COMPARATIVE STUDY OF ECHOCARDIOGRAPHIC DOPPPLER FLOW VELOCITIES IN LEFT VENTRICULAR APICAL, MID AND OUTFLOW AREA IN PATIENTS WITH HEART FAILURE AND NORMAL SUBJECTS.

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TABLE OF CONTENTS PAGE

ABBREVIATION

A	-Away (from transducer)
AHA	-American Heart Association
CI	-Confidence Interval
CLT	-Central Limit Theorem
CO	-Cardiac Output
DTI	-Doppler Tissue Imaging
E/A ratio	-Early/active ratio
ECHO	-Echocardiography
E/e'	-Early/early(prime) ratio
EF	-Ejection fraction
EIVPD	-Ejection intra ventricular pressure gradient
FS	-Fractional shortening
HF	-Heart Failure
HFpEF	-Heart Failure preserved Ejection Fraction
HFrEF	-Heart Failure reduced Ejection Fraction
HUSM	-Hospital Universiti Sains Malaysia
IVPG	-Intra Ventricular Pressure Gradient
IVS	-Intra Ventricular Septum
LAD	-Left atrial dimension
LV	-Left Ventricle
LVD	-Left Ventricle Diameter
LVEDP	-Left Ventricle End Diastolic Pressure

LVIDd	-Left Ventricle Internal Diameter diastolic
LVIDs	-Left Ventricle Internal Diameter systolic
LVM	-Left Ventricle Mass
LVOT	-Left Ventricular Outflow Tract
MAPSE	-Mitral Annular Plane Systolic Excursion
NHANES	-National Health and Nutritional Examination Survey
PG	-Pressure Gradient
RA	-Right Atrium
RV	-Right ventricle
RWMA	-Regional Wall Motion Abnormality
SD	-Standard Deviation
STI	-Speckled Tracking Image
SV	-Stroke Volume
T	-Towards (to the transducer)
TAPSE	-Trans Annular Pulmonary Systolic Excursion
TEI index	-Myocardial Performance Index

LIST OF TABLES PAGE

LIST OF FIGURES PAGES

ABSTRACT (ENGLISH VERSION)

INTRODUCTION : Heart failure remained as a one of the major contributory factor for hospitalization and mortality, not only in Malaysia, but the whole world wide as well. Thus, detection at the earlier phase especially at the preclinical phase is crucial for preventive measure. Ejection fraction (EF) is one of the ECHO parameters that has been widely used, particularly to asses systolic LV function. Nevertheless, its value limited in preclinical phase and load dependence indices, thus regional wall motion abnormality assessment has been postulated as one of the modalities for LV systolic indices. This has been proven from the previous study as tissue Doppler imaging has been useful to detect regional myocardial wall strain and further studies showed myocardial wall strain rate and speckled tracking image had given an accurate measurements of regional LV wall contractility and correlate better with the global systolic function.

Unfortunately, those parameters were not widely used as it required high technical skills and experience. Thus, other modalities to assess regional wall motion abnormality were studied. This study primarily design to evaluate intraventricular velocities and pressure gradient that might representing one of the modalities to asses regional LV wall contractility in a simple way yet accurate. We used earlier animal data illustrating the usefulness of those parameters in assessment of regional contractile function.

METHOD AND RESULTS : This was comparative cross sectional echocardiography pilot study. Approximately 42 patients presented to HUSM with heart failure symptoms were identified and screening ECHO were done. 12 patients were excluded from this study as not fulfilled inclusion and exclusion criteria. 30 healthy volunteered from HUSM staff were recruited into normal group after screening ECHO was applied.

We evaluate intraventricular velocities and pressure gradient at 3 area in LV cavity (left ventricular outflow tract (LVOT), mid and apical) which were sampled by pulse wave Doppler.

Mean of intraventricular velocities and pressure gradient were recorded highest at LVOT area compare to other area among heart failure patients (1.51 and 3.01 respectively), also those values were higher if sampled towards (T) the transducer compare to away (A) the transducer in each area of LV cavity.

Comparative study between heart failure patients and normal group revealed significant value ($p<0.01$) by using intraventricular pressure gradient that was sampled at the LVOT and mid area (away and towards the transducer). Meanwhile, no significant value in comparison between those 2 groups by using intraventricular velocities.

There were no significant value in relationship between intraventricular velocities and pressure gradient with other systolic indices and ECHO parameters.

