Seminar

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Dilated cardiomyopathy

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Dilated cardiomyopathy is characterised by left ventricular dilation that is associated with systolic dysfunction. Diastolic dysfunction and impaired right ventricular function can develop. Affected individuals are at risk of left or right ventricular failure, or both. Heart failure symptoms can be exercise-induced or persistent at rest. Many patients are asymptomatic. Chronically treated patients sometimes present acutely with decompensated heart failure. Other life-threatening risks are ventricular arrhythmias and atrioventricular block, syncope, and sudden death. Genetic inheritance arises in 20–48% of patients, and inflammatory disorders such as myocarditis or toxic effects from medications, alcohol, or illicit drugs also result in dilated cardiomyopathy. Genes that cause dilated cardiomyopathy generally encode cytoskeletal and sarcomeric (contractile apparatus) proteins, although disturbance of calcium homeostasis also seems to be important. In children, disrupted mitochondrial function and metabolic abnormalities have a causal role. Treatments focus on improvement of cardiac efficiency and reduction of mechanical stress. Arrhythmia therapy and prevention of sudden death continue to be mainstays of treatment. Despite progress over the past 10 years, outcomes need to be improved.

Introduction

Cardiomyopathies are diseases of the heart muscle, characterised by abnormal findings of chamber size and wall thickness, or functional contractile abnormal findings—mainly systolic or diastolic dysfunction in the absence of coronary artery disease, hypertension, valvular disease, or congenital heart disease.[1] Cardiomyopathies are classified as either primary or secondary. Primary cardiomyopathies consist of disorders solely or predominantly confined to the heart muscle, which have genetic, non-genetic, or acquired causes. Secondary cardiomyopathies are disorders that have myocardial damage as a result of systemic or multiorgan disease.[2]

Dilated cardiomyopathy is the most common cardiomyopathy worldwide and has many causes. In this disorder, dilation and impaired contraction of the left or both ventricles develops. It can be primary (genetic, mixed or predominantly familial non-genetic, or acquired) or secondary (eg, infiltrative or automimmune). This disease can also be diagnosed in association with recognised cardiovascular disease; however, to qualify as dilated cardiomyopathy, the extent of myocardial dysfunction cannot be explained exclusively by abnormal loading or ischaemic damage.[3] Dilated cardiomyopathy is associated with sudden cardiac death and heart failure, resulting in a large cost burden because of the very high rate of hospital admission and the potential need for heart transplantation. In this Seminar, we focus on the clinical features, genetics and causative mechanisms, diagnostic strategies, treatments, outcomes, and controversies in the care of primary and secondary dilated cardiomyopathy.

Search strategy and selection criteria

We searched PubMed for reports mainly from the past 5 years, including some reports from 2000 onwards, Online Mendelian Inheritance in Man, and peer-reviewed reports on dilated cardiomyopathy. We used the search terms "dilated cardiomyopathy", "heart failure", "cardiomyopathy", "DCM genetics" and "final common pathway". No languages were excluded. We included reports that covered adult and childhood dilated cardiomyopathy from clinical and basic-science journals, and relevant reports of our research. We excluded outdated textbook chapters. Our reference list was modified on the basis of comments from peer reviewers.

Epidemiology and clinical features

Dilated cardiomyopathy, is characterised mainly by left ventricular systolic dysfunction (abnormality of contraction), with an associated increase in mass and volume. In some cases, left ventricular diastolic abnormal findings are present. Right ventricular dilation and dysfunction can also develop but are not needed for diagnosis. Prevalence in the general population remains undefined. This disorder develops at any age, in either sex, and in people of any ethnic origin.[2, 4–6] In adults, dilated cardiomyopathy arises more commonly in men than in women. 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, p<0·006, in black people than in white people (0·98 *vs* 0·46 cases per 100 000, p<0·001), and in babies younger than 1 year than in children (4·40 *vs* 0·34 cases per 100 000, p<0·001). Two-thirds of children are thought to have idiopathic disease.[4] In adults, the prevalence is one in 2500 individuals, with an incidence of seven per 100 000 per year (but it could be underdiagnosed).[5] In many cases, the disease is inherited, and is called familial dilated cardiomyopathy. The familial type might account for 20–48% of all cases.[5] To achieve improved care and outcomes in children and adults, a broadened understanding of the causes of these disorders is needed.

