RELATIONSHIP BETWEEN PLASMA NATRIURETIC PEPTIDE LEVEL AND SPECT-DERIVED DIASTOLIC PARAMETERS

BY

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DISSERTATION SUBMITTED IN PARTIAL FULFILMENT OF THE REQUIREMENT FOR THE DEGREE OF MASTER OF MEDICINE (NUCLEAR MEDICINE)

ADVANCED MEDICAL AND DENTAL INSTITUTE (AMDI)
UNIVERSITI SAINS MALAYSIA (USM)
2022

DECLARATION

I hereby declare that this research was sent to Universiti Sains Malaysia (USM) for the degree of Master of Medicine in Nuclear Medicine. It has not been sent to other universities. With that, this research can be used for consultation and photocopied as reference.

Sincerely,

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ACKNOWLEDGEMENTS

My praise and worship goes to the Almighty, the most gracious, most merciful for this journey of life and experiences.

I would like to thank all who had supported and guided me in the preparation of this dissertation, particularly my supervisors Dr. Noor Khairiah A Karim, Dr. Jazilah Abd Rahim and Dr. Ng Chen Siew.

My thanks is also extended to all of the Nuclear Medicine staff of Hospital Sultanah Aminah Johor Bahru for their help and assistance throughout this study, to all patients that had volunteered for this study and importantly my family for their continuous support and encouragement. Finally I would like to dedicate this dissertation to Nurhani Aliumar, without my mother 1 wouldn't be inspired to keep moving, be brave and explore the unknown.

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LIST OF ABBREVIATIONS

ACE inhibitors	Angiotensin-Converting Enzyme inhibitors
BNP	Brain-type Natriuretic Peptide
BMI	Body Mass Index
BP	Blood Pressure
cMyBP-C	Cardiac Myosin Binding Protein-C
CAD	Coronary Artery Disease
CZT	Cadmium Zinc Telluride
CT	Computed Tomography
CardioREPO	cREPO (FUJIFILM RI Pharma, Co. Ltd., Tokyo, Japan/EXINI Diagnostics, Lund, Sweden)
CABG	Coronary Artery Bypass Graft
DM	Diabetes Mellitus
e'	Peak Early Mitral Annular Velocity
e/e'	Ratio Peak Early Mitral Annular Velocity
ESC	European Society of Cardiology
ECG	Electrocardiogram

ESV	End-Systolic Volume
EDV	End-Diastolic Volume
ESRF	End- Stage Renal Failure
EDTA	Ethylene-Diamine-Tetra-Acetic Acid
Gated MPS	Gated Myocardial Perfusion SPECT
GFR	Glomerular Filtration Rate
HR	Heart rate
HF	Heart Failure
HFpEF	Heart Failure with preserved Ejection Fraction
HFrEF	Heart Failure with reduced Ejection Fraction
HFV	Heart Function View (Nihon MediPhysics Co., Ltd)
IHD	Ischaemic Heart Disease
HPT	Hypertension
ICA	Invasive Coronary Angiography
LV	Left Ventricle
LVEF	Left Ventricle Ejection Fraction
LVH	Left Ventricular Hypertrophy

LVEDP	LV End Diastolic Pressure
mL/s	milli Liter per second
ms	milli second
mSv	milli Sievert
mCi	milli Curie
MBq	Mega Becquerel
MUGA	Multi-Gated Acquisition
MRI	Magnetic Resonance Imaging
MAP	Mean Arterial Pressure
MI	Myocardial Infarction
NT-proBNP	N-Terminal pro Brain-type Natriuretic Peptide
NPV	Negative Predictive Value
NaI	Sodium Iodide
PET	Positron Emission Tomography
PPV	Positive Predictive Value
PFR	Peak Filling Rate
PFR2	Second Peak Filling Rate

QGS	Quantitative Gated SPECT (Cedars-Sinai Medical Center, Los Angeles, CA, USA)
QPS	Quantitative Perfusion SPECT (Cedars-Sinai Medical Center, Los Angeles, CA, USA)
SPECT	Single Photon Emission Computed Tomography
SV	Stroke Volume
SD	Standard Deviation
SCD	Sudden Cardiac Death
Tc-99m	Technetium-99m
TTPF @ TPFR	Time to Peak Filling @ Time to Peak Filling Rate
Tl-201	Thalium-201
WHO	World Health Organisation
1/3 MFR	First Third Mean Filling Rate
4DM-SPECT	4DM-SPECT/Corridor 4DM (Michigan University/INVIA, LLC, Ann Arbor, MI)

// ABSTRAK

Tajuk: Hubungan antara Plasma Peptida Natriuretik dan Parameter Diastolik 'SPECT'.

Pendahuluan: Kepincangan fungsi diastolik selalunya mendahului kepincangan fungsi sistolik dan kegagalan jantung. Pesakit dengan paras peptida natriuretik seperti 'N-Terminal pro Brain-type Natriuretic Peptide' (NT-proBNP) yang meningkat tanpa gejala kegagalan jantung dan memiliki pecahan pancutan ventrikal kiri (LVEF) yang normal berkemungkinan menghidap kepincangan fungsi diastolik tidak bergejala yang dikategorikan sebagai kegagalan jantung peringkat B. Teknik imbasan untuk mengesan kepincangan ventrikal selalunya menggunakan kaedah ekokardiografi. Namun, begitu, imbasan perfusi miokardium menggunakan 'single photon emission computed tomography' (SPECT) juga mampu memberikan maklumat berkenaan fungsi ventrikal seperti LVEF untuk fungsi sistolik, kadar pengisian puncak ventrikal (PFR), PFR kedua (PFR2), kadar pengisian purata sepertiga awal (1/3MFR), tempoh kadar pengisian puncak (TTPF) dan tempoh kadar pengisian puncak bagi satu kitaran kardiak (TTPF/RR) untuk fungsi diastolik.

