INTRODUCTION

Heart failure is a complex clinical syndrome characterized by impaired myocardial performance and progressive activation of the neuroendocrine system leading to circulatory insufficiency and congestion, With the increasing age of the population, the incidence of heart failure and the cost of managing heart failure continue to increase[226]. In the Framingham study, the annual age adjusted incidence of heart failure among persons aged ≥45 years was 7.2 cases/1,000 in men and 4.7 cases/1,000 in women, whereas the age adjusted prevalence of overt heart failure was 24/1,000 in men and 25/1,000 in women [227,228].

However recent data from Sweden have demonstrated that although mortality in patients with chronic heart failure is improving, patients admitted to hospital with a principal diagnosis of heart failure still have a mortality of 25% at 1 year, mortality worse than that associated with many cancers [229,232]. Moreover, recent trials of what could now be considered optimal pharmacological therapy for CHF have shown that despite this therapy ,mortality is still >25% at 3 years, and >25% of patients will have an admission to hospital with decompensated heart failure during that time [230,231,232].

High prevalence of inter- and intraventricular dyssynchrony is found in patients with refractory congestive heart failure[233], QRS prolongation usually indicates impaired propagation of electrical input[234], and is frequently associated with increased morbidity and mortality in HF patients, the conduction abnormalities have adverse haemodynamic effects resulting in impaired atrioventricular filling, ventricular dyssynchrony and hence impaired cardiac output and function. The increased QRS duration results in abnormal interventricular septal wall motion, reduced rate of rise in intracavitary pressure (dP/dt), reduced diastolic filling times and prolonged mitral regurgitation duration. The wider the QRS complex, the longer the left ventricular contraction and relaxation times with poorer LV systolic performance, this conduction abnormality may be progressive and is a marker of a poor outcome [228,235,236].

However, recent data has demonstrated that mechanical asynchrony is not necessarily related to electrical asynchrony, some patients with a wide QRS complex do not exhibit LV asynchrony, whereas others with a narrow QRS complex may demonstrate LV asynchrony. Therefore, it is likely that surface ECG is not sensitive enough to detect the presence and severity of electromechanical delay resulting in asynchronous contraction[237]. The correction of ventricular asynchrony is an attractive treatment goal, and therefore methods for evaluating ventricular asynchrony are of great interest for the prognosis and therapeutic optimization of heart failure patients.

Echocardiography is a useful tool for measurement of LV dyssynchrony[223]. Several echocardiographic methods allow the analysis of myocardial systolic performance, myocardial contractility can be analyzed using older techniques such as the M-mode and two-dimensional methods with strain, strain rate and tissue tracking techniques [238], the traditional methods like M mode could just assess the conduction delay between the septal and posterior walls. Visual estimation of dyssynchrony with 2D echocardiography is crude and often difficult, and could assess only two opposing walls due to the scanning slice. With the rapid development of tissue Doppler imaging, it becomes the most important and widely used method for assessing asynchrony, but tissue Doppler imaging also has many limitations. It could not compare all the ventricular segments coordination simultaneously, and in many cases, it could only provide the information of the basal and mid segments. Additionally, that its dependency of correct axis acquisition, the time-consuming analysis process as well as low reproducibility like strain rate imaging, all limit clinical application, so this method may not be the optimal one for assessing dyssynchrony[223].

Recent advances in the analysis software for real-time three-dimensional echocardiography allow simultaneous display of 16 regional volumetric waveforms, enabling temporal comparisons between segments and making it possible to evaluate the LV dyssynchrony[233]. Analysis of cardiac synchrony using three-dimensional echocardiography provides not only quantitative

discrimination of LV synchrony, but also allows the quantification of the cardiac dyssynchrony percentage [238]. Three-dimensional echocardiography allows global LV analysis at the same moment of the cardiac cycle, thus providing measurement of the dyssynchrony index measurement, which gives information on the severity of cardiac dyssynchrony and deternines the LV segment in which the most severe dyssynchrony occurs [238]. So it provides a novel, simple and promising approach in future clinical use [233].

AIM OF THE WORK

The aim of the present study is to assess the feasibility of using real-time three- dimensional echocardiography (RT3DE) for the assessment of left ventricular mechanical dyssynchrony in patients with congestive heart failure and narrow QRS complex

Chapter 1

HEART FAILURE

Introduction & Definition:

Heart failure is usually the result of a diseased heart. The most common cause is a very weak heart muscle. The heart muscle is the strongest muscle in the body. During an average life span, the heart beats about 2.5 billion times, pumping, more than 227 million liters of blood, if this work could be accomplished in one moment, it would be sufficient to lift a weight of about 400 million pounds of the ground [(1)]. Heart failure is a complex clinical syndrome characterized by impaired myocardial performance and progressive activation of the nueroendocrine system leading to circulatory insufficiency and congestion [(2)].

