et al.* [24] found a change of more than 12 EF units between rest LVEF measurements to be significant in a study on 18 patients with studies conducted 2 weeks apart. Wright *et al.* [25], in a study on 23 patients with repeat RNV on the same day, gives 95% confidence limits of 6 EF units. Wackers *et al.* [29] studied 70 patients with repeat same-day studies and 29 patients on separate days and found the same variability of 6 EF units. They also differentiated between normal and abnormal patients and concluded that for normal patients a difference between repeat studies must be 10 EF units in order to be significant but in abnormal patients only 5 EF units is required.

It is interesting that there are actually few data on the long-term repeatability of gated SPECT or RNV. A study by Thorley and Smith [30], who performed repeat gated SPECT studies at a mean of 1 year apart, found 95% confidence limits of 8 EF units for repeat studies. Some studies were performed with low doses (before the ARSAC limit for gated SPECT was increased) and excluding these patients gave a repeatability of 6 EF units. Sciagrà *et al.* [31] also found 95% confidence limits of 8 EF units in 67 patients with stable disease imaged at a mean difference of 25 months.

In conclusion, the repeatability of LVEF measurement by gated SPECT is in the range of 6–8 EF units provided the same acquisition and processing parameters and calculation software are employed, which is similar to that for RNV. With advances in SPECT technology, these studies can now be performed within a fraction of the time taken for RNV and with a significant reduction in ED, while also maintaining cost-effectiveness, all of which are extremely important and practical considerations in patients who are undergoing serial and repeated testing over a long period of time. These are compelling arguments, with a reasonable evidence base, to indicate that gated SPECT can be used for serial assessment of LVEF, as it provides reproducible LVEF measurements within the range of variation that is required for guiding the clinical management of oncology patients on potentially cardiotoxic drugs such as trastuzumab. Gated SPECT should therefore be offered as an alternative to RNV both in the routine clinical and research arenas, within the departmental setting where this best suits the patient workflow. As with any technique, attention to detail in the performance and interpretation of these studies, together with a robust audit of results that involves evaluation of the clinical cardiac outcomes in these patients, is highly desirable to ensure that the test is clinically both relevant and reliable.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

References

1 Jones AL, Barlow M, Barrett-Lee PJ, Canney PA, Gilmour IM, Robb SD, *et al.* Management of cardiac health in trastuzumab-treated patients with breast cancer: updated United Kingdom National Cancer Research Institute recommendations for monitoring. *Br J Cancer* 2009; **100**:684–692.

2 Von Hoff DD, Layard MW, Basa P, Davis HL Jr, Von Hoff AL, Rozencweig M, Muggia FM. Risk factors for doxorubicin-induced congestive heart failure. *Ann Intern Med* 1979; **91**:710–717.

3 Slamon DJ, Leyland-Jones B, Shak S, Fuchs H, Paton V, Bajamonde A, *et al.* Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. *N Engl J Med* 2001; **344**:783–792.

4 Piccart-Gebhart MJ, Procter M, Leyland-Jones B, Goldhirsch A, Untch M, Smith I, *et al.* Herceptin adjuvant (HERA) trial study team. Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. *N Engl J Med* 2005; **353**:1659–1672.

5 Smith I, Procter M, Gelber RD, Guillaume S, Feyereislova A, Dowsett M, *et al.* HERA study team. 2-year follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer: a randomised controlled trial. *Lancet* 2007; **369**:29–36.

6 Morris PG, Hudis CA. Trastuzumab-related cardiotoxicity following anthracycline-based adjuvant chemotherapy: how worried should we be? *J Clin Oncol* 2010; **28**:3407–3410.

7 Nicol A, Avison M, Harbinson M, Jeans S, Waddington W, Woldman S. Procedure guideline for planar radionuclide cardiac ventriculogram for the assessment of left ventricular systolic function. *Nucl Med Commun* 2009; **30**:245–252.

8 De Geus-Oei LF, Mavinkurve-Groothuis AM, Bellersen L, Gotthardt M, Oyen WJ, Kapusta L, van Laarhoven HW. Scintigraphic techniques for early detection of cancer treatment-induced cardiotoxicity. *J Nucl Med* 2011; **52**:560–571.

9 Strauss HW, Zaret BL, Hurley PJ, Natarajan TK, Pitt B. Scintiphotographic method for measuring left ventricular ejection fraction in man without cardiac catheterization. *Am J Cardiol* 1971; **28**:575–580.

10 Administration of Radioactive Substances Advisory Committee (ARSAC). *Notes for guidance on the clinical administration of radiopharmaceuticals and use of sealed radioactive sources*. London: Health Protection Agency; 2006.

11 Germano G, Kiat H, Kavanagh PB, Moriel M, Mazzanti M, Su HT, *et al.* Automatic quantification of ejection fraction from gated myocardial perfusion SPECT. *J Nucl Med* 1995; **36**:2138–2147.

12 Mansoor MR, Heller GV. Gated SPECT imaging. *Semin Nucl Med* 1999; **24**:271–278.

13 Germano G, Berman DS. On the accuracy and reproducibility of quantitative gated myocardial perfusion SPECT. *J Nucl Med* 1999; **40**:810–813.