Objektif: Kajian ini bertujuan menilai hubungan antara peptida natriuretik sebagai petanda biologi ventrikal dan parameter diastolik yang diukur dengan 'electrocardiogram-gated myocardial perfusion SPECT' (Gated MPS) dalam kalangan pesakit yang mempunyai LVEF yang normal dan tiada iskimia atau kematian miokardium, selain menyiasat kaitan antara parameter diastolik SPECT dengan faktor kliniko-sosio-demografi dan seterusnya menghasilkan bacaan rujukan mengikut institusi.

Kaedah: Seramai 137 pesakit dengan keputusan ujian stres & rehat perfusi miokardium dan LVEF yang normal menyertai kajian ini. Graf bacaan isipadu-kadar ventrikal kiri dikira secara automatik menggunakan perisian 'Quantitative Gated SPECT' (QGS) dengan kaedah '16-frame list mode' untuk menghasilkan bacaan parameter diastolik ventrikal kiri daripada ujian rehat seperti PFR, 1/3MFR, TTPF dan TTPF/RR. Seterusnya, hubungan dengan NT-proBNP, kaitan dengan faktor kliniko-sosio-demografi dan bacaan rujukan dikaji.

Keputusan: Parameter diastolik Gated MPS mempunyai hubungan tidak berkolerasi dengan NT-proBNP. PFR dan 1/3MFR berkurang secara konsisten apabila NT-proBNP meningkat. Namun, tidak signifikan ($p = 0.231$ vs 0.348) dan dipengaruhi oleh faktor umur ($p = 0.003$ vs 0.002), tekanan darah diastolik ($p < 0.001$ setiap satu) dan tekanan darah tinggi ($p = 0.031$ vs 0.004). PFR sangat berkait-rapat dengan jantina ($p < 0.001$) dan nadi ($p < 0.001$) tetapi sebaliknya bagi 1/3MFR. Perbezaan statistik yang signifikan bagi 1/3MFR dilihat dikalangan pesakit kencing manis dan tanpa kencing manis ($p = 0.001$); darah tinggi dan tanpa darah tinggi ($p = 0.004$). Keseluruhannya, hanya TTPF dan TTPF/RR menunjukkan bacaan stabil tanpa dipengaruhi oleh umur, jantina, tekanan darah, nadi dan penyakit. Bacaan rujukan untuk PFR, PFR2, 1/3MFR, TTPF dan TTPF/RR sebagai parameter diastolik adalah 1.55 ± 0.41, 0.70 ± 0.42, 0.79 ± 0.21, 333 ± 55 dan 0.197 ± 0.044.

Kesimpulan: Parameter diastolik yang diukur menggunakan 'QGS 16-frame Gated MPS' tidak berhubungkait dengan petanda biologi ventrikal; NT-proBNP. PFR, PFR2 dan 1/3MFR dipengaruhi oleh faktor kliniko-sosio-demografik tetapi tidak bagi TTPF dan TTPF/RR.

Kata Kunci: peptida natriuretik; fungsi diastolik; kegagalan jantung; perfusi jantung; SPECT; penyakit jantung iskemia; penyakit koronari arteri.

(429 patah perkataan)

ABSTRACT

Title: Relationship between Plasma Natriuretic Peptide Level and SPECT-derived Diastolic Parameters.

Introduction: Diastolic dysfunction usually precedes systolic dysfunction and heart failure (HF). Patient with elevated natriuretic peptide such as N-Terminal pro Brain-type Natriuretic Peptide (NT-proBNP) without failure symptoms and normal left ventricular ejection fraction (LVEF) may suffer from asymptomatic diastolic dysfunction which is categorized under stage B HF (pre-failure stage). Imaging technique for assessment of ventricular dysfunction (diastolic and systolic) usually performed using echocardiography. However, myocardial perfusion imaging using single photon emission computed tomography (SPECT) also can provide pertinent information on ventricular function such as LVEF for systolic function, ventricular peak filling rate (PFR), second PFR (PFR2), first third mean filling rate during diastole (1/3MFR), and time to PFR (TPFR or TTPF) for diastolic performance.

Objectives: This study aims to assess the relationship of natriuretic peptide as ventricular biomarker and the diastolic parameters measured by electrocardiogram-gated myocardial perfusion SPECT (Gated MPS) among patient with normal LVEF and no evidence of myocardial ischaemia or infarction, and to analyse the association of SPECT-derived diastolic parameters with clinico-socio-demographic factors as well as to establish the centre-based reference value.

Methods: We enrolled 137 patients with normal stress & rest myocardial perfusion and LVEF. The LV volume-filling curve was automatically calculated by Quantitative Gated SPECT (QGS) software using 16-frames list mode method to derive SPECT's diastolic parameters from rest study including PFR normalised to end diastolic volume (EDV), 1/3MFR normalised to EDV, TTPF (or TPFR) and TTPF normalised to R-R interval of cardiac cycle (TTPF/RR). The potential relationship with NT-proBNP, the association with clinico-socio-demographic factors and the reference values were studied.

Results: The diastolic parameters by Gated MPS showed no correlation with NT-proBNP. PFR and 1/3MFR were consistently reduced as level of NT-proBNP increases but not statistically significant ($p = 0.231$ vs 0.348) and were influenced by age ($p = 0.003$ vs 0.002), diastolic blood pressure ($p < 0.001$ respectively) and hypertension ($p = 0.031$ vs 0.004). PFR had strong association with gender ($p < 0.001$) and heart rate ($p < 0.001$) but not 1/3MFR. There was a statistically significant difference between diabetic and non-diabetic ($p = 0.001$); hypertensive and non-hypertensive ($p = 0.004$) for 1/3MFR. Overall, only TTPF and TTPF/RR showed stable measurement with no influence observed with age, gender, blood pressure, heart rate and co-morbidities. The reference value of PFR, PFR2, 1/3MFR, TTPF and TTPF/RR as diastolic parameters were 1.55 ± 0.41, 0.70 ± 0.42, 0.79 ± 0.21, 333 ± 55 and 0.197 ± 0.044 respectively.

