



**A COMPARATIVE STUDY OF ASSESSING LEFT VENTRICULAR
EJECTION FRACTION BY TWO DIMENSIONAL
ECHOCARDIOGRAPHY WITH REST GATED BLOOD POOL
VENTRICULOGRAPHY USING CONVENTIONAL SODIUM
IODIDE AND CADMIUM ZINC TELLURIDE CAMERAS**

By

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- Attachment 3: Participant's Material Publication Consent Form (Signature Page) in Malay and English versions

DISCLAIMER

I declare that this dissertation records the results of the study performed by me and that it is of my own composition.


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List of Abbreviations

2D	Two-dimensional
3D	Three-dimensional
ACC	American College of Cardiology
AHA	American Heart Association
ASCO	American Society of Clinical Oncology
ASNC	American Society of Nuclear Cardiology
CHF	Congestive heart failure
CMR	Cardiac magnetic resonance imaging
CZT	Cadmium zinc telluride
CZT AUTO	Cadmium zinc telluride camera operated in automatic mode
CZT MAN	Cadmium zinc telluride camera operated in manual mode
ECHO	Echocardiography/Echocardiogram
EF	Ejection fraction
EDV	End diastolic volume
ESV	End systolic volume
ESMO	European Society of Medical Oncology
GBPv	Gated Blood Pool Ventriculography

LVEF	Left ventricular ejection fraction
LVD	Left ventricular dysfunction
MUGA	Multigated acquisition scan
MRI	Magnetic resonance imaging
NaI	Sodium iodide
RVEF	Right ventricular ejection fraction
SV	Stroke volume
SPECT	Single photon emission computed tomography

ABSTRAK

Tujuan: Kajian ini membezakan korelasi dan batasan perjanjian di antara ekokardiogram dua dimensi (2D) dengan kaedah *Rest Gated Blood Pool Ventriculography (GBPv)* yang menggunakan dua jenis kamera yang berbeza, iaitu kamera planar sodium iodide (planar-NaI) dan kamera Cadmium Zinc Telluride (CZT) untuk menentukan pecahan ejeksi ventrikel kiri jantung (LVEF).

Metodologi: Seramai 109 pesakit kanser payu dara yang telah (84) atau akan menerima rawatan kanser kardiotoxik (25) menjalani scan ekokardiografi-2D di Jabatan Kardiologi, diikuti dengan scan GBPv menggunakan dua kamera yang berbeza iaitu kamera planar-NaI dan CZT pada hari yang sama di Jabatan Perubatan Nuklear, Hospital Sultanah Aminah, Johor Bahru. Bagi kamera CZT, kaedah pemprosesan automatik serta manual telah dilakukan dan ini membawakan sejumlah empat kaedah untuk menganalisa LVEF.

Keputusan: Kamera CZT pemprosesan manual menunjukkan purata LVEF yang tertinggi, sebanyak $70.1\% \pm 10.7\%$ dan terendah untuk kamera planar-NaI, sebanyak $58.8\% \pm 10.0\%$. Purata LVEF untuk ekokardiografi-2D adalah $61.8\% \pm 6.1\%$ dan untuk kamera CZT pemprosesan automatik adalah $64.3\% \pm 11.3\%$. Nilai LVEF untuk CZT pemprosesan manual adalah lebih tinggi berbanding dengan CZT pemprosesan automatik, kamera planar NaI dan ekokardiografi-2D ($p < 0.05$). Tiada perbezaan purata LVEF yang signifikan di antara ekokardiografi-2D dengan CZT pemprosesan automatik ($p = 0.24$) atau kamera planar-NaI ($p = 0.10$). Purata LVEF untuk kamera CZT pemprosesan automatik adalah lebih tinggi secara signifikan daripada kamera p-NaI ($p < 0.05$). Walaupun terdapat korelasi

yang signifikan ($p < 0.001$) di antara keempat-empat kaedah tersebut, tetapi kekuatan korelasi di antaranya adalah berbeza. Korelasi sederhana terdapat di antara ekokardiografi-2D dengan modaliti lain: kamera p-NaI ($r = 0.56$), kamera CZT pemprosesan automatik ($r = 0.54$), CZT pemprosesan manual ($r = 0.56$). Kekuatan korelasi yang kuat diperolehi di antara kamera planar-NaI dan kamera CZT ($r = 0.72$ untuk pemprosesan automatik $r = 0.71$ untuk pemprosesan manual). Kekuatan korelasi adalah tertinggi di antara kaedah pemprosesan automatik dan manual untuk kamera CZT ($r = 0.94$).

Batasan perjanjian Bland-Altman di antara tiga skan tersebut adalah luas dan suboptimum. Batasan terlebar adalah di antara ujian ekokardiografi-2D dan CZT pemprosesan automatik dari -21.1 hingga +16.2 (37%). Kaedah pemprosesan automatik dan manual untuk kamera CZT menunjukkan batasan terkecil, iaitu -2.0 to +13.5 (15%).

Kesimpulan: Walaupun korelasi signifikan wujud di antara empat kaedah menganalisa LVEF, kekuatan korelasi hanyalah sederhana di antara ekokardiografi-2D dengan kedua-dua skan planar-NaI dan skan CZT (kaedah pemrosesan manual dan automatik). Batasan perjanjian di antara semua skan adalah lebar dan suboptimum, ini bermaksud keputusan LVEF yang diperolehi di antara mereka tidak boleh ditukar ganti. Mana-mana satu modaliti boleh digunakan untuk menilai LVEF berasaskan ketersediaan modaliti tersebut di institusi masing-masing, tetapi dinasihatkan untuk menggunakan kaedah yang sama untuk skan susulan.