In this disease, the left ventricle is dilated, and more spherical than usual with raised wall stress and depressed systolic function (figure 1). Mitral regurgitation and ventricular arrhythmias can also develop. Occasionally, other rhythm disturbances such as atrioventricular block, supraventricular tachycardia with or without pre-excitation including Wolf-Parkinson-White syndrome,

and atrial fibrillation develop. In the most severe cases, affected individuals present with signs and symptoms of heart failure—diaphoresis, breathlessness at rest or with exertion, orthopnoea, exercise intolerance, early onset fatigue, abdominal pain, and pallor. Cachexia and peripheral oedema typically arise late in the course of the disease. Young children often have poor appetite and, similar to adults, cachexia. Sinus tachycardia, gallop rhythm, jugular-venous distention, pallor, cool hands and feet, hepatomegaly, and a murmur that is consistent with mitral regurgitation are common findings at physical examination. Additionally, peripheral oedema and ascites are late signs in children.

Diagnosis is dependent on patient history, and clinical, echocardiographic (figure 1), or cardiac MRI features of dilated cardiomyopathy or heart failure, or both. Echocardiographic findings are left ventricular dilation and systolic dysfunction (defined by depressed ejection fraction or shortening fraction), with or without mitral regurgitation. Additionally, pericardial effusion (especially in myocarditis) and rhythm irregularities can be noted. Chest radiographs often show cardiomegaly and increased pulmonary vascular markings that are consistent with pulmonary oedema (figure 2). Electrocardiography, another standard diagnostic test, can show sinus tachycardia, ST-T wave changes, Q waves, conduction disease, bundle-branch block, left ventricular hypertrophy, or ectopy, including supraventricular tachycardia, atrial fibrillation, or ventricular arrhythmias (figure 3). In some cases, patients have complications related to dilated cardiomyopathy, such as thromboembolic disease, including stroke. If the right ventricle is affected, evidence of right heart failure—tricuspid regurgitation, raised jugular venous pulse, hepatomegaly, ascites, and peripheral oedema—are noted in some cases.

Biomarkers can be of clinical use in diagnosis, management, and prognosis of patients, especially those with heart failure.[7–10] The most widely used markers are B-type natriuretic peptide (BNP) and N-terminal pro-brain natriuretic peptide (NT-BNP). In adults and children, BNP differentiates symptoms related to lung disease from heart failure.[7–11] Biomarkers are extensively reviewed elsewhere.[7] Endomyocardial biopsy sampling can be used to further define the cause of this disease in some cases.[12] This histology of heart muscle is clinically useful to distinguish between disease processes that need alternative treatment strategies, such as storage diseases, malignancies, sarcoidosis, and haemochromatosis. Confirmation of viral myocarditis is sometimes possible with endomyocardial biopsy, as is identification of virus-negative, immune-mediated myocarditis, which could result in additional treatment such as immunomodulation or immunosuppression therapies.[13–17] From endomyocardial biopsy samples, identification of the causative virus by its viral genome with PCR has been useful to establish the cause of acute myocarditis, and has clarified that some cases of dilated cardiomypathy are the result of chronic myocarditis.[18] Additionally, this diagnostic approach sometimes enables improved treatment strategies and accuracy of prognosis.