Conclusion: Diastolic parameters measured by QGS 16-frame Gated MPS showed no relationship with ventricular biomarker; NT-proBNP. PFR, PFR2 and 1/3MFR were influenced by clinico-socio-demographic factors but not TTPF and TTPF/RR.

Keywords: natriuretic peptide; diastolic function; heart failure; myocardial perfusion; SPECT; ischemic heart disease; coronary artery disease.

(444 words)

CHAPTER ONE

RESEARCH BACKGROUND

1.1 INTRODUCTION

Normal left ventricular (LV) diastolic function is crucial in determining the preload (LV filling) and subsequently the stroke volume (SV). LV diastolic dysfunction occurs when there is abnormal myocardial relaxation and/or increased myocardial stiffness which leads to elevated filling pressure. According to Nagueh *et al.*, 2019, patients with systolic dysfunction (drops in ejection fraction) will have concomitant diastolic dysfunction and LV diastolic dysfunction is known as a prerequisite for the development of heart failure (HF).

Even though diastolic dysfunction is one of the components required to diagnose HF particularly among patients with normal systolic function; term heart failure with preserved ejection fraction (HFpEF), not all patients with diastolic dysfunction will suffer from HF. This group of patients is usually known as asymptomatic LV diastolic dysfunction or pre-clinical diastolic dysfunction. They have normal LV systolic function and do not manifest any failure symptoms. Their risk of developing HF symptoms or death/hospitalisation annually are 10 % and 8 % respectively (Obokata *et al.*, 2019 ; Reed *et al.*, 2015, Yancy *et al.*, 2013).

About 20-30 % of the general population had asymptomatic LV diastolic dysfunction with 21 % had asymptomatic mild diastolic dysfunction and 7 % had moderate or severe diastolic dysfunction. Cardiovascular risk factors such as

hypertension (HPT), diabetes mellitus (DM) and other metabolic syndrome predispose patients in developing diastolic dysfunction (Wan *et al.*, 2014 ; Yancy *et al.*, 2013).

Currently, echocardiography is recommended and plays an important role in assessment of systolic dysfunction, diastolic dysfunction and HF. A few well accepted guidelines are available to measure echocardiographic diastolic parameters (Nagueh *et al.*, 2016 ; Nagueh *et al.*, 2020). However, myocardial perfusion using single photon emission computed tomography (SPECT) is also able to calculate ejection fraction for systolic function and diastolic parameters automatically during the imaging of myocardial perfusion.

Other than imaging, diagnostic values of natriuretic peptides as cardiac biomarkers are well established clinically and can be used to assess ventricular function. Plasma natriuretic peptides such as brain-type natriuretic peptide (BNP) and N-terminal pro brain-type natriuretic peptide (NT-proBNP) can be used to exclude the diagnosis of HF and diastolic dysfunction with negative predictive value (NPV) of 85% (Remmelzwaal *et al.*, 2020).

Patients with failure symptoms such as dyspnoea are unlikely to have HF if BNP <35 pg/mL or NT-proBNP <125 pg/mL in non-acute settings (Ponikowski *et al.*, 2016). Whereas, patient with an elevated BNP or NT-proBNP in the absence of HF symptoms were known to have asymptomatic LV dysfunction because elevated BNP or NT-proBNP reflect worsening of LV function either systolic, diastolic or both (Uraizee *et al.*, 2013 ; McGardy *et al.*, 2013). Mureddu *et al.*, 2013, found that NT-proBNP also has high NPV of 99-100% and 95.4-95.6% to exclude asymptomatic LV systolic dysfunction and diastolic dysfunction respectively in the general population.

Relationships between natriuretic peptides and echocardiographic diastolic parameters were extensively studied for patients with LV dysfunction. However, it is not the case with SPECT- derived diastolic parameters. In view of no extra imaging time, radiation exposure or additional procedure required for assessment of SPECT-derived diastolic parameters during electrocardiogram gated myocardial perfusion single photon emission computed tomography (Gated MPS), this study aims to assess the relationship between plasma natriuretic peptide (NT-proBNP) level as ventricular biomarker and SPECT-derived diastolic parameters measured by Gated MPS imaging.

Furthermore, this study is also conducted to address the lack of scientific knowledge of the SPECT-derived diastolic parameters in our centre and the association with clinico-socio-demographic factors. Subsequently, to establish the centre-based reference values for the SPECT-derived diastolic parameters in our population among patients without LV dysfunction, non-HF and no evidence of myocardial ischaemia or infarction.

CHAPTER TWO

LITERATURE REVIEW

2.1 ELECTROCARDIOGRAM GATED MYOCARDIAL PERFUSION SINGLE PHOTON EMISSION COMPUTED TOMOGRAPHY (GATED MPS)

2.1.1 Principal of Gated MPS Imaging

Myocardial perfusion imaging using single photon emission computed tomography (Gated MPS) is a well-established method as a non-invasive diagnostic tool for exclusion of ischaemic heart disease (IHD), if clinical assessment is equivocal in symptomatic patients. It is able to detect inducible ischaemia or myocardial infarction in obstructive coronary artery disease (CAD) by performing stress and rest tests prior to the imaging. Thus, it plays an important role as a gatekeeper for invasive coronary angiography (ICA) (Flotats *et al.*, 2010 ; Saraste *et al.*, 2019).

