Introduction

Dilated cardiomyopathy is an often fatal cause of heart failure characterized by ventricular dilatation and impaired systolic function, the condition is described by World Health Organization as dilatation of left, right or both ventricles, often severe with impaired systolic function invariably accompanied by hypertrophy. Prognosis of the disease is greatly correlated with the degree of ventricular dysfunction and ventricular enlargement (**Manolio et al., 1992**).

The incidence of dilated cardiomyopathy is reported to be 5 to 8 cases per 100,000 population per year and appear to be increasing; it occurs almost 2.5 times more frequently in blacks than in whites. The incidence appears to increase with age and to be higher in men than in women (**Wynne and Braunwald, 2001**).

The longitudinal contraction of the cardiac muscles plays an important role in the pump function of the ventricles. The longitudinal contraction of the ventricles is reflected by the annular motion. The mitral annulus moves toward a stable apex in systole and this motion reflects the systolic function of the ventricle along its long axis as mitral annulus descent measured by M-mode guided 2D echocardiography was closely correlated to ejection fraction and accepted as a standard reference of ventricular systolic function (**Pai et al., 1991**).

However, measurement of mitral annular motion by M-mode and 2D echocardiography is time consuming and not frequently used clinically**.** Tissue Doppler imaging is a modification of conventional Doppler technology in which signals arising from the tissue (of low velocity and high amplitude) rather than from blood

flow (of high velocity and low amplitude) enter the auto correlation and velocity calculations units **(Gulati et al., 1996).**

Tissue Doppler could be used as an index of left ventricular systolic function by measuring the velocity of the mitral annulus systolic motion **(Alam et al**., **1999**).

Aim of work

Aim of this study is to evaluate Doppler tissue imaging in the assessment of left ventricular systolic function in patients of dilated cardiomyopathy using mitral annular velocity.

Dilated Cardiomyopathy

Dilated cardiomyopathy (DC) is defined as combination of dilatation and systolic dysfunction of the left or both ventricles from idiopathic or specific origin **(Acquatella, 2000).** Heart muscle disease of known cause or associated with disorders such as systemic or pulmonary hypertension, coronary artery disease, valvular heart disease or cardiac congenital anomalies should be excluded from the definition (**Manolio et al., 1992**).

Pathology

Macroscopic examination in dilated cardiomyopathy reveals increased left ventricular mass, normal or reduced left ventricular wall thickness and increased left ventricular cavity size. The cardiac valves are intrinsically normal and intracavitary thrombi particularly in the ventricular apex are common. The coronary arteries usually are normal. The right ventricle is preferentially involved in some cases of dilated cardiomyopathy sometimes on familial bases (**Dec and Fuster., 1994).**

Histological changes within the myocardium include increased myocyte nuclear size, myofibrillary loss within the myocyte, increase in interstitial T lymphocyte\macrophages and interstitial fibrosis.

The individual myocytes are increased in length rather than in width, and lose of the normal of intracellular contractile myofibrils and thus appear empty and vacuolated on histology. The degree of this histological change closely correlates with declining left ventricular function. The myocyte nuclei increase in size because of the synthesis of DNA and become polypoid. Death of the individual myocytes occurs by both apoptosis and necrosis. Fibrosis

characteristically is interstitial and begins to surround and isolate individual myocytes. The number of macrophages and T-lymphocytes in the interstitial spaces is often increased compared with normal hearts **(Davies; 2000**).

Natural history

The prognosis of patients with idiopathic dilated cardiomyopathy (IDC) is poor. Reported annual mortality rates range between 5% and 45% depending on patient selection and severity of the disease. In approximately 20% to 50% of cases with IDC, death is sudden, presumably caused by rapid ventricular tachycardia (VT), ventricular fibrillation (VF), primary bradyarrhythmia, or electromechanical dissociation (**Grimm et al., 2000).**

Factors associated with a more favorable prognosis include mild functional class, age, female sex and certain etiologies including peripartum and myocarditis. Ejection fraction is the most powerful predictor of mortality (**Manolio et al., 1992**). The severity of mitral regurge are the strongest predictors of cardiac events (**Amiya et al 2006**). Poor prognosis is also associated with presence of an S3 gallop on examination, left bundle branch block on electrocardiogram and enlarged cardiothoracic ratio on X-ray. Other poor prognostic factors include decreased wall thickness <0.9 cm, decreased mass-volume ratio, pulmonary artery wedge pressure or left ventricular end diastolic pressure >20mmHg, cardiac index < 2.5 liter/minute/m^2 and increased plasma level of epinephrine, atrial natriuretic factor and renin activity.