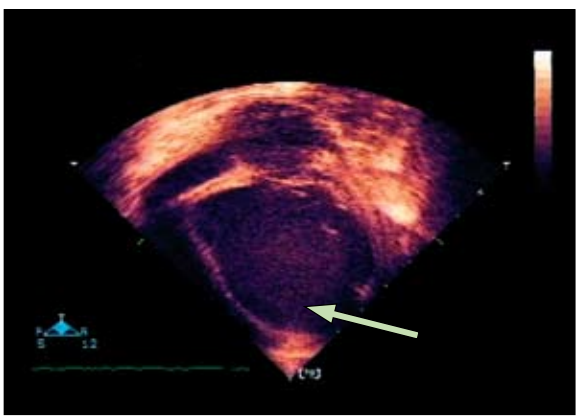

Figure 1: **Transthoracic echocardiogram of patient with dilated cardiomyopathy**
Apical four chamber view shows dilated left ventricle (arrow). In real time, systolic function is greatly diminished.

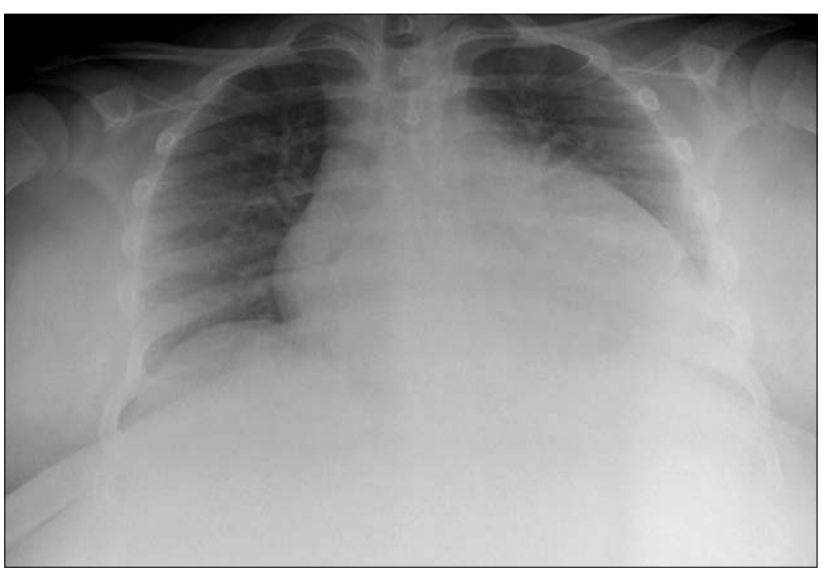

Figure 2: **Chest radiograph of patient with dilated cardiomyopathy and decompensated heart failure**
Image shows pronounced cardiomegaly and pulmonary oedema that is consistent with volume overload.

Dilated cardiomyopathy is associated with complex remodelling of one or both ventricles, resulting in a change of the ventricle shape and the architecture of the myocardium fibres. 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. 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

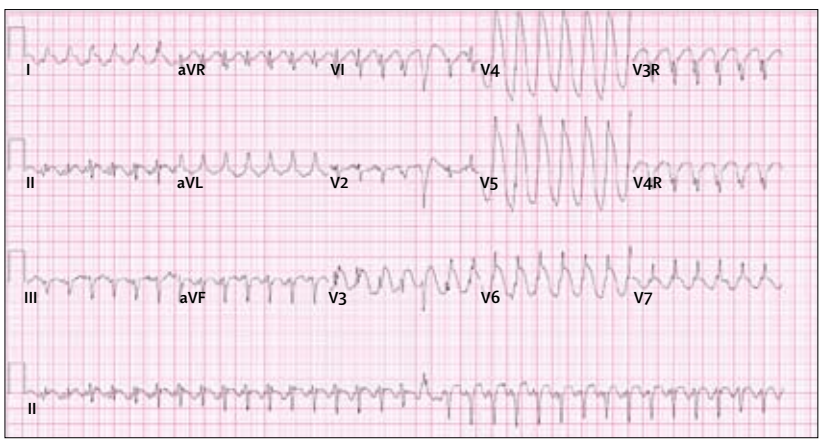

Figure 3: **Electrocardiogram of adult with dilated cardiomyopathy and decompensated heart failure**
Shows sinus tachycardia and significant ST-segment changes.