Kata Kunci: Rawatan kardiotoksik, ekokardiografi dua dimensi, *Gated blood pool ventriculography*, kamera planar, kamera CZT

ABSTRACT

A comparative study of assessing left ventricular ejection fraction by two-dimensional echocardiography with Rest Gated Blood Pool Ventriculography using planar Sodium Iodide and Cadmium-Zinc-Telluride cameras

Aim: To validate and compare the correlation and agreement between two-dimensional (2D) echocardiography and Rest Gated Blood Pool Ventriculography (GBPV) using both planar sodium iodide (NaI) and cadmium-zinc-telluride (CZT) cameras to measure left ventricular ejection fraction (LVEF).

Methodology: A total of 109 breast cancer patients, both receiving (84) and scheduled to receive (25) cardiotoxic cancer treatment, underwent 2D-echocardiography, followed by GBPV using both planar NaI and CZT cameras on the same day at the Cardiology and Nuclear Medicine Department of Hospital Sultanah Aminah, Johor Bahru respectively. For the CZT camera, both automatic and manual processing methods were applied, yielding a total of four different methods for the LVEF analysis in this study.

Results: Data from the 109 patients showed the highest mean LVEF was $70.1 \pm 10.7\%$, for CZT manual-processing, and lowest for planar camera with a mean of $58.8 \pm 10.0\%$. The mean LVEF for 2D-echocardiogram and CZT auto-processing were respectively $61.8 \pm 6.1\%$ and $64.3 \pm 11.3\%$. LVEF values were significantly higher for CZT manual-processing compared to planar camera, CZT auto-processing and 2D-echocardiography ($p < 0.05$). No

significant difference in mean LVEF was noted when comparing 2D-echocardiography with CZT auto-processing ($p = 0.24$) and planar camera ($p = 0.10$). The mean LVEF derived from CZT auto-processing was also significantly higher than that from planar camera ($p < 0.05$).

Although there was significant correlation ($p < 0.01$) among all four methods, the correlation strengths were varied. Moderate correlation was seen between 2D-echocardiogram and other modalities: NaI camera ($r = 0.56$); CZT automatic ($r = 0.54$); CZT manual ($r = 0.56$). Strong correlation was registered between planar and CZT ($r = 0.71$ and 0.72 , respectively for manual- and auto-processing). The strongest correlation was between the automatic- and manual-processing methods of CZT ($r = 0.94$).

The Bland-Altman limits of agreement among the three scans were wide and suboptimal. The widest limits were -21.1 to $+16.2$ (37%) between 2D echocardiography and CZT auto-processing. Good agreement was seen between the auto- and manual-processing methods for CZT camera with a limit agreement of -2.0 to $+13.5$ (15%).

Conclusion: Although there is significant correlation between the four methods of measurement of LVEF, the correlation strength is only moderate between 2D-echocardiography and GBPV using the planar NaI and CZT cameras. All three scans showed suboptimal limits of agreement between them and hence should not be used interchangeably. Any one of the modalities can be used to measure LVEF based on local availability; however, the same method of measurement is advised for serial scans.

Keywords: Cardiotoxic treatment, 2D-echocardiography, Gated blood pool ventriculography, planar NaI camera, CZT camera

CHAPTER 1

RESEARCH BACKGROUND

1.1 Introduction

Breast cancer is the most common cancer in Malaysia and accounts for 32.1% of all cancers among females according to the Malaysian National Cancer Registry Report for 2007-2011 (2016). Advancements in screening and management in the field of oncology have led to earlier detection of breast cancer and improvement in the specific survival rate. According to the Surveillance, Epidemiology, and End Results (SEER)-Medicare linked data for the period 2009-2015 (Howlander *et al.*, 2019), the breast cancer five year relative survival rate was 98% for early stage disease. However, the risk of cancer treatment-related cardiac dysfunction has emerged as a major cause of morbidity and mortality among these patients with early stage disease, particularly for those aged over 65 years (Patnaik *et al.*, 2011). Additionally, such patients are also at higher risk of cardiovascular disease compared with age-matched women without a history of breast cancer (Hooning *et al.*, 2007). In a retrospective study done in Malaysia by Hasbullah *et al.*, (2018), 170 HER2 (human epidermal growth factor receptor 2) positive metastatic breast cancer patients receiving both cardiotoxic chemotherapy and targeted therapy showed a 15.2% risk of cardiotoxicity (all grade one).

The most common form of cardiotoxicity is the subtle reduction in left ventricular ejection fraction (LVEF), attended by a late manifestation of left ventricular dysfunction (LVD). Adriamycin (anthracycline group) and trastuzumab (targeted therapy HER2

receptor blocker) are the two most common drugs associated with cardiotoxicity. A study by Felker *et al.*, (2000) noted that anthracycline-induced cardiomyopathy was associated with a much poorer prognosis than ischemic and idiopathic cardiomyopathy. Trastuzumab therapy causes reversible myocardial dysfunction rather than structural damage and was associated with a twofold increased risk of late heart failure compared to chemotherapy alone (Banke *et al.*, 2019). The incidence of cardiotoxicity was 7% with trastuzumab and up to 27% when it was combined with anthracyclines or other cardiotoxic drugs (Carlos *et al.*, 2017).

Various clinical practice guidelines, which include the 2012 European Society of Medical Oncology (ESMO), 2014 American Society of Echocardiography, and the 2016 American Society of Clinical Oncology (ASCO) guidelines, have all recommended baseline and serial measurements of LVEF during treatment and to repeat scans up to one to two years post-completion of cardiotoxic treatment. The guidelines have advocated the use of two-dimensional (2D) echocardiography or three-dimensional (3D) echocardiography and, if the image quality is poor, then to resort to rest gated blood pool ventriculography (GBPV) or cardiac magnetic resonance imaging (CMR). However, the National Comprehensive Cancer Network (NCCN) Breast Cancer Guidelines (Version 3, 2019) have not specified the optimal method or frequency of LVEF assessment. The Trastuzumab Prescribing Information and Cardiac Review and Evaluation Committee (Keefe, 2002) suggest the use of either echocardiogram or GBPV.