Endomyocardial biopsy features associated with poor prognosis include increase cell size and fibrosis (**Manolio et al., 1992**).

Table (1): Predictors of negative events (cardiac death or hospitalization because of deterioration of heart failure) by univarite analysis

	P value
Age (years)	0.17
Sex (♂ or ♀)	0.53
LVEDD	.0008
EF%	0.020
Severity of MR	0.0006
Rhythm (sinus rhythm or AF)	0.97
QRS duration (ms)	0.0012
Cardiac index l/min/m²	0.88
Pulmonary capillary wedge pressure mmHg	0.047
Body mass index	0.64
LA diameter (mm)	0.35
NYHA class	0.75
B blocker	0.96
ACEI /ARB	0.42

(Amiya et al., 2006).

Causes of dilated cardiomyopathy

Dilated cardiomyopathy is a heart muscle disorder defined by the presence of a dilated poorly functioning left ventricle in the absence of abnormal loading conditions (hypertension, valve disease) or ishaemic heart disease sufficient to cause global systolic impairment.

A large number of cardiac and systemic diseases can cause systolic impairment and left ventricular dilatation but in the majority of patients, no identifiable cause is found hence the term idiopathic dilated cardiomyopathy (**Elliott, 2000**)

Although the causes remain unclear, interest has centered on three basic mechanism of damage:

1. Familial and genetic factors.

2. Viral myocarditis and other toxic factors.

3. Immunological abnormalities (**Wynne and Braunwald, 2001**)

1- Familial and Genetic Factors

Familial linkage is common in dilated cardiomyopathy. In 20% of patients, a first-degree relative show evidence of DCM suggesting that familial transmission is relatively frequent. Some asymptomatic relatives of patients with DCM have subclinical left ventricular enlargement and or dysfunction that may progress to overt symptomatic dilated cardiomyopathy **(Baig et al**., **1998).**

Different patterns of inheritance are observed in dilated cardiomyopathies as autosomal dominant, X linked, autosomal recessive, and mitochondrial transmission. About 30% of all DCMs are considered to be inherited and the remaining 70% are sporadic. It is becoming increasingly clear, however, that a number of "sporadic" cases of DCM may be accompanied by de novo mutations in genes (**Cohen and Muntoni., 2004)**. Duchenne (DMD) and Becker (BMD) muscular dystrophies are common causes of inherited skeletal myopathy with cardiac involvement. Although skeletal myopathy is the prominent clinical manifestation of both disorders, most patients have evidence of cardiomyopathy **(Kelly and Strauss,1994).** Cardiac involvement in DMD develops insidiously during the first decade of life, at a time when skeletal muscle weakness is already significant. Despite the high incidence of cardiac involvement, most patients with DMD remain

asymptomatic. Respiratory failure caused by diaphragm muscle weakness is the most common cause of death in DMD, BMD is a milder allelic form of DMD with an incidence of one in 14000 live male births. Patients with BMD also have a high incidence of clinical cardiac involvement despite their milder skeletal muscle disease. In fact, some patients with BMD have initially presented with cardiomyopathy that became severe enough to require cardiac transplantation. The most common cause of death in BMD is heart failure. Female carriers of DMD and BMD, an X linked recessive disorder, have a surprisingly high incidence of cardiac involvement that progresses with age and manifests primarily as cardiomyopathy. An intriguing example of cardiomyopathy, without any clinical sign of skeletal muscle weakness, is XLDC, an allelic condition to DMD and BMD. (**Cohen and Muntoni., 2004)**

2- Viral myocarditis and toxic factors

A progression from viral myocarditis to dilated cardiomyopathy has long been hypothesized but the actual extent of this progression has been uncertain **(Kawai, 1999**). Long term follow up studies on patients with acute myocarditis have shown a variable incidence of DCM ranging from 0-52% over a mean period of 3 years (range 3 months to 13 years) (**D'Ambrosis et al., 2001).**

Lymphocytic myocarditis accounts for around 10% of recent onset cardiomyopathy, and this figure may be higher in children. Viruses are the main causes in developed countries, coxsackie B and adenovirus accounting for most cases; Chagas disease is the most common cause in Central and South America, and other infectious causes should be considered. The genetics of the host may determine the outcome (**Burch et al., 2002)**.

3-immunological abnormalities

Abnormalities of both humoral and cellular immunity have been found in-patients with DCM. There is speculation that antibodies might be the result of myocardial damage rather than the cause. There appears to be an association with specific HLA class II antigens suggesting that abnormalities of immunoregulation may play a role in DCM. Circulating antimitochondrial antibodies to a variety of antigens (including myosin heavy chain, the beta adenoreceptor) have been identified.