Panel: **Mechanisms responsible for dilated cardiomyopathy**

- Disturbed cytoskeletal-sarcomeric link:
  - Genetic mutation (sarcolemma-sarcomere genes)
  - Viral infection (coxsackievirus myocarditis)
  - Non-viral infection (Chagas disease)
  - Toxicity (adriamycin and alcohol)
- Apoptosis
- Autoantibodies and autoimmune disease
- Metabolic disturbance storage disease
- Mitochondrial dysfunction
- Ion-channel disruption
- Chronic incessant tachyarrhythmias
- Peripartum
- Infiltrative disease
- Endomyocardial disease
- Endocrinopathies
- Nutritional deficiencies
- Electrolyte disturbance

numbers of mitochondria (with or without inclusions), abnormal glycogen stores, or abnormal lysosomes with vacuolisation might be seen on microscopy. Causes of dilated cardiomyopathy are many (panel). For primary dilated cardiomyopathy, causes are genetic, mixed (predominantly non-genetic), and acquired. Acquired primary disease can be secondary to inflammatory disease such as myocarditis, stress-provoked (takutsobo), secondary to peripartum state, or can be tachycardia induced. Secondary dilated cardiomyopathy has many causes that are systemic in nature.

Causes of primary dilated cardiomyopathy

Familial and genetic

Inherited dilated cardiomyopathy was first thought to account for a small percentage of cases only, until Michels and co-workers[19] showed that about 20% of probands had family members with echocardiographic evidence of this disease when family screening was undertaken. Inherited familial dilated cardiomyopathy develops in 30–48% of cases,[20] with autosomal-dominant inheritance as the predominant pattern of transmission—X-linked, autosomal recessive, and mitochondrial inheritance are less common than is autosomal-dominant inheritance. 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.[21]

Causative genes in dilated cardiomyopathy seem to predominantly encode two major subgroups of proteins—cytoskeletal and sarcomeric proteins.[20,22–24] The cytoskeletal proteins identified so far include dystrophin,[25,26] desmin,[27] lamin A/C,[28] δ-sarcoglycan,[29] β-sarcoglycan,[30] and metavinculin[31] (table). In the case of sarcomere-encoding genes, the same genes identified for hypertrophic cardiomyopathy seem to be responsible, including β-myosin heavy chain, myosin-binding protein C, actin, α-tropomyosin, and cardiac troponin T and C.[32–35] Additionally, a new group of sarcomeric genes, those encoding Z-disk proteins,[36] have been identified—ZASP,[37] muscle-LIM (lin11, isl-1, and mec-3) protein,[38] α-actinin-2,[38] myopallidin,[39] cardiac ankyrin repeat protein,[40] and telethonin.[41] Furthermore, phospholamban,[42] tafazzin,[43] and the sodium-channel gene *SCN5A*[44] have also been reported (table).

Genetic testing for cardiovascular disease is becoming common, with several fee-for-service laboratories offering testing in the USA. For hypertrophic cardiomyopathy, the diagnostic yield of testing is 60–70%; however, testing for dilated cardiomyopathy has a yield much lower than 60%. The most frequently identified gene is lamin A/C, but only when the disease is associated with atrioventricular block (with or without skeletal myopathy). In pure dilated cardiomyopathy, the yield screening for a large number of genes is about 20%. Most frequently identified genes are the Barth syndrome gene *TAZ*, *ZASP*, desmin, and in men, dystrophin.