Given pathophsiological and clinical hetergenicity, it is not surprising that there is not yet any firm consensus definition of the clinical syndrome of heart failure (table 1) [(3)]. Over the past several decades, basic and clinical research elucidating the complex and continuous interplay of adaptive and maladaptive myocyte, myocardial extracellular matrix, hemodynamic, biochemical, energetic, genetic, neurohormonal, renal, pulmonary, skeletal muscle, vascular endothelial alterations and adaptationsin HF has rendered consensus definition even more challenging[(4)]. However, virtually all clinical instances of HF may be broadly conceptualized as a primary failure of the heart to render sufficient pressure-volume work over the range of physiological resting and exercise pressure-volume conditions, and thereby maintain organ perfusion at ventricular filling pressures below

the threshold for the precipitation of systemic or pulmonary venous congestion[5].

Table (1): *Definitions of Heart Failure:*

"A condition in which the heart fails to discharge its contents adequately"—Thomas Lewis, 1933
"A state in which the heart fails to maintain an adequate circulation for the needs of the body despite a satisfactory filling pressure"—Paul Wood, 1950
"A pathophysiological state in which an abnormality of cardiac function is responsible for the failure of the heart to pump blood at a rate commensurate with the requirements of the metabolizing tissues"—Eugene Braunwald, 1980
"A clinical syndrome caused by an abnormality of the heart and recognized by a characteristic pattern of hemodynamic, renal, neural and hormonal responses"—Philip A. Poole-Wilson, 1985
"A syndrome which arises when the heart is chronically unable to maintain an appropriate blood pressure without support"—Peter Harris, 1987
"A syndrome in which cardiac dysfunction is associated with reduced exercise tolerance, a high incidence of ventricular arrhythmias and shortened life expectancy"—Jay Cohn, 1988
"Symptoms of heart failure, objective evidence of cardiac dysfunction and response to treatment directed towards heart failure"—Task Force of ESC, 1995
"Heart failure is a complex clinical syndrome that can result from any cardiac disorder that impairs the ability of the ventricle to eject blood"—Consensus Recommendations for the Management of Chronic Heart Failure, 1999
"Heart failure is a complex clinical syndrome that can result from any structural or functional cardiac disorder that impairs the ability of the ventricle to fill with or eject blood"—ACC/AHA Consensus Guidelines, 2001

Source: *from Ref. 5.*

Incidence & prevalence:

Incidence refers to the number of new cases observed in a year in a defined population. Prevalence refers to the number of cases observed at a specified point in time in a defined population. The crude incidence of heart failure (unadjusted for age) ranges from 1 to 5 cases per 1,000 population per year and increases sharply with advancing age to as high as 40 cases per 1,000 population more than 75 years old [(6)].

A reflection of the incidence of heart failure in the United States is made from the Framingham Study and the Framingham Offspring Study, representing a population of more than 10,000 [(7)]. The prevalence of heart failure rises with age in both men and women, as shown in Figure 1&2.

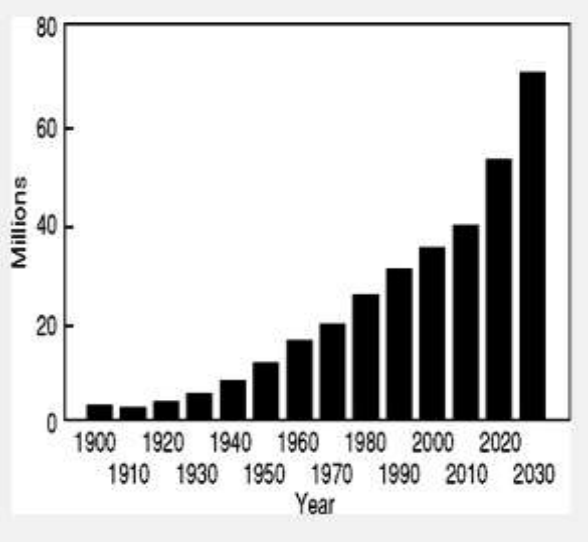

Figure (1): *Growth of the elderly population (1990 to 2030). (Adapted from U.S. Bureau of the Census).*

