INTRODUCTION

Dilated cardiomyopathy is the most common cardiomyopathy worldwide. In this disorder, dilation and impaired contraction of the left or both ventricles develop. It can be primary (genetic, mixed or predominantly familial non-genetic, or acquired) or secondary (e.g., infiltrative or autoimmune). This disease can also be diagnosed in association with recognized cardiovascular disease ***(Elliott et al., 2008).***

Mechanical dyssynchrony, the uncoordinated wall motion of different ventricular segments in systole and diastole, is an important contributor to left ventricular (LV) dysfunction in cardiomyopathy both in adults and in children with dilated cardiomyopathy (DCM). Although systolic mechanical dyssynchrony has been studied more than diastolic mechanical dyssynchrony, diastolic dyssynchrony is more common than systolic dyssynchrony in adults with both systolic and diastolic heart failure and may be associated with ventricular dysfunction and poor outcome. However, mechanical dyssynchrony and its quantification by echocardiography have not been extensively studied in children with cardiomyopathy, moreover diastolic wall motion has not been well delineated in children in general, and diastolic mechanical dyssynchrony has not been studied in children with DCM ***(Friedberg et al., 2008).***

Cardiac resynchronization therapy (CRT) is a novel and promising non pharmacologic therapy for patients with advanced heart failure and wide QRS morphology. According to the current functional and electrocardiographic (ECG) eligibility criteria, however, one third of the patients receiving CRT have shown no symptomatic improvement and may actually develop adverse left ventricular (LV) remodeling, resulting in further severe symptomatic impairment. In addition, LV mechanical dyssynchrony has been proven to occur even in patients with preserved QRS duration. This has highlighted the need for alternative techniques to assess LV dyssynchrony and the need for redefining the selection criteria for CRT ***(Sonne et al., 2009).***

The most widely used methods for echocardiographic assessment of left ventricular (LV) function and mechanical dyssynchrony are two-dimensional (2D) echocardiography and tissue Doppler imaging (TDI).never the less, tissue Doppler presents limitations inherent to the method, such as the dependency on the ultrasonic beam angulations, image acquisition of different ventricular segments at different times, limited observation of cardiac segments and little information regarding the apical segments ***(Yu et al., 2007).***

Real time three-dimensional echocardiography (RT-3DE) is a relatively novel imaging technique. It offers the unique opportunity to rapidly and accurately evaluate global LV function. It increases the possibility of observing the

cardiac synchrony because it allows the simultaneous and real-time determination of overall cardiac synchrony in relation to the image acquisition. Combined with specially designed software, RT-3DE provides detailed quantitative information regarding mechanical dyssynchrony ***(Mu et al., 2010).***

Recent multicenter study found that pediatric patients undergoing CRT exhibited a significant increase in mean ejection fraction (EF); however, long term results regarding percentage of responders and degree of benefit are not yet available. Although CRT is increasingly used in this population, there is currently few published data that evaluate dyssynchrony in healthy children or in children with ventricular dysfunction and that delineate the selection criteria for CRT ***(Dubin et al., 2005).***

An important event in LV myocardial remodeling is alterations in the extracellular matrix (ECM). The extracellular matrix contains a fibrillar collagen network, a basement membrane, proteoglycans and glycosaminoglycans and bioactive signaling molecules ***(Janicki et al., 2004)***. A family of zinc-dependent proteases implicated in facilitating myocardial tissue remodeling by degrading components of the ECM are the matrix metalloproteinases (MMPs). The serum level of MMP2 is elevated in patients with chronic heart failure. Furthermore, mortality and serum level of MMP-2 are correlated and MMP-2 values above mean serum level are associated with poorer prognosis ***(Shirakabe et al., 2010)***. The

resulting carboxy-terminal telopeptide (CITP) released by the action of MMP on collagen type I (CITP) is found in an immunochemically intact form in blood ratio of 1:1 exists between the number of collagen type I molecules degraded and of CITP molecules released. Furthermore the amount of CITP that reaches the circulation is proportional to the amount of fibrillar collagen degraded. So elevated serum levels of CITP and MMP-2 suggest increased degradation of myocardial collagen and other components of the extracellular matrix, which is seen in more severe phases of dyssynchrony, which suggests a direct relationship between dyssynchrony and collagen excess ***(Kitahara et al., 2007).***