Of the X-linked forms of dilated cardiomyopahty, two disorders have been well characterised—X-linked dilated cardiomyopathy, which presents in adolescence and young adults, and Barth syndrome, which is most frequently identified in babies and children.[45] In 1987, Berko and Swift,[45] first described X-linked dilated cardiomypathy as dilated cardiomyopathy that develops in young men in the teen years and early twenties, with rapid progression from heart failure to death, which is attributable to ventricular tachycardia or ventricular failure, unless transplantation intervenes. These patients are identified by raised amounts of the muscle isoform of serum creatine kinase. Female carriers (ie, mothers) tend to develop mild-to-moderate dilated cardiomyopathy in the fifth decade, with slow progression. Towbin and colleagues,[46] were first to identify the disease-causing gene and characterise the functional defect in which the dystrophin gene was shown to be responsible for abnormal clinical findings.[46] Protein

analysis by immunoblotting showed severe reduction or absence of dystrophin protein in the heart. These findings were later confirmed by Muntoni and colleagues[47] when a mutation in the muscle promoter and exon 1 of dystrophin was identified in another family with X-linked cardiomyopathy.[47] Subsequently, many mutations have been identified in dystrophin in patients with this disease.

The dystrophin gene, when mutated, is also responsible for Duchenne and Becker muscular dystrophy; these skeletal myopathies present early in life. Boys with Duchenne muscular dystrophy become wheelchair-bound before age 12 years, whereas Becker muscular dystrophy is a milder muscle disease than is Duchenne muscular dystrophy, in which boys are ambulatory after the age of 16 years, although this prognosis has been modified by early, high-dose steroid treatment.[26,48] 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, immunohistochemical analysis shows reduced concentrations (or absence) of dystrophin, similar to findings in hearts of patients with X-linked cardiomyopathy. Information gained from studies of X-linked cardiomyopathy and Duchenne and Becker muscular dystrophy led us to suggest[22–24] that dilated cardiomyopathy is a disease of the cytoskeleton and sarcolemma that affects the sarcomere—a final common pathway of dilated cardiomyopathy. Our findings that three of 22 boys with idiopathic dilated cardiomyopathy had dystrophin mutations and raised muscle isoform of serum creatine kinase lend support to our results[25] showing that dystrophin mutations play a part in idiopathic dilated cardiomyopathy in male individuals.

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.[49] Mitochondrial dysfunction is noted on electron microscopy and electron transport-chain biochemical analysis. Abnormal findings in cardiolipin are crucial in disease development.[50]

The genetic basis of Barth syndrome is mutations in the gene tafazzin (*TAZ*), which encodes the tafazzin protein, an acyltransferase.[43] Mutations in *TAZ* result in a wide range of findings, including dilated cardiomyopathy, hypertrophic dilated cardiomyopathy, endocardial fibroelastosis, or left ventricular non-compaction.[20,51] Arrhythmias are also frequent in these patients, and clinical disease is typically associated with symptoms of heart failure, syncope or sudden death, acidosis, or infectious complications.[52]

Ion channels in the heart are crucial for normal electrophysiological functioning of the heart. Dysfunction of ion channels leads to rhythm disorders, such as long QT syndrome, Brugada syndrome, catecholaminergic polymorphic ventricular tachycardia, atrial fibrillation, and atrioventricular block.[53] This final common pathway for arrhythmias also plays a major part in the clinical behaviour of the heart in dilated cardiomyopathy. Many ion channels seem to interact with the sarcolemmal and sarcomeric proteins, with these binding-partner relations placing the rhythm of the heart at risk. Another ion-channel homeostasis gene associated with dilated cardiomyopathy is phospholamban, which has a role in calcium homeostasis. The importance of these proteins in the clinical presentation of this disease was shown by their inclusion in the American Heart Association's classification scheme[4] and the National Institutes of Health workshop report.[54]