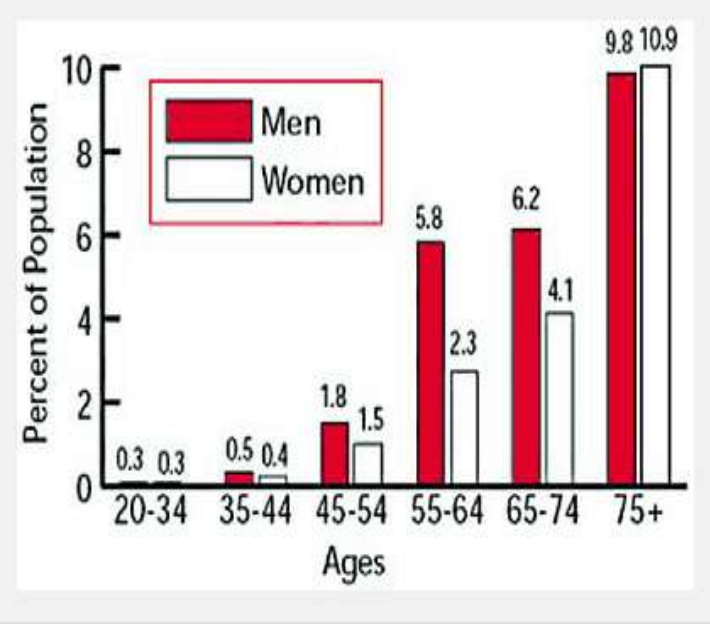

Figure (2): *Prevalence of congestive heart failure by sex & age, national health and nutrition examination survey 1999 to 2002. Source: centers for disease control and prevention/national center for health statistics and national heart, lung and blood institute. (From American heart association. Heart disease and stroke statistics: 2005 update. Dallas, TX: American Heart Association, 2005).*

In the United States, HF afflicts approximately 4.8 million people [(8)] with approximately 400,000 to 700,000 new symptomatic cases, and 250,000 deaths annually. Between 1.5 % and 2 % of the U.S. population has symptomatic HF, with a prevalence of 6 % to 10 % in those more than age 65 years (figure 3) [(7)]. In the Framingham Heart Study, the lifetime HF risk for men and women free of HF at age 40 was 21% for men and 20.3% for women [(9)]. There is a marked age-dependence in HF prevalence and incidence with elderly patients being proportionately afflicted [(10)]. Given the recent and continued

successes in managing coronary artery disease, the incidence and prevalence of HF will likely only increase in the future [11].

A recent analysis of the Framingham Heart Study cohort demonstrated over the past 50 years that the incidence of heart failure has declined among women, but not among men; however, survival after the onset of heart failure has improved in both sexes [12]. When established clinical criteria are used to define heart failure, the lifetime risk for heart failure is 1 in 5 for both men and women [14]. Both hypertension and antecedent myocardial infarction significantly affect the lifetime risk for heart failure between ages 40 and 80 years in both men and women. These findings highlight the importance of risk factor modification to reduce ischemic heart disease and the potential impact of antihypertensive therapy to reduce the development of overt clinical heart failure. The incidence of heart failure is 550,000 cases per year in the United States [2].

Heart failure poses an enormous societal financial burden with an estimated cost of between $20 and $40 billion dollars annually in the United States [8]. Care of HF consumes approximately 11% of total expenditure for cardiovascular disease [14, 15]. The elderly bear a disproportionate economic burden given the rising prevalence of heart HF with age [10].

Etiology & classification:

Heart failure may be classified as either predominantly systolic or diastolic [3]. Almost all instances of systolic HF also exhibit diastolic abnormalities; most instances of diastolic HF also exhibit systolic abnormalities, usually inadequate systolic functional reserve [16, 17]. The cardiomyopathies have traditionally been classified as either dilated, restrictive, or hypertrophic (figure 3) [11]. Neither classification schema necessarily provides sufficient insight into disease etiology, severity, or prognosis [5].

Although still debated, the primary ‘‘locus’’ of dysfunction in most instances of systolic HF appears to reside largely within the myocyte compartment of the heart. At least in the end-stage human heart, both in vivo and in vitro studies support a marked reduction in ‘‘contractility reserve’’ in response to increasing heart rate of sympathetic stimulation [18]. Whether this reduction in myocardial ‘‘contractility reserve’’ results from intrinsic abnormalities of myocyte contractile function or myocyte response to alterations in the myocardial and extracellular matrix neurohormonally modulated ‘‘milieu,’’ is still uncertain [5].

Normal integrated function of the heart depends upon a host of factors that include normal ultrastructural and gross architecture of the heart, an adequate number of myocytes, normal myocyte contractile and relaxant function, normal structure and function of cardiac valves, normal structure, composition, and metabolism of the myocardial extracellular matrix, adequate myocardial perfusion, and normal myocardial metabolism[5].

Not surprisingly, abnormalities in any of these major anatomic and functional components may result in HF. Among the more common causes of HF are loss of myocytes (ischemic, inflammatory or toxic necrosis, apoptosis), acute or chronic contractile dysfunction of myocytes (Inflammation, alcohol, chemotherapeutic agents, sepsis, hypoxia), excessive myofiber architectural disorganization or disarray (hypertrophic cardiomyopathy, infiltrative cardiomyopathy), extracellular matrix structural or functional abnormalities (excessive fibrosis leading to abnormal force transduction, myocyte linkage, and inadequate ‘‘compressive force’’ efficiency), distortion of the three-dimensional shape of the heart itself (aneurysm, infarction, chronic valvular disease), and intractable pressure or volume overload (hypertension, valvular heart disease) (Table 2)[5].