AIM OF THE WORK

This work aims to study the role of real time three-dimensional echocardiography in evaluating mechanical systolic and diastolic dyssynchrony and their impact on global systolic and diastolic LV function in pediatric DCM patients.

Moreover, biochemical markers (MMP 2 and CITP) of LV remodeling will be correlated to the RT-3DE values of dyssynchrony.

DILATED CARDIOMYOPATHY

Pediatric cardiomyopathies represent the new frontier in pediatric cardiology. During the past decade there has been intense clinical research into their epidemiology, causes, and management ***(Daphne and Canter, 2010).***

Cardiomyopathy is defined as: A myocardial disorder in which the heart muscle is structurally and functionally abnormal, in the absence of coronary artery disease, hypertension, valvular disease and congenital heart disease sufficient to cause the observed myocardial abnormality ***(Maron et al., 2006).***

Cardiomyopathies are divided into five major forms: dilated (DCM), hypertrophic (HCM), restrictive (RCM), right ventricular (RVCM), and non-classifiable cardiomyopathies (NCCM). Furthermore, the most recent WHO/WHF definition also comprises, among the specific cardiomyopathies, inflammatory cardiomyopathy as a distinct entity, defined as myocarditis in association with cardiac dysfunction ***(Asakura and Kitakaze, 2014).***

Definition

Dilated cardiomyopathy (DCM) is a myocardial disorder characterized by dilatation and contractile dysfunction of the left - right ventricles ***(Lewis, 2014).***

Epidemiology

It is the most common form of cardiomyopathy and reason for cardiac transplantation in adults and children, accounting for more than half of all cardiomyopathies in pediatric population ***(Lewis, 2014).***

In children, the yearly incidence is 0.57 cases per 100 000 per year overall, but is higher in boys than in girls (0.66 *vs.* 0.47 cases per 100 000) in black people than in white people (0.98 *vs.* 0.46 cases per 100 000), and in babies younger than 1 year than in children (4.40 *vs.* 0.34 cases per 100 000). Two thirds of children are thought to have idiopathic disease ***(Lewis, 2014).***

Etiology

A DCM phenotype can accompany myocarditis, mutations in myocardial proteins, inborn errors of metabolism, and myocardial toxins. Although an increasing number of myocardial protein mutations and metabolic disorders are being associated with a DCM phenotype in children, most cases remain idiopathic, followed by myocarditis (16%), neuromuscular disorders (9%), and familial DCM (5%), inborn errors of metabolism (4%), and malformation syndrome (1%), also, the DCM associated with chemotherapy for neoplasm is an important cause of heart failure in children ***(Hershberger et al., 2009).***

Table (1): Diverse etiologies of dilated cardiomyopathy.

■■ Ischemic heart disease: coronary heart disease, myocardial infarction, and associated conditions
■■ Structural heart disease: valvular, pressure or volume overload, left to right shunts
■■ Congenital heart disease
■■ Drugs: anthracyclines (such as doxorubicin), chemotherapeutic agents, cocaine, imatinib, sympathomimetics
■■ Endocrine: acromegaly, Cushing disease, hypothyroidism, pheochromocytoma, thyrotoxicosis
■■ Immune-mediated: autoimmunity (systemic lupus erythematous, Churg–Strauss syndrome), hypersensitivity myocarditis (allergen, serum sickness, vaccines), transplantation rejection
■■ Infiltrative: amyloidosis, sarcoidosis
■■ Infectious: bacterial (staphylococcus, streptococcus), fungal, mycobacterial, parasitic (toxoplasmosis, trichinosis, Chagas disease), Rickettsial (Q fever, Rocky Mountain spotted fever), viral (coxsackievirus, Enteroviruses, HIV, influenza, parvovirus)
■■ Metabolic: electrolyte disturbances (hypocalcaemia, hypophosphatemia), nutritional deficiencies (carnitine, selenium, thiamin)
■■ Toxins: cadmium, carbon monoxide, cobalt, ethanol, lead, mercury
■■ Other: radiation, tachycardia-mediated