CONCLUSION : Intraventricular pressure gradient remain as one of the significant modalities to asses regional wall motion abnormality if sampled at the LVOT and mid area.

ABSTRACT (MALAY VERSION)

PENGENALAN : Kegagalan fungsi jantung merupakan salah satu faktor major dalam menyumbang kepada penyebab kemasukan hospital dan kematian, bukan hanya di Malaysia malah di serata dunia. Justeru itu, pengesanan awal terutamanya di fasa pra klinikal merupakan perkara yang penting sebagai langkah pencegahan awal. Ejection fraction (EF) atau fraksi keluaran merupakan salah satu parameter dalam ujian ECHO dan diguna pakai secara meluas terutamanya dalam menentukan fungsi sistolik kamar kiri jantung. Namun demikian, penggunaanya terhad dalam fasa pra klinikal dan kebergantungan muatan indikator. Keabnormalan pergerakan dinding setempat dikatakan salah satu cara untuk menentukan fungsi sistolik kamar kiri jantung. Ini telah dibuktikan melalui kajian terdahulu yang dimana kajian tisu Doppler boleh diguna pakai untuk mengenal pasti keabnormalan pergerakan dinding setempat dan kajian seterusnya telah membuktikan kadar keregangan dinding jantung dan imej penjejak bertaburan adalah salah satu kaedah yang tepat untuk menentukan kontraksi dinding setempat di kamar kiri jantung dan seterusnya dihubung kait dengan fungsi sistolik global

Namun demikian, parameter tersebut tidak diguna pakai secara meluas disebabkan penggunaanya yang memerlukan daya teknik yang tinggi dan pengalaman yang meluas. Disebabkan itu, kaedah lain dikaji untuk menentukan keabnormalan dinding setempat. Kajian ini dibentuk untuk menentukan samaada kelajuan dan beza tekanan dalam kamar kiri jantung boleh dijadikan salah satu kaedah untuk menentukan keabnormalan dinding jantung setempat secara mudah dan tepat. Kami menggunapakai data terdahulu ke atas haiwan untuk memberi gambaran penggunaan parameter ini dalam menentukan keabnormal pergerakan dinding jantung setempat.

KAEDAH DAN KEPUTUSAN : Ini adalah kajian rintis perbandingan ekokardiografi secara keratan rentas. Kira-kira seramai 42 pesakit yang datang ke HUSM dengan tanda-tanda kegagalan fungsi jantung telah dikenal pasti dan tapisan ECHO telah dibuat. Seramai 12 pesakit telah dikeluarkan dari kajian ini kerana tidak memenuhi ciri-ciri inklusif dan ekslusif yang dikehendaki. 30 sukarelawan yang terdiri dari kakitangan anggota HUSM telah dikenal pasti dan dimasukkan ke dalam kumpulan normal setelah tapisan ECHO dibuat. Kami menilai kelajuan dan beza tekanan di tiga tempat dalam kamar kiri jantung (laluan keluar kamar kiri jantung,tengah dan hujung) melalui persampelan denyutan gelombang Doppler.

Purata kelajuan dan beza tekanan dalam kamar jantung direkodkan tertinggi di laluan keluar kamar kiri jatung berbanding di tempat lain dalam kumpulan pesakit kegagalan jantung (1.51 dan 3.01 setiap satu), juga nilai tersebut direkodkan tinggi jika persampelan dibuat ke arah transduser berbanding menjauhi transduser di setiap tempat dalam kamar jantung kiri.

Kajian perbandingan antara kumpulan pesakit kegagalan jantung dan kumpulan normal menunjukkan nilai yang signifikan dengan menggunakan beza tekanan melalui persampelan di laluan keluar kamar kiri jantung dan kawasan tengah (ke arah(A) dan menuju (T) ke trasduser). Namun demikian, tiada nilai signifikan jika pebandingan antara dua kumpulan tersebut dengan menggunakan persampelan kelajuan.

Tiada nilai yang signifikan dalam kesaling hubungan antara purata kelajuan, beza tekanan dalam kamar kiri jantung berbanding indikator fungsi sistolik dan parameter ECHO yang lain.