	Gene	Protein	Protein location
Xp21.2	DMD	Dystrophin	Cytoskeleton/SL
Xq28	G4.5	Tafazzin	Phospholipid
1q12	TNNI1	Cardiac troponin I	Sarcomere
1q32	TNNT2	Cardiac troponin type 2	Sarcomere
2q31	TTN	Titin	Sarcomere
2q35	DES	Desmin	Cytoskeleton
5q34	SGCD	δ-sarcoglycan	Cytoskeleton/SL
6q12–q16	CMD1K	Unknown	
6q22.1	PLN	Phospholamban	Calcium
9q13-q22	CMD1B	Unknown	
9q22-q31	SEMA4D	Unknown	
10q22.1	MYPN	Myopalladin	Sarcomere
10q22.3–23.2	ZASP/Cypher (LDB3)	LIM domain binding protein 3	Sarcomere
1q42–q43	α2-actinin	ACTN	Sarcomere
10q22.1–q23	VCL	Metavinculin	Cytoskeleton
10q23.22	ANKRD1	CARP	Sarcomere
10q25.3	RBM20	RNA binding motif protein 20	Unknown
11p11.2	MYBPC3	Myosin binding protein C	Sarcomere
11p15.1	CSRP3	Muscle-LIM protein	Sarcomere
14q11.2–q13	MYH7	β-myosin heavy chain	Sarcomere
15q11–q14	ACTC1	Cardiac actin	Sarcomere
15q22.1	TPM1	α-tropomyosin	Sarcomere

Table 1: **Genetic causes of dilated cardiomyopathy by chromosome locus**

Infectious causes

Infectious causes of left ventricular dysfunction that are consistent with the dilated cardiomyopathy phenotype are common, including viral, bacterial, fungal, parasitic, rickettsial, and spirotricheal infections. In viral myocarditis, many viral pathogens cause the human disorder. In the past, causal diagnosis was dependent on viral culture of peripheral specimens (and rarely heart tissue) and serial serological testing. During the past 15–20 years, molecular-based testing of myocardial tissue has become a useful diagnostic method, especially PCR analysis of viral genomes in the heart. The most common viruses identified by this method from endomyocardial biopsy samples are parvovirus B19, adenovirus, coxsackievirus B and other enteroviruses, influenza A,

human herpes virus 6, cytomegalovirus, Epstein-Barr virus, herpes simplex virus type 1, and hepatitis C.[18,55]

The predominant viral cause of this disease seems to change every decade (coxsackievirus in the 1980s, adenovirus in the 1990s, and parvovirus B19 since 2000). Presentation of disease can vary, ranging from minor symptoms of malaise to acute decompensated heart failure, chest pain and myocardial infarction, or sudden cardiac arrest.[56] Use of endomyocardial biopsy sampling in suspected myocarditis remains under-used, especially in children. However, many advances in diagnosis and therapy have occurred on the basis of use of this technique, and from studies with histology and PCR. Use of non-invasive techniques, such as cardiac MRI, are diagnostically effective and are becoming more widely used than they were previously.[57] Chagas' cardiomyopathy, caused by the protozoan *Trypanosoma cruzi*, remains the leading cause of chronic systolic heart failure in endemic areas.[58] It is characterised by heart failure, thromboembolic disease, conduction disease and malignant arrhythmias, and sudden cardiac death.

Causes of secondary dilated cardiomyopathy

Toxicity-related causes

Many causes have been associated with myocardial damage and development of dilated cardiomyopathy. Long-term use of drugs such as cocaine result in heightened activation of the sympathetic nervous system, causing left ventricular dysfunction both directly and through promotion of coronary thrombosis, coronary spasm, and atherosclerosis.[59] Chronic alcohol abuse is one of the most important adult causes of this disease in developed countries. Alcohol cardiomyopathy is a diagnosis of exclusion, and relates to the average daily intake of alcohol and duration of alcohol use. Alcohol, taken both acutely and chronically, depresses cardiac contractility by poorly understood mechanisms, activating the neurohormonal system.[60] The estimated 4-year mortality rate approaches 50% in patients without complete abstinence after diagnosis.[61]

Anthracyclines, such as doxorubicin and daunorubicin, are very effective anticancer drugs that are prescribed worldwide. However, many patients treated with these drugs, irrespective of age, develop insidious dilated cardiomyopathy and heart failure. The scope of the problem remains to be adequately defined. Causative mechanism of the disease is multifactorial, but seems to be associated with generation of reactive oxygen species, disruption of mitochondria, and uncoupling of the electron-transport chain.[62,63] Use of dexrazoxane might be cardioprotective by attenuation of the formation of free radicals. Early detection of disease by both non-invasive and serological techniques shows promise.[64]