Additional for the significance of circulating antimicrobial antibodies comes from the demonstration of short term clinical improvement in the manifestations of heart failure in a small number of patients treated with immunoadsorption and elimination of anti-beta I-adrenergic receptor antibodies, abnormalities of various T cells, suppressor T lymphocytes and natural killer cells have been found in some studies. These immunological abnormalities may be the consequence of prior viral myocarditis **(Wynne and Braunwald, 2001).**

Diagnosis of dilated cardiomyopathy

Clinical presentation

a) History

Patients present with signs and symptoms of pulmonary congestion and or low cardiac output often on a background of exertional symptoms and fatigue for many years before diagnosis. Right-sided heart failure is a late and ominous sign and is associated with poor prognosis. First presentation may be with systemic immobilization or sudden death.

Some patients are asymptomatic and yet have left ventricular dilatation for months or even years; this dilatation can be recognized during routine medical screening or family evaluation of patients with established diagnosis (**Elliott, 2000**)

b) Physical examination

- The patient may be breathless on exertion or at rest.

- The arterial pulse is small in volume, and pulses alternans is an ominous finding, tachycardia or arrhythmia especially AF are common findings.

- The blood pressure is usually normal.

- Cold extremities due to peripheral vasoconstriction and low cardiac output are a sign of advanced decompensation.

- Signs of biventricular failure as elevation of the jugular venous pressure and peripheral edema are present in less than a third of patients at diagnosis and indicates poor prognosis.

- The apical impulse is usually diffuse, prolonged and displaced laterally and is typically hypokinetic.

- The first heart sound may be: I) normal; ii) soft due to decreased systolic differential L.V. pressure (dp/dt).

- The second heart sound may be: I) accentuated by pulmonary hypertension; ii) reversely splitted by LBBB; iii) widely splitted by RBBB.

- The third heart sound: may be audible in 40-80% of the patients with dilated cardiomyopathy.

- The fourth heart sound may be audible in 20-60% of the patients with dilated cardiomyopathy.

- A murmur of mitral insufficiency due to mitral annular dilatation or L.V. dilatation and papillary muscle dysfunction is more frequent than that of tricuspid regurgitation (**Kopecky and Gersh,1987**).

Electrocardiography

ECG in-patients with IDC may be remarkably normal but abnormalities ranging from isolated T wave changes to septal Q waves in-patients with extensive left ventricular fibrosis, prolongation of atrioventricular conduction and bundle branch block may be observed. Sinus tachycardia and supraventricular arrhythmias are common in particular atrial fibrillation. Approximately 20-30% of patients have non-sustained ventricular tachycardia and a small number present with sustained tachycardia (**Elliott, 2000**).

Echocardiography

2D & Doppler echocardiography are useful in assessing the degree of impairment of left ventricular function and for excluding concomitant valvular or pericardial disease.

Echo allows evaluation of the size of ventricular cavity and thickness of ventricular walls.

Doppler studies are useful in delineating the severity of mitral regurgitation.

Echocardiographic diagnostic criteria of DCM

- Ejection fraction (EF) < 45%
- Fractional shortening (FS) <25%
- Left ventricular end diastolic dimension, of > 112% predicted value corrected for age and body surface area. (predicted LVEDD was calculated according to the formula :

LVEDD = (45.3x body surface area 0.3) – (0.03x age)-7.2 ±12% **(Baig et al**., **1998 and Henry et al., 1980)**.

Radionuclied ventriculalography

It is used in-patient with poor echo windows, like echo radionuclide Ventriculography reveals:

- Increased end diastolic and end systolic left ventricular volumes.
- Reduced EF in one or both ventricles.

Exercise testing

Symptom limited upright exercise testing is of considerable value when assessing functional limitation in-patients with IDC particularly when combined with respiratory gas analysis. Metabolic exercise testing provides an objective measure of exercise capacity facilitates assessment of disease progression, helps assess prognosis and is useful in selecting patients for cardiac transplantation.

Viral serology

In children and adults with acute myocarditis, viral culture and serology may be useful in establishing a diagnosis of viral myocarditis by demonstrating rising titre of neutralizing antibodies or virus specific IgM class antibodies to entroviruses indicative of recent infection.