KESIMPULAN: Beza tekanan dalam kamar kiri jantung masih boleh dijadikan sebagai salah satu kaedah yang signifikan untuk menentukan keabnormalan pergerakan dinding setempat jika persampelan dilakukan di laluan keluar dan tengah kamar kiri jantung

CHAPTER ONE

INTRODUCTION

1.1 Prevalence of heart failure

Heart failure (HF) is a major health problem because of its high prevalence and incidence with almost 65 million worldwide, and poor prognosis (Roger VL et al,AHA circ.2011). In the United States, prevalent cases of HF now exceed 5.8 million and each year >550 000 new cases are diagnosed (Hunt SA et al,JM Coll Cardiol.2009).

The prevalence of HF in South East Asia was estimated ranges from 1.3%-6.7% throughout the region (Guo et al.2013). According to Ponikowski et al, limited single-centre data in Malaysia and Singapore suggest that the prevalence of HF in Southeast Asian countries was higher compared with countries in the rest of the world (4.5–6.7% vs. 0.5–2% respectively), including North America and European countries (Ponikowski et al,ESC HF 2014). Based on article by Carolyn S.P Lam, published in ESC HF 2015, the high prevalence of HF in south east Asia was largely attributed by the high prevalence of cardiovascular risk factors among south east Asian population. Firstly, the prevalence of hypertension in Southeast Asians was high (>24% in Cambodia and Laos) compared with the UK (15.2%) or US (13.4%). Secondly, raised blood glucose /diabetes is a notable risk factor among Southeast Asians, reaching similarly high prevalence in Brunei, Malaysia, Singapore and Thailand compared with the UK and USA. Finally, the high prevalence of smoking was of concern, with smoking rates much higher in Southeast Asian countries (up to 36.5% in Indonesia) than UK or USA. This adverse lifestyle habit,

coupled with physical inactivity particularly in Malaysia (51.6%), may contribute to the high premature mortality from cardiovascular diseases in these Southeast Asian countries (Carolyn S.P et al,ESC HF 2015).

In Malaysia, HF was an important cause of hospitalization accounting for about 6% - 10% of all acute medical admissions (Chong AY,European J HF,2003). About 25% of patients with HF were readmitted within 30 days for acute decompensation. Therefore HF poses a major health and economic burden (Go AS et al,AHA circ. 2013).

1.2 Pathophysiologic changes in heart failure.

Based on the European society of cardiology (ESC) guideline 2016, HF was defined as a clinical syndrome characterized by typical symptoms which are breathlessness, ankle swelling and fatigue that may be accompanied by signs such as elevated jugular venous pressure, pulmonary crackles and peripheral edema. These symptoms and signs occurred resulted from a structural and/or functional cardiac abnormality that may leads to reduced cardiac output and/or elevated intra cardiac pressures at rest or during stress (P.Ponikowski et al, ESC guideline 2016).

Most common causes and attributed risk factors for heart failure were hypertension, coronary artery disease and diabetes mellitus. Those risk factors prevalence were illustrated by using data from Framingham and Olmsted County studies(Levy D et al, JAMA 1996 and Dunlay Sm et al,Am J med 2009).

Nevertheless, several studies demonstrated the most prevalence of attributed risk factors among HF patients was coronary artery disease. This was proven from Fox et al, using angiography, concluded that coronary disease was causal in 52% of new HF cases in patients aged >75 years old (Fox KF et al,Eur Heart J 2001), Gheorghiade and Bonow concluded the prevalence of coronary disease in HF was 68% by reviewing randomized trial data (Gheorghiade et al,Circulation 1998). Also from the observational report of patients with HF suggest that the prevalence of coronary disease in HF is 50% (Teerlink JR et al,Am Heart J 1991) and last not to be least from the first National Health and Nutrition Examination Survey (NHANES I), coronary disease had the largest population attributable risk for HF at 62% compared with the other risk factors analyzed (hypertension, obesity, diabetes mellitus, and smoking) (He J et al,NHANES I,Arch Intern Med 2001).

Now we know that coronary artery disease was the major culprit for HF. Thus following myocardial injury due to coronary artery disease, the surviving cardiomyocytes and extracellular matrix will undergone maladaptive changes that may lead to pathological 'remodelling' of the ventricle with dilatation and impaired contractility, in which the most accurate measurement was reduction in ejection fraction (Mc Murray et al,N eng.J med 2010).

After an insult to the myocardium, the LV progressively dilates or hypertrophies, a process followed by spherical remodeling. These morphologic changes cause

further stress on the myocardium by increasing wall tension and cause or exacerbate mitral regurgitation, which, in turn results in further dilatation and contractile dysfunction in a vicious cycle (Hunt S A et al,2005).