Progressive development of the software and hardware SPECT machine allows the nuclear physician to do an electrocardiogram (ECG) gating. According to Germano *et al.*, 2010, photons counting in the quantitative gated SPECT (QGS; (Cedars-Sinai Medical Centre, Los Angeles, CA, USA) software is triggered by the QRS complex of a patient's ECG wave which is called gating. This gated mode is able to reduce artifacts and improve the imaging quality from the effect of contraction-induced cardiac motion. This data can be used to represent the phase of the cardiac cycle and provide an opportunity to assess the cardiac images at specific cardiac cycles.

Thus, Gated MPS imaging offers both LV perfusion data for the assessment of myocardial perfusion and the functional parameters such as end-systolic volume (ESV), end-diastolic volume (EDV), systolic function and diastolic function from the same data source. The LV volume-filling curve is automatically calculated during the Gated MPS imaging and may help to investigate the LV systolic and diastolic functions (Yoshino *et al.*, 2010 ; Assante *et al.*, 2018).

One cardiac cycle can be manually reframed into a few subsets for LV functional assessment. Storing and splitting the R-R interval data in a list mode file can help the user to determine the number of frames needed per cardiac cycle. It is known that standard 8 frames Gated MPS does not give any meaningful diastolic function measurement, 12 frames are adequate, but 16 frames are more effective for diastolic measurement in Gated MPS (Germano *et al.*, 2010 ; Sarebani *et al.*, 2020).

2.1.2 Conventional sodium iodide and cadmium zinc telluride gamma camera

The basic component of the SPECT machine is the gamma camera that has the ability to produce tomographic images. Further technological advancement in the SPECT machine allows the user to reduce the imaging time because of the use of new detector materials. Conventionally, gamma cameras utilises the property of sodium iodide (NaI) on the detector to convert the emitted photons into light and finally become an electric signal in the form of electrons.

Recent technology uses cadmium zinc telluride (CZT) instead of NaI especially for cardiac-dedicated SPECT machines. CZT detectors are able to convert the detected

'emitted photons' from the patient directly into the electrical signals, thus reducing the imaging time.

Cardiac imaging performed using CZT SPECT camera is proven to be able to reduce the imaging time by 4 times as compared to conventional NaI SPECT camera without affecting the image quality. Gimelli *et al.,* 2014, reported that it is feasible to measure LV diastolic function in the Gated MPS using CZT SPECT camera. Patel *et al.,* 2008, stated that SPECT's diastolic parameters are able to predict the presence of elevated LV filling pressure.

2.1.3 Gated MPS Protocol

2.1.3.1 Clinical indication

In general, Gated MPS is indicated for diagnostic exclusion of IHD, risk stratification among patients with known CAD prior non-cardiac surgery or post-acute coronary syndrome without prior coronary angiogram as well as for prognostic evaluation prior intervention.

According to 2019 ESC Guidelines for the Diagnosis and Management of Chronic Coronary Syndromes, Gated MPS as a non-invasive diagnostic test is indicated in intermediate pre-test probability of IHD in which moderate clinical likelihood of obstructive CAD is suspected (Knuuti *et al.*, 2019).

Appropriate use criteria by ACCF/ASNC 2009 stated that radionuclide imaging is appropriate in all symptomatic patient with chest pain, angina equivalent or ischaemic ECG changes (ischaemic equivalent) which belongs to intermediate or high risk pre-test probability of IHD based on The Diamond and Forrester model. Imaging is also

appropriate for symptomatic patients with low risk pre-test probability of IHD but has uninterpretable ECG, unable to perform physical exercise stress test or patient with acute chest pain without ECG changes or elevated troponin.

Asymptomatic patient with high cardiovascular risk factors such as DM, peripheral artery disease, elevated troponin without other evidence of acute coronary syndrome, ventricular tachycardia, episode of syncope in intermediate risk patient without 'ischemic equivalent' or recently diagnosed with HF and LV systolic dysfunction for investigation are considered appropriate to undergo radionuclide cardiac imaging (Hendel *et al.*, 2019).

2.1.3.2 Technique and protocol

Gated MPS imaging can be performed using 1-day or 2-day protocol at rest or following a stress test. Separating rest and stress Gated MPS imaging into 2 separate days (2-day protocol) allow more patients to be imaged in 1 day. However, it requires the patient to come for the next follow-up imaging. The 1-day protocol Gated MPS requires administration of a lower radiotracer activity (approximately one-fourth of the total dose) for the first injection and a higher activity (about three-fourths of the total dose) for the second injection.

Stress tests can be performed either by physical exercise or using pharmacologic stress agent injection such as adenosine, dipyridamole or dobutamine. However, the majority of the patients referred for Gated MPS are unable to perform or have a non-diagnostic physical exercise stress test.

The initial protocol in 1990's required a 2-hour delay between the injections for a 1-day protocol. It is to allow the first dose to decay, maximising count density ratio and

minimising shine-through on the second scan. By increasing the activity of the second injection, it can provide the same count density ratio achieved by letting the first dose decay for 20 % in 2 hours. Thus, a 3:1 dose ratio with a 2-hour delay and a 3.5 to 4:1 dose ratio with no delay can provide comparable imaging results for 1-day stress/rest and rest/stress protocols (Henzlova *et al.*, 2016).

2.1.3.3 Technetium-99m as radiotracer

Initially, the radiotracer of choice for cardiac perfusion imaging was thalium-201 (Tl-201). After the development of technetium-99m based radiotracers (Tc-99m), it has become the preferred radiotracer due to lesser radiation exposure, which is approximately 0.3 mSv per mCi (0.009mSv per MBq) of injected Tc-99m.