Currently, the three most common methods used to measure LVEF include 2D-echocardiography, CMR and GBPV (also known as multigated acquisition scan or MUGA). The clinician or cardiologist has to choose a sensitive, non-invasive and non-expensive

imaging method to accurately detect cardiac dysfunction at an early or subclinical and reversible stage. It is imperative that the clinician who has access to these methods knows whether the results of LVEF from these various methods are comparable and whether the results are interchangeable, as this could reduce the need for unnecessary multiple tests and thereby the burden of cost.

Various studies (Altena *et al.*, 2009; Kaputsa *et al.*, 2001; Bellenger *et al.*, 2000; Ganz *et al.*, 1996 and Schwartz *et al.*, 1987) have regarded serial GBPV or MUGA as the historical gold standard for assessing LVEF. MUGA scans were initially performed in the 1970s using planar NaI cameras, and later with planar SPECT (single-photon emission computed tomography) cameras. Since 2001, a novel cardiac dedicated SPECT camera with multiple solid-state detectors called the CZT (cadmium zinc telluride) camera was introduced in clinical practice. It was designed to acquire 3D image data with the benefits of improved count sensitivity, spatial and energy resolution, and shortened imaging time, all of which translated to reduced patient radiation exposure. MUGA scans also have the advantage of not relying on geometric based models.

In recent times, cardiac magnetic resonance imaging (CMR) is becoming the gold standard for assessing LVEF (Huang *et al.*, 2017; Oreto *et al.*, 2012; Hendel *et al.*, 2006; Bellenger *et al.*, 2000; Cranney *et al.*, 1990). However, due to its high cost and less widespread availability, periodic measurement of LVEF by using echocardiography has become the most frequently used modality for detecting cardiotoxicity. The main advantage of echocardiography is that it is readily available, highly portable, and relatively easy to perform, besides being non-invasive and bearing no radiation exposure.

Although these methods of measuring LVEF can show significant linear relationship among themselves, it is a known fact that such correlation of methods does not necessarily imply agreement (Naik *et al.*, 1995). An agreement between two methods evaluates the bias between the mean differences and provides an estimated agreement interval within which 95% of the differences between the two methods would fall (Bland *et al.*, 1986). The narrower the agreement interval, the more interchangeable are the techniques. To the best of our knowledge, this is the first study that compares the correlation and agreement of modified Simpson's method 2D echocardiography with both the conventional planar camera and the new cardiac dedicated CZT camera for LVEF measurements among breast cancer patients to assess for cardiotoxicity.

1.2 Literature Review

1.2.1 Cardiotoxicity and its types

The well-established NICE (National Institute For Health And Care Excellence) Guideline (2009, amended 2018) has been adopted by the Oncology and Radiotherapy Department, Hospital Sultan Ismail in defining cardiotoxicity due to cancer therapy, particularly in respect of breast cancer patients, and thus was adhered to in this study. Cardiotoxicity is defined as a drop in LVEF by 10% or more from baseline value (before start of treatment), and to a current value below 50%. Going by this criteria, treatment should then be suspended and LVEF reassessed with similar scanning method after three to four weeks. Post-completion of treatment, the guideline also suggests six monthly assessment of LVEF for up to two years.

There are two forms of cardiotoxicity which have been described in literature (Suter *et al.*, 2013; Ewer *et al.*, 2005). Type I cardiotoxicity is induced by cytotoxic agents like adriamycin, epirubicin, and cyclophosphamide. It is induced by oxidative stress on the cardiac muscle, which results in free radical formation and cell death. It is irreversible and typically associated with significant ultrastructural changes at biopsy. Type II cardiotoxicity is induced by biological agents like trastuzumab or pertuzumab and is associated with reversible myocardial dysfunction rather than structural damage. It is also non-dose dependent (Carmen *et al.*, 2014).

The clinical presentation of cancer therapeutic related cardiac dysfunction (CTRCD) varies from subclinical reduction in LVEF, mild transient hypertension and electrocardiogram (ECG) changes to more serious arrhythmias, thrombotic events, cardiomyopathy and myocardial infarction which may lead to LVD, congestive heart failure (CHF) or and ultimately cardiac mortality (Yeh *et al.*, 2009).

1.2.2 Ejection fraction

Ejection fraction (EF) is the fraction of blood that is ejected from the ventricles of the heart with each heartbeat. The LVEF is calculated by dividing the stroke volume, SV [SV = end-diastolic volume (EDV) - end-systolic volume (ESV)] by the end-diastolic volume (EDV) : ($LVEF = SV / EDV$). SV is an absolute measurement, whereas EF is inherently a relative volumetric measurement that represents the pumping efficiency of the heart. LVEF is a strong predictor of cardiac outcome and is used to assess the global left ventricular function. Serial measurements of LVEF have long been used for cardiotoxicity assessment. The Food and Drug Administration (FDA) has mandated that all registrational breast cancer

adjuvant trials involving either anthracycline or trastuzumab containing regimens serially monitor the LVEF (Ewer *et al.*, 2009).

Right ventricular ejection fraction (RVEF) is seldom measured as it is found to be important in only certain subgroups of patients to demonstrate right ventricular dysfunction (Hesse *et al.*, 2008). The indications include arrhythmogenic right ventricle, lung transplant candidates, right ventricular infarction. Echocardiography can be used to measure RVEF, although first-pass radionuclide ventriculography is the preferred method. The MUGA scan using planar NaI camera in the left anterior oblique projection (LAO) underestimates the RVEF due to overlap with right atrium and right ventricle and this method is not recommended by the European Association of Nuclear Medicine and European Society of Cardiology (EANM/ESC) guidelines for radionuclide imaging of cardiac function, (2008). According to these guidelines, the mean RVEF at rest for a normal population is 52%, and RVEF dysfunction is defined as RVEF <50%. The new cardiac dedicated CZT camera is capable of measuring RVEF more accurately than the planar camera, and the mean RVEF value obtained by CZT is $42.2 \pm 8.0\%$ (Jensen *et al.*, 2015) and this study will aim to validate these findings.