These changes in cardiac structure and function, corresponding to stage B of the American Heart Association (AHA)/American College of Cardiology HF Stages, were best characterized by increases LV mass (LVM), left atrial dimension (LAD), and LV geometric patterns indicative of adverse remodeling which were concentric remodeling, concentric and eccentric hypertrophy (M Nayor et al,2016).

Main consequences of untreated systolic dysfunction was progressive worsening of these changes over time, with increasing enlargement of the left ventricle (LV) and decline in EF, even though the patient might be asymptomatic initially.

Thus, evaluation by echocardiography was useful in detecting either systolic or diastolic LV dysfunction especially in preclinical phase

1.3 Evaluation of echocardiography in assessing cardiac function.

Because this morphologic process began before the onset of symptoms, the recent HF guidelines place special emphasis on detecting subclinical LV systolic and diastolic dysfunction (Hunt S A et al,2005). Several studies have emphasized that standard physical examination maneuvers were suboptimal in detecting either systolic or diastolic LV dysfunction, especially in the preclinical phase. Similarly, physical

examination was limited in its ability to accurately characterize the volume and cardiac output status in patients with LV dysfunction (Capomolla S et al,2005).

As a rapid and accurate modality, echocardiography can improve the noninvasive detection and definition of the hemodynamic and morphologic changes in HF.

Senni et al,reported use of echocardiography in patients with congestive HF and its impact on outcomes, first demonstrated in a population-based study that patients with HF who received echocardiographic evaluation had better survival than patients who were not assessed by echocardiography, even after adjusting for symptomatic status at presentation (Senni et al,1999).

Evaluation of cardiac function by echocardiography not only in assessing **LV functio**n which are measuring by LV ejection fraction (EF),LV volume and LV mass, but also in assessing **RV function** too, which is by measuring trans annular pulmonary systolic excursion (TAPSE), ratio of right ventricular effective systolic to diastolic duration, right atrium (RA) area and ratio of RA to left atrial area.

Furthermore, echocardiography also can provide a considerable **prognostic value** in symptomatic and asymptomatic patients with either preserved or abnormal LV systolic function. This can be done by measuring diastolic dysfunction (using E/A ratio, ratio e/e' septal and lateral), increased left atrial pressure , high left ventricular end-diastolic pressure (LVEDP) and also myocardial performance index (TEI index).

According to Pinamonti et al, persistence diastolic dysfunction may lead to restrictive filling as further increment of left atrial pressure will portends a particularly grim prognosis (Pinamonti et al,1997). Increased left atrial volumes (>32 ml/m^2), which were usually larger in diastolic compared with systolic HF, had shown to predict morbidity (Takemoto et al,2005). Based on Rossi et al, elevated of LVEDP (>15mmHg),which could demonstrated by >30-ms difference between pulmonary vein atrial flow reversal and mitral A-wave durations, predict an indeed poor prognosis (Rossi A et al,2001). The Tei index consists of the ratio of the isovolumic contraction -isovolumic relaxation times/the ejection time. Tei index with value of >0.77 proving superior to EF in predicting cardiac death and disease severity especially in a case of dilated cardiomyopathy (Dujardin et al,1998).

CHAPTER TWO

Literature review

2.1 Current measurement of LV systolic function by echocardiography.

Adequate cardiac function was defined as the ability of the heart to fill at a low enough pressure not to cause pulmonary congestion, then deliver a sufficient quantity of blood to the vasculature at a high enough pressure to perfuse the tissue, and to augment this performance during exercise (J.D Thomas et al,2006). Unfortunately, there was no measurable quantity that corresponds to this integrated functional assessment, so we must use surrogates that approximate one or another aspect of cardiac function.

The most common measurement was by assessing ejection fraction by using Teicholz and Quinones method .However calculating EF from linear dimensions might resulted in inaccuracies, particularly in patients with regional asymmetrical LV. Thus, the apical biplane method of discs (the modified Simpson's rule), gives more accurate measurements as it relies on accurate tracing of the endocardia border (Paulus et al 2007,Rudski et al 2010).

Apart from that, we could used Fractional shortening(FS).There were 2 different sites of FS measurement which were Conventional FS ,whereby the predictive power of HF was enhanced with lower FS. Meanwhile midwall FS had higher correlated with LV mass index, thus higher predictive future heart failure (Gerard et al,2001).