(Hershberger et al., 2009)

Myocarditis

Myocarditis refers to the clinical and histological manifestations of a broad range of pathological immune processes in the heart. Alterations in the number and function of lymphocyte subsets and macrophages and antibody-mediated injury are typically found in patients with acute and chronic

myocarditis. The immune reaction in the heart causes structural and functional abnormalities in cardiomyocytes, which in turn leads to regional or global contractile impairment, chamber stiffening, or conduction system disease ***(Hershberger et al., 2009).***

Many infectious, inflammatory and toxic causes of myocarditis have been identified **(Table 1).**

Table (2): Common causes of myocarditis.

Infectious		Immune-mediated		Toxic
Viral	• Coxsackievirus B • Adenovirus • Hepatitis C virus • Human immunodeficiency virus	**Autoantigens**	• Churg-Strauss syndrome • Inflammatory bowel disease • Giant cell myocarditis • Diabetes mellitus • Sarcoidosis • Systemic lupus erythematosus • Thyrotoxicosis • Takayasu's arteritis • Wegener's granulomatosis • Sulphonamides	Anthracyclines Cocaine Interleukin-2 Ethanol Heavy Metals
Bacterial	• Mycobacteria • Streptococcus sp. • Mycoplasma pneumoniae • Treponema pallidum			
Fungal	• Aspergillus • Candida • Coccidioides • Cryptococcus • Histoplasma			
Protozoal	• Trypanosoma cruzi	**Hypersensitivity**	• Cephalosporins • Diuretics • Tricyclic antidepressants • Dobutamine	
Parasitic	• Schistosomiasis • Larva migrans			

(Magnani and Dec, 2006)

The importance of arriving at a diagnosis of myocarditis for children and their families is the better prognosis for survival and eventual recovery with myocarditis compared with other diseases with similar echocardiographic findings ***(Magnani et al., 2006).***

Although myocarditis and idiopathic DCM have differing outcomes, suggesting that they are separate disease entities, an increasing consensus has evolved suggesting that there is a continuum between viral infection of the myocardium and the ultimate development of a chronic DCM. In this scenario, many cases of idiopathic DCM represent an end stage of previously undiagnosed myocarditis. Thus myocarditis and idiopathic DCM may represent different stages of a disease process that share a common echocardiographic phenotype ***(Magnani et al., 2006).***

Familial Dilated Cardiomyopathy

A positive family history of cardiomyopathy suggests the presence of a genetic defect. No particular clinical or morphologic features within individual patients have distinguished familial from idiopathic disease, emphasizing the need for evaluation of families when a diagnosis of DCM is made ***(Daphne and Canter, 2010).***