1.2.3 Methods to measure LVEF

1.2.3.1 Echocardiography

The echocardiogram is a well-established technique to measure LVEF. There are many ways to perform the echocardiography, which include the M-mode, 2D Modified Simpson's and the 3D method. The Linear M-mode method is quick and easy to perform but comes with limitations. Foremost among these is that it assumes the left ventricle is ellipsoid in

shape (geometrical assumption). It also requires perpendicular parasternal imaging and a good acoustic window. It is thus the least accurate of these methods (Wood *et al.*, 2013; Bellenger *et al.*, 2000).

The 2D Modified Simpson's biplane method requires area tracings of the endocardial border of the LV cavity in four and two chamber views in both the end-diastole and end-systole phases (Figure 1) and these tracings eventually divide the LV cavity into a predetermined number of disks (usually 20). Disk volumes are based on the tracings obtained from the study (Figure 1). This makes it more accurate and reproducible than the M-mode (Schiller *et al.*, 1989). However, it is time-consuming and comes with limitations, namely, geometrical assumptions, high dependence on good endocardial border definition, requirement of a good acoustic window, and a high level of operator experience (Wood *et al.*, 2013). Despite these limitations, the 2D Modified Simpson's method is strongly recommended by the American Heart Association for assessing LVEF. In 2014, the American Society of Echocardiography recommended using the 3D echocardiogram over 2D echocardiogram as there were concerns that the 2D method was only sensitive to detect changes in LVEF close to 10% and not beyond. However, the 3D method is not widely available and most centres in Malaysia unfortunately perform the M-mode method.

Many studies have examined the limitations associated with echocardiogram. In a study by Bellenger *et al.*, (2000), which compared MUGA, CMR, M-Mode echocardiography and 2D echo with Modified Simpson's method in heart failure patients, it was shown that echocardiogram is an unreliable method to measure LVEF due to geometrical assumptions and high interobserver variability. The authors found that echocardiogram suffered from errors introduced by gain-dependent edge identification and

transducer position during imaging. Although the 2D echocardiography was more accurate than the M- mode, it was time-consuming and more dependent on good endocardial border definition. There were wide limits of agreement between M-mode and 2D Modified Simpson's methods (47%) and wider limits of agreement between CMR and echocardiograms (44% for 2D echo and 66% for M-mode), compared to CMR and MUGA (31%). The CMR was considered the gold standard. Another study by Fatima *et al.*, (2011) showed that Modified Simpson's method 2D echocardiogram tends to significantly overestimate the % LVEF by 5.2% ($p < 0.001$) and causes an increase in the incidence of false-negative results arising from operator dependence, inadequate window, and the imprecise edge detection algorithm that 2D suffers from relative to 3D-echocardiogram. Earlier, Himelman *et al.*, (1988) had also observed inadequate assessment and poor reproducibility of 2D echocardiography, with an interobserver variability of 11% for the measurement of LVEF, which worsens in badly impaired ventricles.

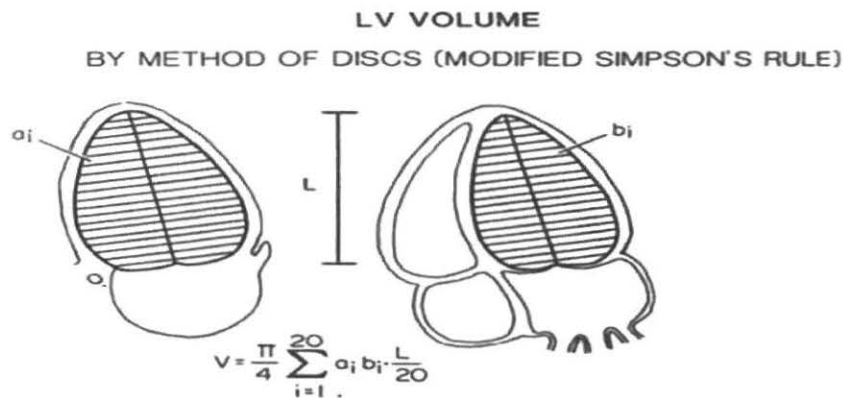


Figure 1: Modified Simpson's method or biplane algorithm calculating chamber volume from 2D echocardiogram. Adapted from Schiller *et al.*, (1989).

In recent times, two-dimensional strain echocardiography has emerged as a novel method for early diagnosis of subtle myocardial dysfunction in patients receiving cardiotoxic cancer therapy. This method measures the regional or global deformation of the myocardium that occurs as a result of myocardial ischemia or infarction, which causes the affected part of the myocardium to weaken. This subsequently leads to a reduction and alteration of the systolic function (Toufan *et al.*, 2017). According to Yang *et al.* (2018), the global deformation that is measured in 2D strain echocardiography is called the global longitudinal peak systolic strain (LPSS), which is a simple parameter that expresses longitudinal shortening as a percentage (change in length as a proportion to baseline length).

The study by Toufan *et al.*, (2017), showed that a reduction of global LPSS of >15% from baseline is considered clinically significant in patients with cardiotoxicity. The same study also showed, that the LPSS method is dependent on blood pressure and heart rate; a higher heart rate was found to adversely affect the clarity of endocardial borders in certain views, thereby causing errors in measurement. It was also noted that the global LPSS may not reflect regional or segmental LPSS changes of the myocardium as the contribution of each segment of the myocardium to the global LPSS may not be equal. Documented cases were noted where the global LPSS could be normal, but the patient may have had segmental reduction due to fibrosis which may be compensated by another segment, and thus not affecting the global value. The authors have, therefore, highlighted the need for further studies and validation and assessment of the segmental values. However, according to current recommendations, the modified Simpson method still remains the preferred method for measuring LVEF on two-dimensional echocardiography.