Tc-99m Tetrofosmin and Tc-99m Sestamibi are widely used for Gated MPS imaging. They have similar physical and chemical characteristics such as half-life of 6 hours, emitting 140 keV photons, lipid-soluble and diffuse into myocardium tissue depending on blood flow and subsequently retain in the mitochondria with negligible washout (no significant redistribution).

Majority of the injected Tc-99m radiotracer are excreted via the hepatobiliary system and into the gastrointestinal tract. Therefore, optimal imaging time is mostly dependent on the hepatobiliary and gastrointestinal activity after Tc-99m radiotracer is injected (Henzlova *et al.*, 2016 ; Flotats *et al.*, 2010).

2.1.3.4 Advantages and radiation precaution

The 'new technology reduced-dose protocol' in Gated MPS has shown dramatic reduction of radiation exposure because CZT SPECT camera can provide better image quality despite the reduction of radiotracer dosage.

The 1-day protocol Gated MPS using CZT SPECT camera is shown to have one-half of radiation effective dose from 1-day protocol Gated MPS using conventional NaI SPECT camera. There is also a report of total radiation exposure of 5.4 mSv from hybrid imaging of cardiac SPECT combined with computed tomography (CT) which is lower than ICA (Flotats *et al.*, 2010 ; Husmann *et al.*, 2009).

2.2 EVALUATION OF LEFT VENTRICULAR FUNCTION

2.2.1 The cardiac cycle

Cardiac cycle of the heart reflects its ability to alternately switch between two functional states of ventricular relaxation for filling during diastole and ventricular contraction to eject the blood into vascular circulation during systole. A normal cardiac cycle is important to provide adequate LV filling and LV ejection during strenuous or resting state. Therefore, understanding the normal cardiac function is necessary to appreciate the pathophysiological process and information derived from the cardiac imaging.

2.2.2 Heart failure

Heart failure (HF) is a clinical syndrome with a collection of symptoms such as breathlessness and signs of excessive fluid retention such as peripheral oedema caused by cardiac functional and/or structural abnormality such as IHD, conduction disorder and valvular heart disease. When the heart fails, it is unable to maintain a sufficient blood supply to the organs.

There are 4 stages of HF which can be divided into pre-failure (stage A & stage B) and establish HF (stage C & stage D). Patients are classified as stage A HF if they have high risk co-morbids to develop HF such as HPT, DM or metabolic syndrome but do not have any clinical symptoms, structural or functional heart disease. Stage B HF has no sign or symptoms of HF but has structural/functional heart disease such diastolic dysfunction. Stage C & D patients have clinical HF symptoms and can be further classified based on their systolic function (Yancy *et al.*, 2013).

In Malaysia, a HF patient has 22.9 % mortality incidence within 4 years follow-up and 38 % is due to IHD (Zainal Abidin *et al.*, 2019). Historically, measurement of LV ejection fraction (LVEF) during systole is used to classify HF. Patients with normal LVEF (typically ≥50 % is called HF preserved ejection fraction (HFpEF) and patients with low LVEF are called HF reduced ejection fraction (HFrEF). This classification is important due to the difference underlying aetiology, therapeutic response and prognostication.

Based on Ponikowski *et al.*, 2016, the diagnosis of HFrEF depends on 2 criteria; the clinical signs and/or symptoms of HF and the presence of reduced LVEF. Whereas, HFpEF is more difficult to diagnose. HFpEF patients often have increased LV pressure with additional sign of impaired LV filling or suction ability, term as diastolic dysfunction. Diagnostic criteria for HFpEF are sign and/or symptoms of HF, normal LVEF of 50 or more, increased natriuretic peptide level (BNP more than 35 pg/mL or NT-proBNP more than 125 pg/mL), evidence of diastolic dysfunction by echocardiography or presence of LV hypertrophy (LVH) and/or left atrial enlargement.

2.2.3 LV diastolic dysfunction

LV dysfunction is a cardinal sign of HF. Systolic component of the LV function is easily assessed by measuring the LVEF. However, diastolic function is clinically more difficult to assess. The changes in LV stiffness, volume and pressure are the important components that ideally should be assessed invasively by cardiac catheterisation to directly measure the LV filling pressure and volume.

LV diastolic dysfunction occurs when there is an impairment of myocardial relaxation and/or LV chamber stiffness (Obokata *et al.*, 2020). The normal ventricular myocardium has an ability to generate force through an active process to return to a

relaxed state. During diastole, energy is required for re-uptake of the bound calcium on the troponin into the sarcoplasmic reticulum. This results in actin-myosin cross bridge detachment and reducing cellular tension. Prolongation or impairment of these processes lead to impaired LV relaxation and subsequently causing elevated LV filling pressure either at rest or during exertion (Nagueh *et al.*, 2019).

Wan *et al.*, 2014, stated that the prevalence of asymptomatic LV diastolic dysfunction in the general population is about 20-30 %. Based on Yancy *et al.*, 2013, patients with asymptomatic LV diastolic dysfunction can be categorised as stage B HF and their risk of developing HF symptoms are about 10 %. Meanwhile, an 8 years follow-up study by Kosmala *et al.*, 2020, showed that a patient with LV dysfunction has 2.5 times annualized event rate of overt HF progression as compared to those with normal LV function.

A meta-analysis by Echouffo-Tcheugui *et al.*, 2016, showed that the risk of LV systolic dysfunction versus LV diastolic dysfunction progressing to HF were 500 % and 70 % respectively. However, diastolic dysfunction usually precedes systolic dysfunction. On top of that, Nagueh *et al.*, 2019, stated that patients with systolic dysfunction will have concomitant diastolic dysfunction. Therefore, detection of LV diastolic dysfunction is essential because an appropriate treatment can positively impact the disease outcome.