Three dimensional echocardiography may give a further details of ventricular volumes quantification and EF calculation (Lang RM et al,2006), but it required a costly special ECHO machine. There are 2 ways of 3D echocardiography, the first was 3D reconstruction from a set of 2D planes obtained by either rotating or tilting the transducer, a method that was time consuming and requires stable heart rate, but can be done with conventional 2D transducers. The second approach was real-time 3D echocardiography, which uses an array of crystals to direct ultrasound anywhere within a pyramid of space but required costly machine.

Although EF was universally used, it was limited by its sensitivity to preload and afterload, exemplified by the false reassurance of a high EF in severe mitral regurgitation and the low EF with severe aortic stenosis. Because of this, much effort is given to develop less load-dependent methods to measure true contractility.

Assessing LV twist and torsion definitely was superior to LVEF in characterizing hemodynamic aberrations in patients with HF (Kim *et al*. 2009). An impairment of LV twist after myocardial infarction correlates with the reduction of LVEF (Takeuchi *et al*. 2007). However this method had a technical demanding, thus limiting its usage.

Using the LV longitudinal strain by entails the movement of the mitral annulus toward the cardiac apex which was depended on the shortening of the LV longitudinal myocardial fibers (Ho SY 2009) also had value in measuring the LV function.

2.2 Previous studies of ECHO parameters in correlating with systolic dysfunction.

Measuring ejection fraction particularly if using Teicholz and Quinones method required calculation from several values from the ECHO parameters. This include measurement from intraventricular septum(IVS), left ventricular diameter(LVD) and posterior wall diameter(PWD).

Normal septal thickness would be 0.6-1.2cm. The thickness of the septum will greatly affect the systolic function as proven from Djordjevic et al, the greater IVS thickness at baseline was associated with worse cardiovascular outcome (Djordjevic et al,2012). Same went to posterior wall thickness (PWT), thicker wall indicated of pathological cardiac remodeling changed in heart failure, thus responsible for 50% of hospitalization due to congestive heart failure and 47% for mortality (Parfey et al,1990). Ineffective of cardiac pump in heart failure would lead to increase end diastolic volume in left ventricles, thus increment of myocardial wall thickness would occur to compensate this problem. However increasing LV wall thickness would bring a greater incidence of heart failure (Aurigemma et al,2001).

Despite on compensatory changes, it would progress till the ventricles became dilated and ineffective of cardiac pump function would continue to remain. This had been proven from Gibson et al, as increasing LV cavity size portends worsening prognosis with adverse remodeling (Gibson et al,2014).

2.3 Doppler velocities measurement as a tool for systolic function.

Using Doppler tissue imaging (DTI) by sampling pulsed wave Doppler at the septal, lateral myocardium and averaged might gave an accurate value of myocardial strain. It measured accurately longitudinal deformation of the heart and was sensitive in early stages of ischemia.

The initial application of TDI in quantifying myocardial mechanical activity was to measure the peak systolic tissue velocities of several segments in LV (Palka et al,1995). According to Katz et al, peak systolic velocity obtained by TDI could be a quantitative and objective measure of local systolic function both in rest and stress studies(Katz et al,1997). However, this simplistic application of TDI did not efficiently discriminate between actively contracting and "tethered" myocardium, where a given akinetic segment will demonstrate motion in relationship to the fixed transducer if it was "pulled" by a more proximal contracting segment of myocardium.

Thus, to overcome this problem, TDI-derived strain and strain rate have been recently proposed as new parameters of regional LV function. Strain rate measures a vector component of regional myocardial contraction independent of the effect of tethering and translation. From Edvardsen et al, they had stated that potential advantage of strain rate imaging over conventional TDI in regional analysis of cardiac function. This had been demonstrated from the clinical feasibility of strain rate imaging in quantifying regional

systolic function in a relatively objective manner and its superiority over TDI alone for analysis of regional myocardial function (Edvardsen et al,2001).

Nevertheless, tissue doppler imaging–derived strain and strain rate have several limitations. As TDI strain measures only the deformation occurring in the direction of the ultrasound scanline, it yields only a single component of the strain tensor. To avoid this angle dependence of all Doppler techniques, Speckle Tracking Imaging (STI) has recently been introduced. Speckle tracking imaging identifies characteristic speckles within the myocardium and tracks them frame-by-frame to yield tissue deformation in 2 dimensions. This had been demonstrated in the recent studies whereby this method had shown good accuracy and usefulness in the clinical setting (Amundsen et al 2006,Suffoletto et al 2006).