1.2.3.2 Cardiac Magnetic Resonance Imaging (CMR)

CMR is considered the gold standard for LVEF measurements and has been recognized by the ACC/AHA guideline as a technique to detect cancer therapy induced cardiotoxicity. The main advantage of cardiac MRI according to Hendel *et al.*, (2006) is that it offers complete information regarding myocardial performance as well as valvular and pericardial involvement. Jiji *et al.*, (2012) showed that in obese patients for whom echocardiography often yields suboptimal image quality, cardiac MRI was able to measure left ventricular function successfully. The study also demonstrated that CMR was able to detect myocardial edema that often attends acute myocardial injury. Despite the obvious advantages of the method, however, it is less routinely used as a screening and monitoring method of cardiotoxicity due to the widespread availability of echocardiography.

1.2.3.3 Rest Gated Blood Pool Ventriculography

In GBPV or MUGA studies, when the cardiac blood pool is labelled with a radiotracer, changes in count density relate proportionately to changes in blood volume; thus ventricular contraction and high count densities allow for (endocardial) blood volume edge detection by mathematical criteria and the LVEF is calculated. A gamma camera is used to record the counts. The method uses the electrical signals of the heart to trigger the camera to take a series of pictures that records the heart's motion and its contractility. The image acquisition is 'gated' with ECG so as to obtain information over several cardiac cycles. Each cardiac cycle is divided into a pre-determined number of intervals (24 in this study), corresponding to 24 number of frames per cardiac cycle. The frame with the highest counts is considered end-diastole and the frame with the lowest counts is considered end-systole. LVEF equals net counts in the end-diastolic frame minus net counts in end-systolic frame divided by net

counts in end-diastole. Net counts are calculated by subtracting counts from a background (a region of interest which is placed next to the left ventricle) from measured LV counts (Corbett *et al.*, 2006).

The 2D planar NaI camera was the historical gold standard used in MUGA to assess LVEF for serial assessment of cardiotoxicity until the advent of cardiac MRI. Later, a higher efficiency SPECT camera technology was introduced that allowed for faster acquisition times, lower radiation doses to the patient, provided calculated ventricular volumes and was able to assess right ventricular function. It was proven to be diagnostically more accurate and reproducible compared to traditional planar scans. The latest cardiac dedicated CZT SPECT camera system enables full 3D coverage of the heart which allows for true volumetric determination of the left ventricular volumes. Compared to conventional cameras, it is five to eight times more efficient (increased count sensitivity). It has improved energy, spatial and contrast resolution, through direct conversion of photons to electrical pulses without the use of photomultiplier tubes (Slomka *et al.*, 2009; Garcia *et al.*, 2011). It has faster recording speeds and, from a tomographic perspective, helps avoid overlap of the cardiac chambers and also reduces the time-consuming process of needing to find the best septal separation. Jensen *et al.*, (2014) found that CZT had a higher reproducibility and lower variability compared to planar cameras. Chen *et al.*,(2016) showed that despite reducing the imaging time, the quality of the image to assess LVEF and RVEF was preserved with the CZT camera.

The CZT camera uses the QBS Cedars Sinai Software to process the LVEF values. The software offers both automatic and manual processing methods to measure the LVEF. This gives the physician the ability to support manual identification of the left-ventricular (LV)

region and to separate it from the right ventricle (RV) in cases where the automatic algorithm fails or returns unsatisfactory results. Daou *et al.*, (2001) compared automatic and manual processing of this software using a SPECT gamma camera and found moderate correlation ($r = 0.6$; $p = 0.0001$) and wide limits of agreement. To the best of our knowledge the present study would be the first of such to compare the various processing methods of this software in a CZT camera in this cohort of patients.

McKillop *et al.*, (1983) and Ershler *et al.*, (2006) showed that LVEF estimation by GBPV was superior to echocardiography in terms of accuracy, reproducibility and was in agreement with the angiographic method. Various studies (Sivak *et al.*, 2011; Fatima *et al.*, 2011; Corapçioğlu *et al.*, 2006 and McKillop *et al.*, 1983) found that MUGA is more sensitive than echocardiography for the estimation of subtle changes in LVEF. The ASCO 2016 guidelines also recommended that cardiac MRI or MUGA be used if echocardiogram is technically not feasible in cases like chronic lung disease, poor image quality due to body habitus, and history of mediastinal surgery.

The 2012 ESMO guidelines noted that the advantage of MUGA is its low interobserver variability, while cardiac MRI has better spatial resolution than that of echocardiography. The American College of Cardiology (ACC)/ American Heart Association (AHA)/ American Society of Nuclear Cardiology (ASNC) guidelines (Klocke *et al.*, 2003) indicate that GBPV has a class IA indication for initial and serial assessment of LV function in patients receiving cardiotoxic drugs. The ASNC has noted that parameters that can be drawn from the MUGA scan include ejection fraction (EF), ventricular volumes, wall motion, peak ejection rate (PER) and peak filling rate (PFR) (Glenn *et al.*, 2013; Corbett *et al.*, 2006). This study however, focuses only on the two parameters of LVEF and RVEF as

per its stated objectives.

In Malaysia, most nuclear medicine centres possess the conventional planar NaI and SPECT cameras, with some centres also having the new CZT cardiac dedicated camera. The Nuclear Medicine Department, Hospital Sultanah Aminah Johor Bahru (HSAJB), where this study is conducted, has both the planar NaI and SPECT CZT cameras. It is standard practice to perform GBPV studies using either the planar NaI camera or the CZT camera, depending on the local availability in the various hospitals. However, a need to compare the correlation and agreement between these cameras in a local setting has yet to be performed and this study fulfills that need. If the results of the cameras prove to be interchangeable, then centres that do not have the CZT camera can continue using the conventional planar NaI method.

1.3 Research Problem

The advancement in management of breast cancer has led to better survival rates, but more patients as a consequence are suffering from the late effects of chemotherapy and targeted therapy, manifesting in the form of cardiotoxicity. There is thus a growing need for oncologists to prevent cardiac related morbidity and mortality due to these medications. The field of nuclear medicine has long provided a method to assess the subtle changes in LVEF with baseline and serial MUGA studies which have been proven to be highly reproducible. However, on account of MUGA's limited availability and its associated radiation exposure, echocardiography with its ease of access has emerged as the modality of choice to assess LVEF. With the advent of the new CZT cardiac dedicated camera,

nuclear medicine physicians can now provide true 3D volumetric assessment of the left ventricular volume and overcome the limitations of geometric assumptions made by echocardiography. Apart from this, the dose of radioactivity can be reduced with the new CZT cameras that also provide for shorter imaging time.