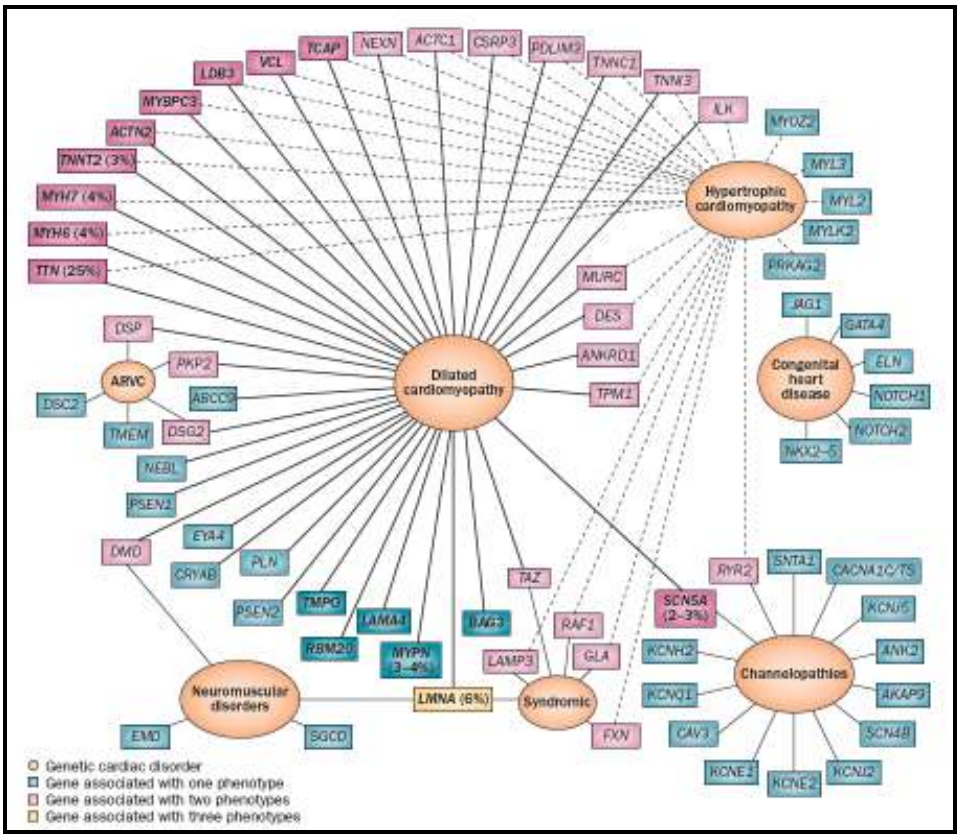

Figure (1): Relationships between genes associated with cardiomyopathies and related phenotypes. The genetic architecture underlying selected genetic cardiac disorders is shown. Edges (lines) connect each phenotype to the genes that have been implicated in the aetiology. Gene nodes associated with familial dilated cardiomyopathy are darker and have bold text if they have been found to cause disease in ≥1% of patients, and include frequency information if they have been found to cause disease in ≥3% of patients ***(Daphne and canter, 2010).***

More than 20 genes have been identified as being associated with a DCM phenotype with dominant (the predominant pattern of transmission), X-linked, recessive, and mitochondrial inheritance patterns. The clinical onset of most familial DCM is in adulthood, with only sporadic presentation in infants or children. Penetrance of disease in familial

cardiomyopathy has been estimated to be 10% before 20 years of age; 34% between ages 20 and 30 years; 60% between 30 and 40 years; and 90% at 40 years of age ***(Daphne and Canter, 2010).***

At presentation, a family history and pedigree (family tree) should be done to further delineate a possible mode of inheritance. Screening of first-degree relatives should be considered ***(Lindenfeld et al., 2009).***

Causative genes in dilated cardiomyopathy seem to predominantly encode two major subgroups of proteins—cytoskeletal and sarcomeric proteins. The cytoskeletal proteins identified so far include dystrophin, desmin, lamin A/C, δ-sarcoglycan, β-sarcoglycan, and metavinculin. In the case of sarcomere-encoding genes, β-myosin heavy chain, myosin-binding protein C, actin, α-tropomyosin, and cardiac troponin T and C. Additionally, a new group of sarcomeric genes, those encoding Z-disk proteins, have been identified—ZASP, muscle-LIM (lin11, isl-1, and mec-3) protein, α-actinin-2, myopallidin, cardiac ankyrin repeat protein, and telethonin. Furthermore, phospholamban, tafazzin, and the sodium-channel gene *SCN5A*44 have also been reported ***(Moulik et al., 2009).***

Autosomal dominant inheritance accounts for approximately one-quarter of all cases, and was the commonest mode of inheritance in the study from North America,

accounting for two-thirds of familial cases ***(Towbin et al., 2006)***.