Echocardiography has become the main imaging modality to study systolic and diastolic function. In the setting of diastolic dysfunction, a few echocardiographic parameters such as peak early mitral annular velocity (e'), ratio peak early mitral annular velocity (e/e') and many other parameters have become a part of the standard measurement in the guideline. (Nagueh *et al.*, 2016 ; Nagueh *et al.*, 2019).

Nevertheless, the diastolic parameters measured during Gated MPS also had been extensively studied. The most common SPECT parameters representing diastolic functions are peak filling rate (PFR) which indicates greatest filling rate in early diastole, second peak filling rate (PFR2) due to left atrial contraction, first third mean filling rate (1/3MFR) at the first 3rd diastolic phase, time to peak filling rate (TTPF) which is also known as TPFR and TPFR/RR which normalised to heart rate (refer Table 1). The rule of thumb is PFR and 1/3MFR will be reduced and TTPF will be increased in patients with LV dysfunction of various aetiology. (Nakae *et al.*, 2014 ; Nakajima *et al.*, 2016).

2.2.4 Imaging of the left ventricle

In view of clinical practicality, there are a few non-invasive methods available to measure LV function such as echocardiography, multi-gated acquisition (MUGA), cardiac SPECT, cardiac positron emission computed tomography (PET) and cardiac magnetic resonance imaging (MRI). Currently, transthoracic echocardiography is the gold standard for non-invasive LV function assessment due to its availability, radiation-free and excellent temporal resolution. Unfortunately, it still suffers from low spatial resolution as compared to cardiac MRI.

2.2.5 Overview of natriuretic peptide level in LV diastolic dysfunction

Natriuretic peptides such as BNP and NT-proBNP are cardioprotective hormones secreted by the ventricular myocardium. The binding of active natriuretic peptide which is BNP to natriuretic peptide receptor leads to vasodilation, natriuresis, diuresis and kaliuresis.

The production of BNP and NT-proBNP occur when there is stretching of the ventricular myocardial wall in response to volume or pressure overload. Elevated

ventricular wall stress activates the BNP-encoding gene known as NPPB in the myocardium leading to the production of an intracellular polypeptide with 134 amino acid residues called preproBNP.

Subsequently, a signal peptide of the preproBNP is cleaved to produce a 108 amino acid proBNP. The proBNP is further cleaved by serine protease corin into physiologically active 32 amino acid BNP and a biologically inactive 76 amino acid NT-proBNP. The BNP and NT-proBNP are released into the circulation mainly through the coronary sinus. The half-life of NT-proBNP is longer than the BNP and about 25% of these natriuretic peptides are cleared by the kidney (Verstreken *et al.*, 2019).

European Society of Cardiology (ESC) on acute and chronic heart failure guidelines 2016, stated that patient with mild dyspnoea in non-acute setting that has BNP or NT-proBNP value of less than 35 pg/mL and 125 pg/mL respectively do not have heart failure (HF). Any patient presented to casualty with acute failure symptoms most likely do not have HF if BNP less than 100 pg/mL or NT-proBNP less than 300 pg/mL. The overall negative predictive value (NPV) of the natriuretic peptides to exclude HF was 0.94-0.98 (Ponikowski *et al.*, 2016 ; Nabeshima *et al.*, 2020).

However, in obese patient with body mass index (BMI) more than 30, NT-proBNP less than 100 pg/mL is used as the cut off value for diagnostic exclusion of HF due to suppression of BNP gene by circulating factors produced by adipocytes (Galinier *et al.*, 2018).

Remmelzwaal *et al.*, 2020, stated that the BNP and NT-proBNP are able to exclude diastolic dysfunction in patients with cardiovascular risk factor but normal systolic function with a NPV of 0.85. NT-proBNP level was found to be similar (NT-

proBNP <70 pg/mL) among healthy control and hypertensive patients without echocardiographic diastolic dysfunction (Dhungana *et al.*, 2019).

An elevated BNP or NT-proBNP in healthy individuals or patients with cardiovascular risk factors without failure symptoms are indicative for the presence of subclinical ventricular dysfunction (Uraizee *et al.*, 2013 ; McGardy *et al.*, 2013). PONTIAC trial follow-up 300 diabetic patients with an elevated NT-proBNP level of >125 pg/mL but no evidence of cardiac diseases except LV diastolic dysfunction. They found that these diabetic patients will benefit from renin-angiotensin system antagonist and beta blocker to prevent progression to HF (Huelsmann *et al.*, 2013).

Unfortunately, an elevated plasma BNP or NT-proBNP are unable to distinguish between systolic or diastolic dysfunction that cause the myocardial wall stress or the heart to fail. These cardiac biomarkers need to be interpreted in conjunction with other modalities such as imaging to assess ventricular function (Mueller *et al.*, 2019).

It is found that as the function of LV declines, the level of this natriuretic peptide increases. Therefore, its concentration level in the circulation can indirectly determine those with asymptomatic LV diastolic dysfunction as well as its severity (Gong *et al.*, 2016 ; Stępień-Wałek *et al.*, 2015 ; Verstreken *et al.*, 2019).

Plasma natriuretic peptide level in diastolic dysfunction was extensively studied using echocardiography parameters but not with Gated MPS. Thus, the relationship between plasma natriuretic peptide and SPECT- derived diastolic parameters is not known.

Uraizee *et al.*, 2013, assessed diastolic function using echocardiography and found that NT-proBNP elevation in asymptomatic HPT patients with preserved LVEF

was due to subclinical diastolic dysfunction. Dhungana *et al.*, 2019, found that hypertensive patients without echocardiographic diastolic dysfunction had NT-proBNP <70 pg/ml and patients with diastolic dysfunction had elevated NT-proBNP. Hence, NT-proBNP may be useful for detection of early LV diastolic dysfunction.