A crude method of measuring LVEF with M-mode echocardiography is unfortunately performed routinely in most centres in Malaysia. However, when cardiac function is assessed on a serial basis to assess the cardiotoxic effects of cancer therapy, a more precise measurement is required as it is important to detect the change in LVEF confidently and accurately. The clinician needs to know if the change in LVEF is valid and does not occur solely by chance. If the same patient is investigated with different methods, then different results will be obtained that may impact the patient's management like unnecessary delay in treatment or wrongly continuing the treatment regime. With the various methods available to assess cardiotoxicity, the clinician needs to know what the correlation and agreement are between the various methods and, most importantly, if these methods are interchangeable and have low interobserver variability.

1.4 Justification of Study

Cardiotoxicity is a serious public health issue and has an impact on patient management and outcome. Left ventricular dysfunction is a late manifestation of cardiotoxicity and if untreated can lead to congestive cardiac failure. A sensitive, non-invasive and non-expensive imaging method is required to accurately detect cardiac dysfunction at an early/subclinical and reversible stage. Although echocardiography is the

most commonly used method, nuclear imaging provides a sensitive and accurate estimation of LVEF by detecting a change in the biological processes preceding anatomical involvement and physiological consequences of myocardial damage induced by antineoplastic drugs (Carmen *et al.*, 2014). Previously published reports suggest high correlation among two-dimensional echocardiography and GBPV, but fewer reports specifically analyze the agreement among the values obtained by each of these methods (Naik *et al.*, 1995; Quinones *et al.*, 1981; Schiller *et al.*, 1979; Folland *et al.*, 1979). This study will aim to validate and compare the agreement and correlation among these studies, particularly in the context of the local availability of the new CZT camera for use with GBPV.

1.5 Objectives

1.5.1 General Objective

To compare the correlation and agreement of left ventricular ejection fraction measured by 2D echocardiography with different gated blood pool studies using conventional NaI gamma camera and CZT camera among breast cancer patients planned for or receiving cardiotoxic anticancer therapy.

1.5.2 Specific Objectives

1. To correlate and compare the agreement of left ventricular ejection fraction results measured with 2D echocardiography, conventional NaI gamma camera and CZT cardiac dedicated camera among breast cancer patients planned for or receiving cardiotoxic anti-cancer agents.

2. To compare interobserver variation in measuring LVEF in two different gamma cameras
3. To evaluate right ventricular ejection fraction using CZT cardiac dedicated camera among patients receiving cardiotoxic agents

1.6 Research Hypothesis

NULL HYPOTHESIS

- There is no statistical correlation and agreement between CZT cardiac- dedicated camera, conventional NaI gamma camera and 2D echocardiography in measuring and detecting changes in LVEF.
- There is no statistical significant difference in interobserver variation between CZT cardiac- dedicated camera and conventional NaI gamma camera.

ALTERNATIVE HYPOTHESIS

- There is statistical correlation and agreement between CZT cardiac- dedicated camera, conventional NaI gamma camera and 2D Echocardiography in measuring and detecting changes in LVEF.
- CZT cardiac- dedicated camera is superior to conventional NaI gamma camera in having lower interobserver variation.

CHAPTER 2

MATERIALS AND METHODS

2.1 Study Design and Location

This is a prospective, observational and comparative study which was conducted in the Nuclear Medicine Department and Cardiology Department of Hospital Sultanah Aminah, Johor Bahru.

2.2 Study Population and Recruitment Time Frame

Reference population comprised of adult female breast cancer patients in Johor Bahru. The source and sampling population comprised of adult female breast cancer patients undergoing or planned to start on cardiotoxic cancer therapy at the Oncology & Radiotherapy Department, Hospital Sultan Ismail, Johor Bahru. The mean duration of time between receiving the anti cancer therapy and performing the scans was 19.4 ± 3.7 days (range 11-30 days). Study subjects were consenting adult female breast cancer patients (clinically and histopathologically proven) who were above 18 years of age and who were receiving or being scheduled to receive cardiotoxic cancer therapy, and referred for Rest Gated Blood Pool Ventriculography Scan to assess for cardiotoxicity. Study period was of 18 months duration (March 2018 – August 2019). Patient recruitment was from March 2018 – March 2019.

2.3 Inclusion and Exclusion Criteria

2.3.1 Inclusion criteria

1. Age above 18 years
2. All breast cancer patients referred to Nuclear Medicine Department for baseline or interim scans for evaluation of chemotherapy / biological therapy induced cardiotoxicity.

2.3.2 Exclusion criteria

1. Body mass index more than or equal to 35
2. Claustrophobia
3. Patient with irregular heart rhythm
4. Patient unable to lie with left arm raised over the head during imaging
5. Pregnancy
6. Breast feeding
7. History of congestive heart failure, congenital heart disease, cardiomyopathy, myocardial infarction, clinically significant valvular disease or angina requiring medication
8. Patient receiving the following medications which include methyldopa, hydralazine, digoxin, prazosin and propranolol.

2.4 Ethical Board

This study was approved by National Institutes of Health in the Ministry of Health Malaysia (Refer to Appendix 1). JEPeM USM has issued an acknowledgement letter to

attest that the study was free from any ethical concerns. Confidentiality and privacy of patient during data collection was maintained by giving each case a code number. Information and data collected during the research period were kept confidential.