Those methods were based on the principle of myocardium velocity measurement differences which could be translated into myocardial strain rate changes that had been proved to be an accurate measurement for systolic function. However, these methods obviously were technically demanding and time consuming, thus limiting from widespread usage as one of the systolic functions measurements.

Was there any other methods that were more simple yet accurate in representing systolic LV function? How about measurement of intraventricular pressure gradient particularly in LV as one of the techniques in predicting systolic function?

Previous study by using invasive methods such as needles inserted into the left ventricular wall or the attachment of metal beads, optical markers or sonomicrometric crystals onto the myocardium recorded high-fidelity pressure tracings at different sites within the left ventricle (LV) . Hence, it demonstrated the existence of regional pressure differences in systole (even in the absence of outflow obstruction) (Waldman et al, 1985, Prinszen et al,1984,1985, Pasipoularides et al,1990,). Due to the invasiveness measurement of intraventricular gradient, so for the alternative, Thomas and Weyman proposed the analysis by Doppler echocardiogram (Thomas JD et al,2005).
Flow velocity measurements with PW-Doppler rely on the principle that the Doppler shift of reflected ultrasound waves induced by moving blood particles is proportional to the velocity of those particles.

By using doppler Pulse wave velocities intraventricular, we could measure the intraventricular pressure gradient difference which might give us an accurate value in more simplified way.

2.4 Intraventricular pressure gradient difference as a predictor for systolic LV function.

Although tissue Doppler-derived myocardial acceleration and systolic strain rate have been recently correlated with systolic function, the performance of these measurements as indicators of global LV function could be limited if regional wall motion was abnormal.

Ejection intraventricular pressure difference (EIVPD) between the LV apex and the outflow tract (LVOT) which was generated by the active force of the contracting ventricle had been show as non-invasive, and relatively load-independent indices of LV systolic chamber function. EIVPDs was defined as the consequence of the resistance of intraventricular blood to inertial and convective acceleration, represent the force applied by the contracting ventricle per unit volume of accelerated blood. (Pasipoularides et al,1990). Furthermore, peak EIVPD had shown a greater sensitivity in relating to the other systolic function indices. This had been proven by Yotti et al, by using animal as a study subjects, the peak EIVPD had been demonstrated to be lower in impaired systolic function and higher value in a good systolic function and directly proportionate to other systolic indices (Yotti et al,2005).

From Firstenberg et al, early diastolic intra ventricular pressure gradient (IVPG), as derived by color M-mode echocardiography, has been proposed to correlate with left ventricular (LV) elastic recoil. Again by using animals as subject study, they have demonstrated the correlation between the IVPG with other systolic indices

(doppler-derived strain rate and myocardial systolic velocities)after comparison with regression analysis (Firstenberg et al,2008).

Based on the recent study by Guerra et al, they managed to illustrate the characteristics of intraventricular pressure gradient in normal subjects and heart failure subjects by measured the interventricular pressure at the apex and outflow tract using animals as their subjects. The heart failure subjects were recruited with the same animals injected with doxorubicin. In heart failure animals, ventricular filling and ejection was delayed and slower when compared with control animals. Moreover, the physiological nonuniformity observed between apical and basal segments in normal hearts was abolished in failing hearts. Simultaneously, physiological IVPGs observed during normal ventricular filling and ejection were entirely lost in heart failure animals (Guerra et al,2013).

2.5 Rationale of the study.

Regional alterations in IVPGs might be an important factor in the characteristic changes that occur in intra ventricular flow in specific cardiac disorders. IVPGs play a physiological role in the healthy heart that was lost in pathological conditions, which may contribute to and represent an early sign of ventricular dysfunction. Thus in this pilot study, we would like to measure intra ventricular velocities in 3 different parts in LV which were apex, mid and at the left ventricular outflow tract that might give us an illustration of intra ventricular pressure gradient in normal human systolic function as well as impaired systolic functions. From this study also, we would like to correlate these measurements with other systolic indices and other ECHO parameters.