Table (2): *Causes of Systolic Heart Failure:*

Coronary artery disease
Hypertension
Alcohol
Valvular heart disease
Familial/genetic cardiomyopathy
Myocarditis
Toxins (chemotherapy, cocaine)
Collagen vascular disease
Metabolic disorders
Endocrine disorders
Electrolyte disorders
Acidosis
Sepsis
Hypoxia
Severe sleep apnea
Peripartum

Source: *from Ref. 5*

There is increasing evidence that abnormalities of systolic function accompany most if not all instances of apparently ‘‘isolated’’ diastolic HF (table3) [17, 19, 20]. In elderly patients, such systolic dysfunction not uncommonly results from the increased impedance to ventricular ejection into an increasingly stiffened arterial vascular circuit. Although a lesser degree of neurohormonal activation accompanies diastolic HF than systolic HF, exercise capacity in elderly patients with diastolic HF is comparably diminished as in patients with systolic HF [21]. It is not possible on the basis of symptoms and signs alone to distinguish systolic from diastolic HF. Most patients with a history of HF and preserved ejection fraction at rest, evidence abnormal indexes of diastolic function by echocardiography, although such measures serve to confirm rather than establish the diagnosis of diastolic HF [22].

Table (3): *Abnormalities Resulting in Diastolic Heart Failure:*

Extreme myocardial overload
Severe hypertension, aortic stenosis, mitral or aortic regurgitation.
Impaired myocardial relaxation.
Ischemia, hypertrophy, hypothyroidism, aging, cardiomyopathy
Impaired ventricular filling
Mitral stenosis, endocardial fibroelastosis
Reduced ventricular distensibility
Constrictive pericarditis, pericardial tamponade, extrinsic compression.
Increased ventricular stiffness
Age, ischemia, myocardial fibrosis or scarring, infiltrative cardiomyopathy, myocardial edema, microvascular congestion

Source: *Adapted from Ref. 17*

The WHO / International Society and Federation of Cardiology (ISFC) classification of cardiomyopathies was recently revised to accommodate our greater understanding of the pathophysiology of these conditions. Since the molecular genetic basis of previously unknown types of heart muscle disease is rapidly being elucidated, it has become unnecessary to reserve the classification for "unknown etiologies" of cardiomyopathy [23].

The mechanisms responsible for progression of myocardial dysfunction and the response to treatment are qualitatively similar in both primary and secondary dilated cardiomyopathies. Because of this, it is no longer justified to exclude secondary or "known cause" cardiomyopathies from inclusion in the classification of dilated cardiomyopathy. This change allows all cardiomyopathies to be classified under one scheme as shown in table 4 [23].

The WHO/ISFC classification of cardiomyopathy utilizes two separate methods to define the individual categories. The first is based on the global anatomic description of chamber dimensions in systole and diastole. Thus the dilated and restrictive categories have definitions based on LV dimensions and function. The justification for this is that these two groups have distinct natural histories and respond differently to medical treatment [23].

The second method of creating individual categories within the WHO/ISFC classification is genetically based. These categories include cardiomyopathies associated with an individual gene mutation that results in a unique myocardial phenotypic feature without extracardiac manifestations. Examples of such individual categories include hypertrophic cardiomyopathy and arrhythmogenic right ventricular dysplasia.

On the other hand, genetic cardiomyopathies without unique phenotypes, such as the dilated cardiomyopathy of Becker-Duchenne, are included as one form of dilated cardiomyopathy (category I) [23].

The WHO/ISFC classification includes another assignment of nomenclature in "secondary" cardiomyopathies, i.e., those associated with known cardiac or systemic processes. These are referred to as specific cardiomyopathies, named for the disease processes with which they are associated. Thus an ischemic cardiomyopathy would be a specific cardiomyopathy related to previous myocardial infarction and the subsequent remodeling process, which would usually fall within the dilated class. On the other hand, a hypertensive cardiomyopathy might be classified as either dilated or restrictive depending on the chamber dimensions. Therefore the correct terms for these cardiomyopathies would be ischemic dilated cardiomyopath and hypertensive dilated (or restrictive) cardiomyopathy [23].

Table (4): *The WHO/ISFC classification of the cardiomyopathies:*

Category
I. Dilated (DCM)
1. Primary
2. Secondary
II. Restrictive (RCM)
1. Primary
2. Secondary
III. Hypertrophic
IV. Arrhythmogenic right ventricular (ARVC)
V. Unclassified
1. Primary
2. Secondary

Source: *Richardson et al, 1996.*