2.5 Sample Size Calculation

The sampling population was derived from female breast cancer patients receiving or planned to receive cardiotoxic cancer therapy from the Oncology and Radiotherapy department of Hospital Sultan Ismail, Johor Bahru and referred to Nuclear Medicine Department, Hospital Sultanah Aminah Johor Bahru for Rest Gated Blood Pool Ventriculography. Based on the Johor Cancer Registry Report 2007-2011 (2014), the total number of breast cancer patients in Johor between 2007-2011 were 2899 cases and the age-standardised rate for breast cancer in Johor was 39.5 per 100,000 females between 2007-2011. The average number of patients with breast cancer subjected to cardiotoxic cancer therapy at the Oncology and Radiotherapy Department in Hospital Sultan Ismail, Johor Bahru was 100 cases/year over a period of two years (2016-2017).

2.5.1 Sample size calculation for correlation and agreement between methods and interobserver variability

The sample size calculation was done using Epi-Info software version 7.0 based on sample size formula for population survey based on a similar study by Jensen *et al.*, 2014 that included 82 patients to compare the correlation, agreement and interobserver variability among different modalities to measure LVEF in breast cancer patients. The required sample size to achieve a power of 80% and confidence interval of 95% with level of significance

at 0.05 is 78 patients (Figure 2A). Considering additional 10-20% of loss of follow-up cases, the sample size required to compare the ejection fraction among three methods will be approximately 85 patients. However, a total of 109 patients were available and successfully recruited in this study to investigate the above objectives.

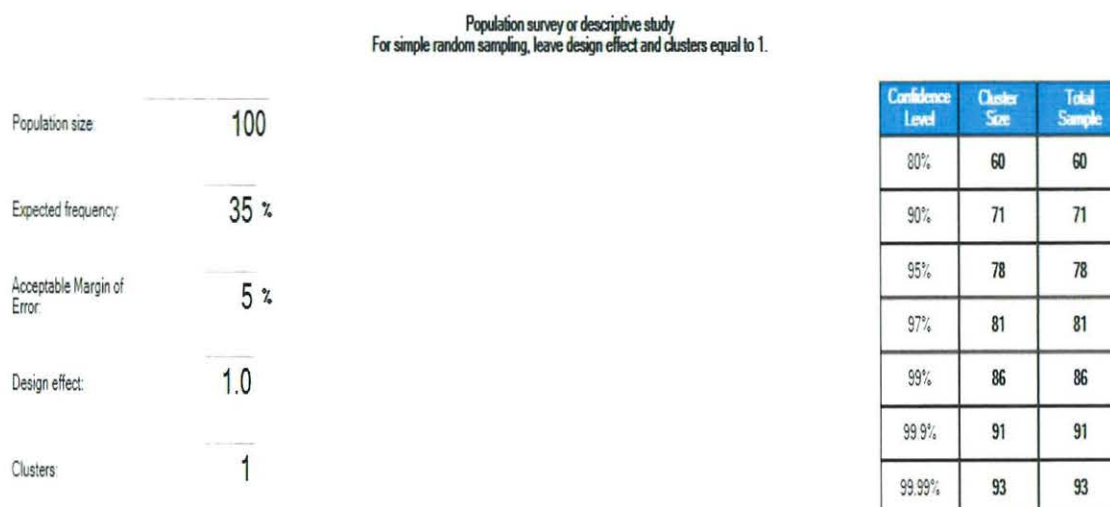


Figure 2A : Sample size calculation for correlation and agreement using Epi-Info Software

2.6 Research Tool

Data collection in this study was recorded into:

Patient's information and data collection data sheet (Refer to Appendix 2)

2.7 Sampling Method and Procedures

2.7.1 Patient recruitment methods :

1. Before the study began, a prior briefing was held to inform the clinicians at the Oncology & Radiotherapy Department, Hospital Sultan Ismail Johor Bahru (HSIJJB) regarding the aim, objective, inclusion and exclusion criteria, risks involved and the protocol used by the Nuclear Medicine Department, HSAJB for this study. Only patients that were keen to enter the study and fulfilled the inclusion and exclusion criteria were referred to the Nuclear Medicine Department and an appointment date was given by the principal investigator.

2. Data which included patient demographics, patient's history of breast cancer and the treatment received or planned to be given, stage of disease and underlying risk factors was collected from history-taking from patient, along with clinical records and imaging reports provided by the referring specialist. An adequate physical examination was performed to exclude patients with these limitations: left arm lymphedema that limits arm motion for imaging, fungating breast or chest wall lesion that limits the 2D echocardiography window. A resting 12-lead ECG was performed to rule out irregular heart rhythms that would affect gating of GBPV studies.

3. Explanations were given to the patients regarding the details of the study which included the procedure, purpose and the risks involved. On the matter of risks, the patients were informed that till date no credible reports exist of cancer resulting from low dose radiation exposure from nuclear medicine cardiology studies (Russel *et al.*, 2016). Their attention was drawn to the ACC/AHA/ASNC guidelines (Klocke *et al.*, 2003) which

indicate that Rest Gated Blood Pool Ventriculography using ^{99m}Tc labelled RBC has a class IA indication for initial and serial assessment of LV function in patients receiving cardiotoxic drugs. The usual radiation exposure with a dose of 20 mCi (740 MBq) of ^{99m}Tc labelled RBC (which has a half-life of six hours) is equivalent to an estimated six to twelve months of natural background radiation that one would normally receive in our external environment, and the incidence of naturally occurring cancers far exceeds the theoretical radiation induced cancer rates. This study with added radiation was thus not harmful and safe. A written informed consent was obtained from each patient prior to the start of the study. The patients were told of their rights to decline entry into the study or withdraw from it at any point. Each patient was given a code number for data entry and analysis (Refer to Appendix 2) .

4. Patients were told that they need not fast prior to the study or withhold any routine medications.

5. Patients were informed that the site for the Modified Simpson's method of 2D echocardiography was at the Cardiology Department, HSAJB. Following the echocardiography, they returned to the Nuclear Medicine Department HSAJB, where they underwent the radiolabeling procedure (this takes approximately 15-20 minutes to perform). This was then followed by the GBPV scans using both planar and CZT cameras, each of which takes approximately 15 minutes to perform. All the above scans were performed as per departmental protocol.