14 Yoshioka J, Hasegawa S, Yamaguchi H, Tokita N, Paul AK, Xiuli M, *et al.* Left ventricular volumes and ejection fraction calculated from quantitative electrocardiographic-gated ^{99m}Tc-tetrofosmin myocardial SPECT. *J Nucl Med* 1999; **40**:1693–1699.

15 Chua T, Kiat H, Germano G, Maurer G, van Train K, Friedman J, *et al.* Gated technetium-99m sestamibi for simultaneous assessment of stress myocardial perfusion, post exercise regional ventricular function and myocardial viability. Correlation with echocardiography and rest thallium-201 scintigraphy. *J Am Coll Cardiol* 1994; **23**:1107–1114.

16 Tadamura E, Kudoh T, Motooka M, Inubushi M, Shirakawa S, Hattori N, *et al.* Assessment of regional and global left ventricular function by reinjection Tl-201 and rest Tc-99m sestamibi ECG-gated SPECT: comparison with three dimensional magnetic resonance imaging. *J Am Coll Cardiol* 1999; **33**:991–997.

17 Bavelaar-Croon CDL, Kayser HWM, van der Wall EE, de Roos A, Dibbets-Schneider P, Pauwels EKJ, *et al.* Left ventricular function: correlation of quantitative gated SPECT and MR imaging over a wide range of values. *Radiology* 2000; **217**:572–575.

18 Nakajima K, Nishimura T. Inter-institution preference-based variability of ejection fraction and volumes using quantitative gated SPECT with ^{99m}Tc-tetrofosmin: a multicentre study involving 106 hospitals. *Eur J Nucl Med Mol Imaging* 2006; **33**:127–133.

19 Acampa W, Caprio MG, Nicolai E, Liuzzi R, De Luca S, Capasso E, *et al.* Assessment of post stress left ventricular ejection fraction by gated SPECT: comparison with equilibrium radionuclide angiocardiography. *Eur J Nucl Med Mol Imaging* 2010; **37**:349–356.

20 Hyun IY, Kwan J, Park KS, Lee WH. Reproducibility of Tl-201 and Tc-99m sestamibi gated myocardial perfusion SPECT measurement of myocardial function. *J Nucl Cardiol* 2001; **8**:182–187.

21 Lee DS, Ahn JY, Kim SK, Oh BH, Seo JD, Chung JK, *et al.* Limited performance of quantitative assessment of myocardial function by

thallium-201 gated myocardial single-photon emission tomography. *Eur J Nucl Med* 2000; **27**:185–191.
22 Verberne HJ, Dijkgraaf MG, Somsen GA, van Eck-Smit BL. Stress-related variations in left ventricular function as assessed with gated myocardial perfusion SPECT. *J Nucl Cardiol* 2003; **10**:456–463.
23 Cherk MH, Ky J, Yap KSK, Campbell P, McGrath C, Bailey M, *et al*. Optimal reproducibility of gated sestamibi and thallium myocardial perfusion study left ventricular ejection fractions obtained on a solid state CZT cardiac camera requires operator input. *J Nucl Cardiol* 2012; **19**:713–718.
24 Hecht HS, Josepson MA, Hopkins JM, Singh BN. Reproducibility of equilibrium radionuclide ventriculography in patients with coronary artery disease: response of left ventricular ejection fraction and regional wall motion to supine bicycle exercise. *Am Heart J* 1982; **104**:567–574.
25 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**:494–498.
26 Schwartz RG, Jain D, Storozynsky E. Traditional and novel methods to assess and prevent chemotherapy-related cardiac dysfunction noninvasively. *J Nucl Cardiol* 2013; **20**:443–464.
27 Heidendal GAK, Bezemer PD, Koopman PAR, den Hollander W, Teule GJJ, van der Wall EE, Hasman A. Reproducibility of ejection fraction measurements by gated equilibrium blood pool scintigraphy. *Eur J Nucl Med* 1983; **8**:467–470.
28 Pfisterer ME, Battler A, Swanson SM, Slutsky R, Froelicher V, Ashburn WL. Reproducibility of ejection-fraction determinations by equilibrium radionuclide angiography in response to supine bicycle exercise: concise communication. *J Nucl Med* 1979; **20**:491–495.
29 Wackers FJT, Berger HJ, Johnstone DE, Goldman L, Reduto LA, Langou RA, *et al*. Multiple gated cardiac blood pool imaging for left ventricular ejection fraction: validation of the technique and assessment of variability. *Am J Cardiol* 1979; **43**:1159–1166.
30 Thorley PJ, Smith JM. Repeatability of left ventricular ejection fraction and volume measurement for ^{99m}Tc tetrofosmin gated SPECT. *Nucl Med Commun* 2005; **26**:345–349.
31 Sciagrà R, Berti V, Genovese S, Pupi A. Reliability of myocardial perfusion gated SPECT for the reproducible evaluation of resting left ventricular functional parameters in long-term follow-up. *Eur J Nucl Med Mol Imaging* 2010; **37**:1722–1729.