Major forms of autosomal dominant dilated cardiomyopathy are recognized, namely, isolated (or pure), and dilated cardiomyopathy associated with disease of the cardiac conduction system. In many cases, there may also be a skeletal myopathy ***(Kaski et al., 2007)***.

X-linked inheritance accounts for up to one-twentieth of familial cases of dilated cardiomyopathy. Two disorders have been well characterized: X-linked dilated cardiomyopathy, which presents in adolescence and young adults, and Barth syndrome, which is most frequently identified in babies and children ***(Cohen and Muntoni, 2004)***.

Barth syndrome, initially described as X-linked cardioskeletal myopathy with abnormal mitochondria and neutropenia, typically presents in male infants as heart failure associated with neutropenia (cyclic) and 3-methylglutaconic aciduria. Mitochondrial dysfunction is noted on electron microscopy and electron transport chain biochemical analysis. Abnormal findings in cardiolipin are crucial in disease development ***(Houtkooper and Vaz, 2008),***

The dystrophin gene, when mutated, is also responsible for Duchenne and Becker muscular dystrophy. Almost all such patients develop dilated cardiomyopathy before their 21st

birthday. In most cases, the muscle isoform of serum creatine kinase is raised, similar to that in X-linked cardiomypathy. Female carriers develop disease late in life, as do those with X-linked cardiomyopathy. Furthermore, immuno histochemical analysis shows reduced concentrations (or absence) of dystrophin, similar to findings in hearts of patients with X-linked cardio myopathy. Information gained from studies of X-linked cardiomyopathy and Duchenne and Becker muscular dystrophy led us to suggest that dilated cardiomyopathy is a disease of the cytoskeleton and sarcolemma that affects the sarcomere—a final common pathway of dilated cardiomyopathy ***(McNally and Pytel, 2007).***

Inborn errors of metabolism are considered to account for only 5% of the cardiomyopathies. A DCM phenotype was present in only 21% of the cardiomyopathies associated with inborn errors of metabolism and were confined to mucopolysaccharidoses, disorders of oxidative phosphorylation, disorders of fatty acid oxidation/carnitine metabolism, and amino/organic acidurias. Thus, although a DCM phenotype is generally not encountered in these diseases, routine evaluation for its presence in a patient with a DCM is important to determine (1) the feasibility of heart transplantation, and (2) the potential to ameliorate or reverse the cardiomyopathy associated with these rare diseases with diet or use of supplements such as carnitine ***(Daphne and Canter, 2010).***

Dilated cardiomyopathy associated with vitamin D deficiency has been reported in infants. Infants with active nutritional rickets show subclinical myocardial dysfunction as detected by M-mode, TVI, S and SR. Treatment was associated by normalization of M-mode and TVI but not S and SR values ***(Kotby et al., 2011)***.

Pathology

Dilated cardiomyopathy is associated with complex remodeling of one or both ventricles, resulting in a change of the ventricle shape and the architecture of the myocardium fibers. Macroscopic examination typically shows enlargement of all chambers, with more dilation of the ventricles than the atria. Additionally, the valves and the epicardial coronary arteries are usually normal. In some cases, intracavitary thrombi are present, most easily seen in the apex of the left ventricle ***(Jefferies and Towbin, 2010).***

Microscopic examination generally reveals areas of interstitial and perivascular fibrosis, and sometimes areas of necrosis and cellular infiltrate. Myocyte size varies greatly, with some atrophied and hypertrophied cells. In children, abnormal findings such as abnormal shapes, sizes, and numbers of mitochondria (with or without inclusions), abnormal glycogen stores, or abnormal lysosomes with vacuolization might be seen on microscopy ***(Jefferies and Towbin, 2010).***