CHAPTER THREE

Methodology

3.1 Objectives

3.1.1 General objective

- To determine and compare flow velocities in the left ventricle apical, mid and outflow area among heart failure patients and normal patients.

3.1.2 Specific objective

- To compare the differences in velocities (pressure gradient) measurement at 3 left ventricles area in heart failure patients only.
- To compare all the 3 left ventricular area velocities (pressure gradient) differences between heart failure and control group.
- To determine the association of these velocities (pressure gradient) with the current measurement of LV function.
- To determine the association of these velocities (pressure gradient) with other echo parameters.

3.2 Null hypothesis

- There were no differences in velocities measurement at 3 left ventricles area in heart failure patients only.
- There were no differences in all the 3 left ventricular area velocities differences between heart failure and control group.
- There was no association between these 3 velocities with the current measurement of LV function and other echo parameters.

3.3 Methodology and Material

3.3.1 Definition of systolic heart failure.

- A syndrome in which patients have typical symptoms (eg; breathlessness, ankle swelling and fatigue as well as signs like elevated jugular venous pressure, pulmunory crackles and displaced apex beat) resulting from an abnormality of cardiac structure or function with ejection fraction less than 45% by Simpsons method.

3.3.2 Definition of ejection fraction

- Is the fraction of blood ejected from a ventricle of the heart with each heart beat. Calculated by dividing the stroke volume by the end-diastolic volume times 100. The best method for estimating volume by echocardiography is Simpsons.

3.3.3 Definition of Echocardiography

- A diagnostic test which uses ultrasound waves to make images of the heart chambers, valves and surrounding structures.

3.3.4 Definition of Doppler ultrasound

- An ultrasound in which measurement and a visual record were made of the shift in frequency of a continuous ultrasonic wave proportional to the blood flow velocity in underlying vessels or of the velocity movement of a structure, such as the beating heart.

3.3.5 Definition of pulse wave Doppler ultrasound

- A method of Doppler interrogation that uses specific time delays to assess the Doppler shifts within a discrete region along the path of the sound beam.

3.3.6 Definition of velocity.

- Rate rapidity of motion changes**.**

3.3.7 Definition of left ventricular outflow tract

- Region of left ventricle that lies between the anterior cusps of the mitral valve and ventricles septum.

3.3.8 Definition of mid area of left ventricle

- Area of the left ventricle in between the basal and apical segment

3.3.9 Definition of apical area of left ventricle

- Area at the extreme tip of the ventricle where there was no longer cavity present.