Endomyocardial biopsy

Although endomyocardial biopsy can be used to diagnose a wide range of myocardial diseases, most are rare causes of IDC and can often be diagnosed by other means. Even the detection of an inflammatory CM is of limited use, given the uncertainties and

inconsistencies surrounding its diagnosis using conventional light microscope criteria. Endomyocardial biopsy may be of use in selected patients, for example those with suspected haemochromatosis and other infiltrative or malignant diseases but in general, it should be confined to carefully conducted clinical trials. As our understanding of the clinical significance immunohistochemical markers improves, it is likely that endomyocardial biopsy will become more important in guiding immunomodulatory treatment (**Elliott, 2000**).

Treatment of IDC

Specific treatments are not available for most patients with IDC. Therefore, the primary aims of treatment are to control symptoms and to prevent disease progression and complication such as progressive heart failure, sudden death and thromboembolism.

Diuretics remain central to the management of congestive symptoms, but they should not be used as monotherapy as they exacerbate neurohumoral activation and may contribute to disease progression unless administered consistently with neurohumoral antagonists.

- **Angiotensin converting enzyme inhibitors:**

Activation of the renin-angiotensin-aldosterone system is central to the pathophysiology of heart failure of whatever underlying etiology. For this reason, ACE inhibitors are the mainstays of treatment in-patients with IDC, irrespective of the severity of heart failure. ACE inhibitors improve dyspnea and exercise tolerance, reduce hospitalization rates and reduce cardiovascular mortality. They also prevent or slow disease progression in asymptomatic patients.

- **Angiotensin II receptor antagonist:**

They have haemodynamic effects broadly similar to those of ACE inhibitors but may be slightly better tolerated and theoretically overcome the escape of angiotensin system blockage observed in some patients on ACE inhibitors. However, unlike ACE inhibitors

all receptor antagonists don't inhibit bradykinin metabolism and thus lack a potential beneficial vasodilatory effect.

The combination treatment with ACE inhibitors and All receptor antagonists may be more beneficial in reducing neurohumoral activation and in preventing ventricular remodeling than either drug alone **(Mckelvie et al., 1999)**.

- **B-blockers:**

Packer et al., 1996 have demonstrated substantial reductions in sudden death and death from progressive heart failure in-patients with predominantly New York Heart association (NYHA) class II and III symptoms treated with B-blockers. They advice to consider B-blockers in IDC patients with mild to moderate symptoms inspite of maximal treatment with ACE inhibitors. Patients should not be started on B-blockers if they have signs or symptoms of decomponsated heart failure and initial dose should be low and increased gradually every 2-4 weeks monitoring closely for hypotension, bradycardia or worsening heart failure until the target dose is achieved or side effects occur.

- **Spironolactone**

High plasma concentrations of aldosterone are frequent in-patients with moderate to severe heart failure and contribute to sodium retention, potassium loss, sympathetic activation, myocardial fibrosis and baroreceptor dysfunction. ACE inhibition usually results in only transient decrease in aldosterone concentration probably because major source of aldosterone is reduced hepatic clearance rather than angiotensin dependent adrenal secretion **(Elliott, 2000)**.

Pitt et al., 1999 have shown that addition of 25 mg of Spironolactone to conventional treatment in patients with an ejection fraction <35% and a history of NYHA class IV heart failure is associated with a 30% reduction in the overall risk of death. Hospitalization rates for cardiac causes and functional status also improved. The drug should be considered in all patients presenting with moderated to severe heart failure symptoms**.**

- **Anticoagulant**

Oral anticoagulants are advised in-patients with a history of thromboembolism or evidence of intracardiac thrombus.

Patients with more than ventricular dilatation and moderate to severe systolic dysfunction should also be advised to take oral anticoagulants **(Elliott, 2000**).

- **Antiarrhythmics**

It may be appropriate to use them in treatment of symptomatic arrhythmia. Because of the adverse effect of most available agents many of which depress myocardial contractility and have a proarrhythmic effect, treatment should be individualized with both efficacy and toxicity carefully monitored **(Wynne and Braunwald, 2001).**

- **Non pharmacological treatment of advanced heart failure**

  - **Heterogeneous heart transplantation** is still the corner stone of advanced heart failure management in-patients with intractable heart failure symptoms and end stage disease.

  - **Partial left ventriculotomy** is based on the hypothesis that as wall tension is related to left ventricular diameter reducing the left ventricular size by excision of a portion of its circumference should reduce wall stress and improved ventricular haemodynamics.

  - **Left ventricular assist devices** have recently received approval from US Food and Drug Administration for use in-patients with end stage heart failure as a bridge for cardiac transplantation **(Elliott, 2000**).

  - **Multisite ventricular pacing:** many patients with advanced IDCM have abnormal ventricular activation that in turns results in prolonged and incoordinate ventricular relaxation. In some patients, ventricular conduction delay is also associated with prolongation of atrioventricular