Takahari *et al.*, 2020, studied the blood pressure (BP) variability during follow up in 72 HPT patient and found that NT-proBNP level was significant and moderately correlated with systolic BP ($r = 0.4$) and diastolic BP ($r = 0.3$) but neither BP variability nor NT-proBNP were significantly correlated with echocardiographic diastolic parameters ($p = 0.52$).

This could be explained by Litwin *et al.*, 2020, whereby they stated that echocardiographic diastolic parameters only had accuracy of 75-84 % in identifying patients with elevated LV filling pressure measured invasively through catheterisation. The individual echocardiographic diastolic parameters such as e/e' had not performed well in predicting LV filling pressure. However, diagnostic value of both echocardiographic diastolic parameters and natriuretic peptides in identifying elevated LV filling pressure showed similar accuracy.

Hata *et al.*, 2020, had divided 4 group of patients based on NT-proBNP level and found that rest PFR ($p = 0.001$) and rest 1/3MFR ($p = 0.008$) by Gated MPS using CardioREPO (cREPO; FUJIFILM RI Pharma, Co. Ltd., Tokyo, Japan/EXINI Diagnostics, Lund, Sweden) software was significantly associated with the NT-proBNP level but not with rest TTPF or rest TTPF/RR. Those patients with NT-proBNP <125 pg/mL showed significantly higher PFR (2.51 ± 1.11) and 1/3MFR (1.41 ± 0.55) values than patients with NT-proBNP level >400 pg/mL. However, among patients with NT-

proBNP <125 pg/mL, they found out that about 15 % of the patients had LV diastolic dysfunction measured by echocardiography.

2.2.6 LV diastolic parameters by cardiac SPECT

A few efforts by previous researchers showed that the changes on diastolic parameters measured by Gated MPS such as PFR, PFR2, 1/3MFR, TTPF, TTPF/RR, % stress/rest PFR can be used to assess the LV diastolic function. It is known that the PFR, 1/3MFR and % stress/rest PFR will usually be lower in patient with cardiac diseases whereas TTPF and TTPF/RR values will be higher than normal people (Mizunobu *et al.*, 2013 ; Nakajima *et al.*, 2016).

The definitive cut-off value for the SPECT diastolic parameters varies considerably due to study heterogeneity. Researchers use different types of SPECT camera (conventional versus newer technology CZT), different software such as QGS, cREPO, 4DM-SPECT/Corridor 4DM (Michigan University/INVIA, LLC, Ann Arbor, MI) or heart function view (HFV; Nihon MediPhysics Co., Ltd), different radiotracer (Tc-99m-based versus Tl-201), different Gated MPS protocol (stress versus rest diastolic parameters) and even compare it with different imaging modalities (ie; echocardiography, MUGA, cardiac MRI). Therefore, it is essential to determine centre-based reference values.

On top of that, there are also mixed findings regarding diastolic function measured by different modalities. Study by Gimelli *et al.*, 2014, found that echocardiographic e/e' was significantly correlated with rest PFR ($r = -0.45$, $p < 0.001$) and rest TPFR ($r = 0.39$, $p < 0.001$) on 16 frames Gated MPS using CZT SPECT camera.

Whereas, Bigdeloo *et al.*, 2019, studied diastolic function in 49 patients using 16 frames Gated MPS and found that only rest 1/3MFR had significant correlation with echocardiography diastolic parameters. Lastly, Bennett *et al.*, 2014, showed that grade I diastolic dysfunction on echocardiography had prolong TTPF (with possible normal or elevated PFR) and grade III or IV has lower PFR (with possible normal or prolong TTPF) if compared with 16 frames Gated MPS.

Chono *et al.*, 2018, showed that PFR, 1/3MFR and TPFR/RR (@TTPF/RR) calculated using 2 different SPECT software; QGS and HFV at rest were significantly correlated with echocardiographic e' if ESV >20 mL. In smaller ESV <20 mL, only PFR measured by HFV was significantly correlated with peak early mitral annular velocity (e′) ($r = 0.47$, $p = 0.006$) but not by QGS.

Patel *et al.*, 2008, reported that post- stress diastolic parameters derived from the dual radionuclide (Tc- 99m/ Tl- 201) Gated MPS was correlated to LV end diastolic pressure (LVEDP) measured by cardiac catheterisation with positive predictive value (PPV) of >54 % and NPV of >90 %. They suggested that the optimal cut-off values for PFR, 1/3MFR (or 1/3FR) and TPFR (or TTPF) for detection of LVEDP of 18 mmHg or more were ≤ 2.57 EDV/s, ≤ 1.52 EDV/s and ≥ 161 ms respectively.

2.2.7 Association of LV diastolic dysfunction with clinico-socio-demographic

Based on Akincioglu *et al.*, 2005, the post-stress PFR showed correlations with age ($r = -0.3, p < 0.01$), LVEF ($r = 0.6, p < 0.01$), and post-stress HR ($r = 0.5, p < 0.01$) but not with gender. However, these parameters (i.e.; age, gender, LVEF, post stress HR) had no correlation with TTPF among 90 participants without known cardiac disease, no diabetes mellitus (DM), no HPT, normal ECG as well as normal exercise Gated MPS imaging using 16 frames/cardiac cycle.

Sayed *et al.*, 2015, had compared the diastolic parameters among 30 patients with and without HPT underwent 1-day protocol stress and rest Gated MPS using 16 frames. They found that stress PFR and 1/3MFR were significantly lower in HPT patients ($p < 0.05$). The rest-PFR and rest-1/3MFR were also lower in HPT patients compared to non-HPT. Meanwhile, the stress and rest TTPF values among HPT patients were higher than non-HPT. However, these parameters were not statistically significant.