3.3.10 Definition of pressure gradient

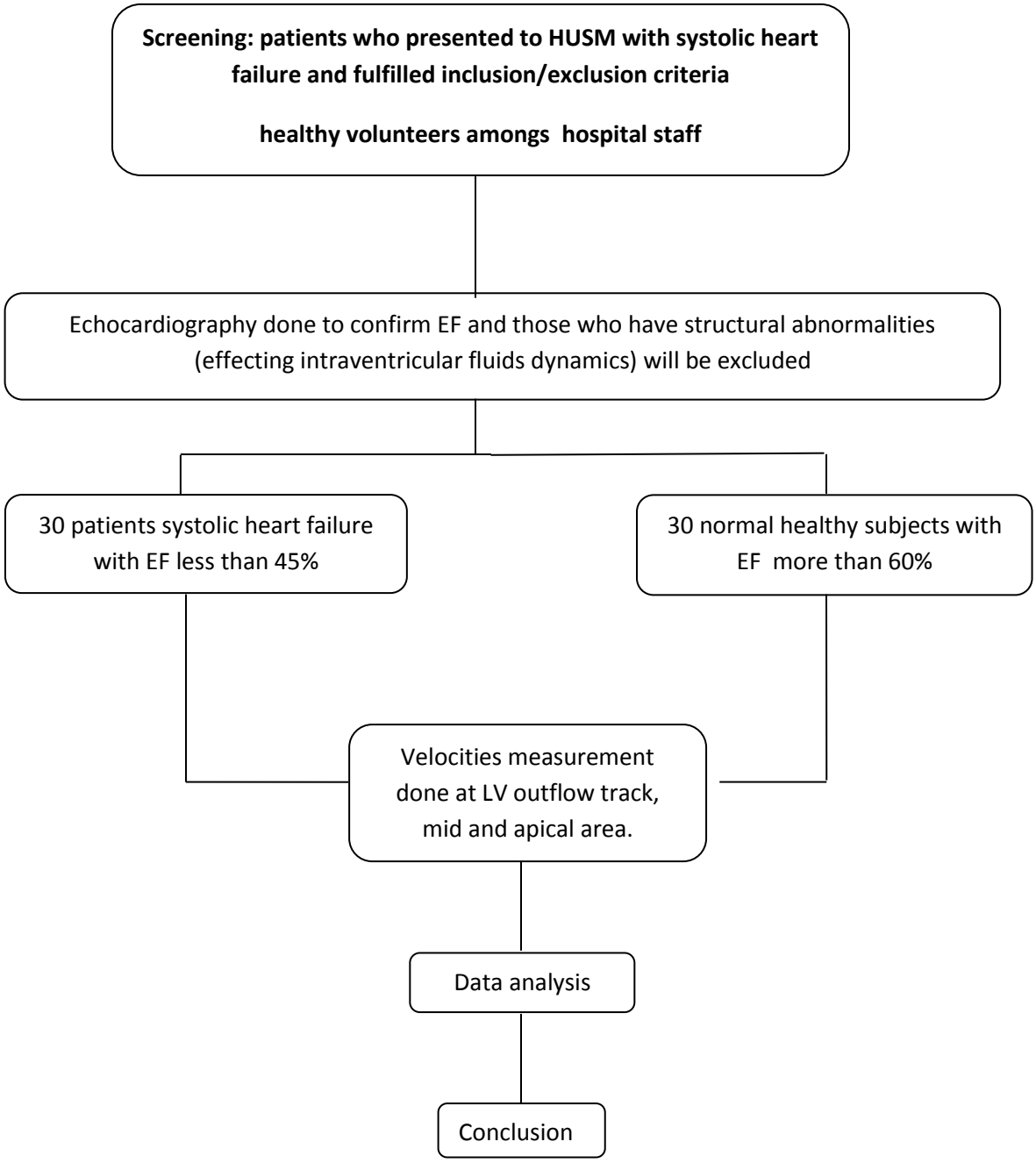
- Total energy in a closed system was a constant (Newton's law of conservation of energy) but when blood flows through a stenotic valve, kinetic energy increases and potential energy decreases proportionately to maintain constant total energy.
- Pressure (P) could be estimated from velocity (V) using the simplified Bernoulli equation: $P=4V^2$.

3.4 Study Design

Comparative cross sectional echocardiography pilot study.

3.5 Study flow chart

Figure 1



3.6 Study Period

- Between March 2017 to May 2018.

3.7 Reference population:

- All systolic heart failure patients who have echocardiographic measurement of ejection fraction less than 45%.

3.7.1 Study population:

- cases group: patient who presented to the study centres with heart failure symptoms. These patients will not directly under researcher's care, but they will be admitted under other medical officer's care.
- control group: healthy Hospital Universiti Sains Malaysia(HUSM) staff.

3.8 Sampling Method

- Patients with systolic heart failure symptoms fulfilling the inclusion and exclusion criteria were selected by convenient sampling

3.9 Inclusion Criteria

3.9.1) Cases group

- Age 18 – 80 years old
- Patients who have typical symptoms (e.g.breathlessness, ankle swelling, and fatigue) and signs (e.g. elevated jugular venous pressure, pulmonary crackles, and displaced apex beat).
- Screening ECHO by conventional method suggestive of systolic heart failure as manifested by impaired LV systolic function which was ejection fraction less than 45% and no structural abnormalities.

3.9.2) Control group

- Age 18-80 years old**.**
- Healthy, asymptomatic (no symptoms of systolic HF) HUSM staff with screening ECHO by conventional method show above 60%.

3.10 Exclusion Criteria

3.10.1)Cases group

- Patient with atrial fibrillation and/or cardiogenic shock at the time of screening.
- Patient with asymmetrical septal hypertrophy
- Patient with permanent pacemaker or biventricular pacing.
- Patient who have moderate and severe MR,AR and/or post valve replacement therapy
- Patient with corrected/non corrected congenital heart disease
- Patient with hyperdynamic heart failure (anaemia, thyroid disease etc)
- Conventional ECHO screening showed EF >45%

3.10.2)Control group

- Underlying structural cardiac abnormalities
- Pregnant.

3.11 Study sites

- Echocardiography Unit Hospital Universiti Sains Malaysia (HUSM), Kubang Kerian, Kelantan.