2.7.2 Scan methodology for 2D echocardiography, planar NaI and CZT camera

1. Modified Simpson's method 2D echocardiography (Image 2A) was done using the Philips Epic Series 7C machine at the Cardiology Department of HSAJB prior to the GBPV scans on the same day and took approximately 15-20 minutes to perform.

2. GBPV using conventional planar NaI camera and CZT cardiac dedicated camera was performed in the Nuclear Medicine Department at HSAJB on the same day after the 2D echocardiography. The acquisition parameters for both the cameras have been summarised in Table 2.1. The LVEF for these camera were processed by two doctors, namely a nuclear medicine specialist and a nuclear medicine medical officer who were blinded to each other's scan results and not privy to the 2D echocardiography results.

- The CZT camera used was the Discovery NM 530c (GE healthcare, Milwaukee, WI, USA) equipped with 19 stationary CZT detectors arranged in a semi-circle, simultaneously imaging 19 views of the heart through pinhole collimators. The software used to process the LVEF was the Quantitative Blood Pool SPECT (QBS-Cedars Sinai, Los Angeles, CA, version 2009) using both manual and automatic processing methods (Image 2B and Image 2C) for all 109 patients.

- Planar NaI gamma camera used was the Siemens Symbia E Dual Head camera (Siemens Medical Solutions Inc. USA). The processing method was semiautomatic, using the Siemens Gated Bloodpool Software and re-orientated with the Syngo MI application software. The LVEF was calculated by drawing regions of interest (ROI) over the left ventricle at ES and ED and the background at five o'clock position in immediate proximity

of the left ventricle (Images 2D and 2E). The planar LVEF was calculated by counting the difference in counts using the formula : $[(\text{Background corrected end-diastolic counts} - \text{Background corrected end-systolic counts}) / (\text{Background corrected end-diastolic counts})] \times 100$ (Jensen *et al.*, 2014).

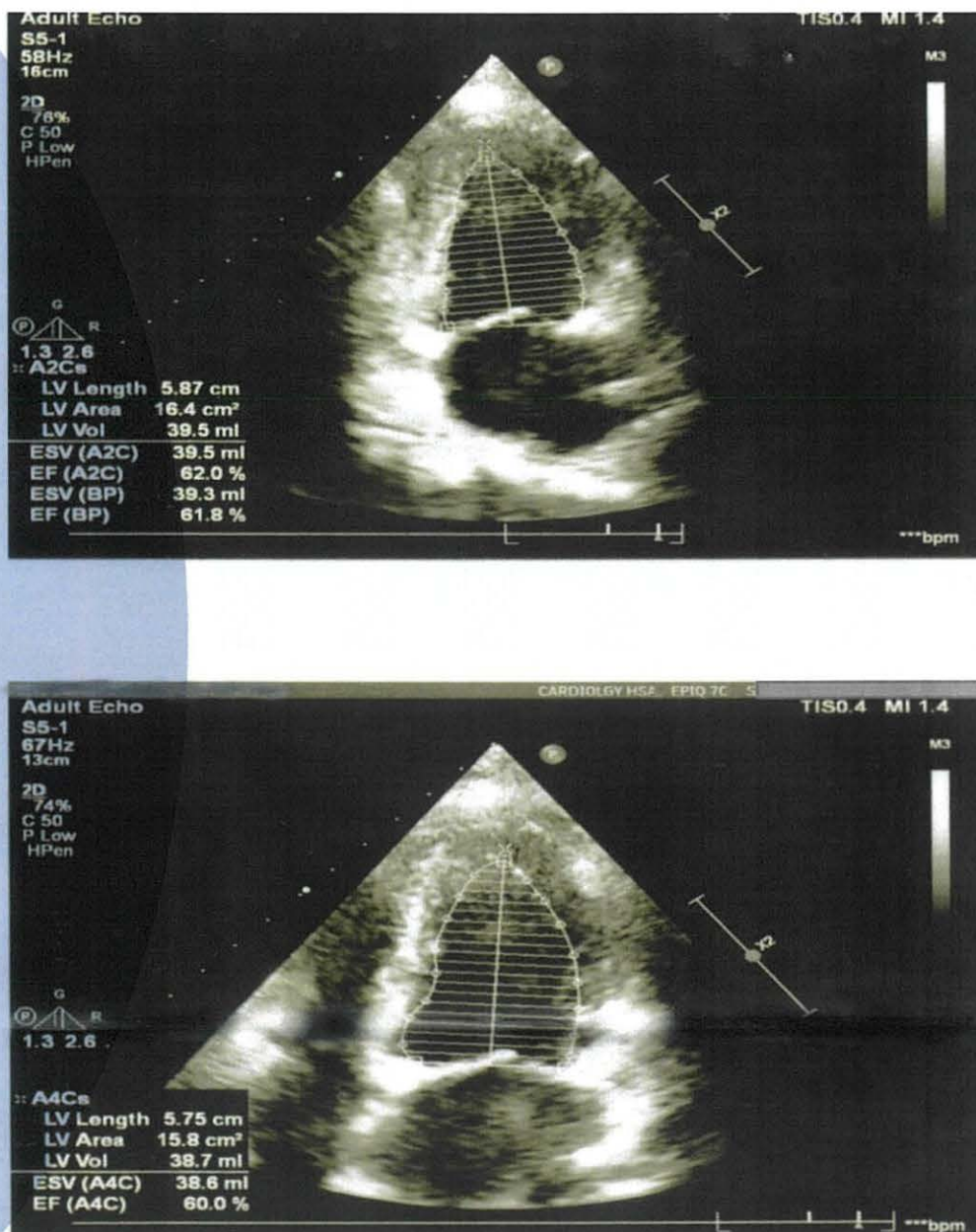


Image 2A : Modified Simpson's method of measurement of LVEF performed at the Cardiology Department, HSAJB