Korkmaz *et al.*, 2017, also studied diastolic parameters of 40 DM and 40 non-DM patients with similar age and gender. They underwent 1-day stress & rest Gated MPS 8 frames and their diastolic parameters were calculated by QGS software. They noted that PFR was significantly lower in DM than non-DM patients (2.31 ± 0.68 vs. 2.76 ± 0.68, respectively; $P = 0.004$) but not 1/3MFR and TTPF. They also noted that PFR was significant negatively correlated with EDV, ESV and significant positively correlated with LVEF in both DM and non-DM patients.

CHAPTER THREE

RATIONALE & BENEFIT OF THE STUDY

Natriuretic peptide is an excellent ventricular biomarker for an exclusion of HF and its elevation indicates ventricular dysfunction. It is well known that progression of HF is preceded by diastolic dysfunction and/or systolic dysfunction. Even though echocardiography plays an important role in the diagnosis of HF and LV dysfunction, Gated MPS is also an established method for simultaneous assessment of LV function during myocardial perfusion study. The ability to automatically measure the LV systolic and diastolic parameters by Gated MPS may improve clinical detection of LV diastolic dysfunction in a single diagnostic test without any extra cost. Subsequently, raise a clinical awareness about possible diagnosis of LV diastolic dysfunction or HFpEF among the nuclear physician.

On top of that, previous studies showed that definitive reference values for the interpretation of diastolic parameters from Gated MPS must be done based on centre-specific imaging protocol. At Hospital Sultanah Aminah, Johor Bahru (HSAJB), Gated MPS imaging is widely used as one of the cardiology diagnostic tools among our cardiologists and district physicians. Therefore, we can use the data from our pool of patients with normal LV systolic function and no evidence of myocardial perfusion defect on Gated MPS imaging and analyse the relationship of the diastolic parameters with plasma natriuretic peptide. The results from the study could provide deeper understanding of the diastolic parameters measured from Gated MPS for the utilisation in daily clinical work.

3.1 AIM

This study aims to address the lack of scientific knowledge of the SPECT- derived diastolic parameters measured during Gated MPS imaging using CZT SPECT gamma camera.

3.2 OBJECTIVES

3.2.1 General Objectives

The objective of this study is to assess the relationship between plasma natriuretic peptide level and diastolic parameters measured during rest scan/study of Gated MPS, to analyse the association of SPECT-derived diastolic parameters with clinico-socio-demographic factors as well as to establish the reference values of the SPECT-derived diastolic parameters.

3.2.2 Specific Objectives

1. To assess the relationship between plasma natriuretic peptide; NT-proBNP as a ventricular biomarker and SPECT-derived diastolic parameters among patient with normal LV systolic function and myocardial perfusion from Gated MPS imaging.
2. To evaluate the association between SPECT-derived diastolic parameters among patients with normal LV systolic function and myocardial perfusion from Gated MPS imaging and its clinico-socio-demographic data.
3. To establish reference value of SPECT-derived diastolic parameters among patients without LV dysfunction, non-HF and no evidence of myocardial ischaemia or infarction in the southern region of Malaysia using Gated MPS imaging and NT-proBNP as ventricular biomarkers.

3.3 HYPOTHESIS STATEMENT

Null Hypothesis

- There is no relationship between the level of plasma natriuretic peptide (NT-proBNP) as ventricular biomarker and SPECT-derived diastolic parameters among patients with normal LV systolic function and myocardial perfusion from Gated MPS imaging.

Alternative Hypothesis

- There is a relationship between the level of plasma natriuretic peptide (NT-proBNP) as ventricular biomarker and SPECT-derived diastolic parameters among patients with normal LV systolic function and myocardial perfusion from Gated MPS imaging.

CHAPTER FOUR

MATERIALS AND METHODS

4.1 STUDY POPULATION AND CRITERIA

We enrolled 137 patients with normal Gated MPS at the Nuclear Medicine department of Hospital Sultanah Aminah Johor Bahru between February 2020 to February 2021. The Gated MPS was imaged by cardiac-dedicated CZT SPECT gamma camera for 5 minutes each scan/study. Normal Gated MPS imaging is defined as normal myocardial perfusion and normal LV systolic function post stress & rest (LVEF > 50 %).

The images were selected to study the LV diastolic function (SPECT-derived diastolic parameters) from rest scan using list mode method. Their clinical and sociodemographic data were taken at the time of the imaging day. About 2mL of peripheral venous blood taken in ethylene-diamine-tetra-acetic acid (EDTA) tube during branula insertion were used for NT-proBNP point-of-care measurement for evaluation of LV function.

Participants aged more than 70 years old, long-standing HPT, DM, dyslipidaemia of more than 5 years, renal failure, known history of myocardial infarction, previous coronary artery bypass graft (CABG) surgery, previous imaging or angiogram-proven CAD, cardiomyopathy, structural heart disease, valvular heart disease, congenital heart disease, presence of cardiac arrhythmia on ECG or positive ECG-stress test were excluded from the study.

4.1.1 Inclusion Criteria

i. Normal Gated MPS defined by normal myocardial perfusion and normal LV systolic function post stress & rest (LVEF > 50 %).

ii. Plasma natriuretic peptide (NT-proBNP) measurement available.

4.1.2 Exclusion Criteria

i. Age >70 years old

ii. Pregnancy/ breast feeding

iii. Known obstructive CAD proven by angiogram/history of myocardial infarction (MI) / CABG.

iv. Previous history of cardiomyopathy, structural heart disease, valvular disease, cardiac arrhythmia or heart failure

v. Long standing hypertension (HPT) or diabetes mellitus (DM) >5 years

vi. Renal failure on dialysis (ESRF)

vii. ECG evidence of arrhythmia, ischaemia or infarction

4.2 STUDY DESIGN AND SAMPLING METHOD

Prospective, universal sampling, single centre study. Sampling was among patients with normal Gated MPS imaging who fulfilled inclusion & exclusion criteria.