Peripartum cardiomyopathy

Peripartum cardiomyopathy is a disorder in which initial left-ventricular systolic dysfunction and symptoms of heart failure develop between the late stages of pregnancy and early postpartum period, typically within 1 month of predelivery and 5 months postdelivery.[65] Its causes and pathogenesis are poorly understood. The disorder is common in some countries and rare in others. In most patients with this disorder, molecular markers of an inflammatory process are identified. Affected women generally present clinically with typical signs and symptoms of heart failure; signs of thromboembolism are also frequent. Conventional heart-failure treatment is typically used, such as diuretics, β-blockers, and angiotensin-converting enzyme inhibitors. Effective treatment reduces mortality rates and increases the number of women who fully recover left-ventricular systolic function. Outcomes for subsequent pregnancies after peripartum cardiomyopathy are better for women who have fully recovered heart function after their initial presentation than for those who do not.

Mechanisms responsible for genetically defined dilated cardiomyopathy

Mechanisms associated with disease causation are force generation and transmission defects, metabolic and mechanosensory abnormalities, and disturbed calcium homeostasis.[66,67] Most genes identified so far encode either cytoskeletal or sarcomeric proteins. For cytoskeletal proteins, defects of force transmission are thought to result in the dilated cardiomyopathy phenotype, whereas defects of force generation have been speculated to cause sarcomeric protein-induced dilated cardiomyopathy However, sarcomeric mutations frequently lead to a clinical phenotype because of force transmission defects.[33,68,69]

Mutations in the sarcomere can produce hyertrophic cardiomyopathy or dilated cardiomyopathy. In cases of dilated cardiomyopathy, abnormalities in force generation or transmission are thought to contribute to development of this phenotype. Apart from mutations in the thin filament protein, actin, mutations in the thick filament protein-encoding gene β-myosin heavy chain have caused dilated cardiomyopathy with associated sudden death in at least one infant, and dilated cardiomyopathy in children and adults. Mutations in this gene are thought to perturb the actin-myosin interaction and force generation or alter cross-bridge movement during contraction. Mutations in cardiac troponin T, a thin filament protein, might disrupt calcium-sensitive troponin C binding.[68] Mutations in phospholamban have also been identified, further lending support to calcium handling as a potentially important mechanism in development of this disorder. Haghihi and co-workers[70] identified homozygous mutations that cause dilated cardiomyopathy and heart failure, whereas they noted that heterozygotes had cardiac hypertrophy.[70] Recessive mutations in troponin I could impair the interaction with troponin T,[71] whereas α-tropomyosin mutations have been identified and were predicted to alter the surface charge of the protein, impairing interaction with actin.[31]

An area of interest for assessment at the molecular level is the Z disc.[36] Knoll and colleagues[72] identified mutations in muscle-LIM protein and showed that these mutations result in defects in the interaction with telethonin.[72] With mouse models, they also showed that muscle-LIM protein acts as a stretch sensor and that mutant versions of this protein cause defects in this activity. Additionally, Mohapatra and co-workers[38] identified mutations in this protein in families, described sporadic cases, and identified abnormal findings in the T-tubule system and Z disc architecture by electron microscopy, corresponding to the histopathology seen in muscle-LIM protein knockout mice.[72] Findings[73] of reduced expression of muscle-LIM protein in chronic human heart failure further lend support to those of Mohapatra and colleagues. Additionally, mutations in α-actinin 2, which has a role in crosslinking actin filaments and shares a common actin-binding domain with dystrophin, were also identified in familial dilated cardiomyopathy, disrupting binding of α-actinin 2 to muscle-LIM protein.

Vatta and co-workers[37] identified mutations in the Z-band alternatively spliced PDZ-motif protein (ZASP), the human homolog of the mouse cypher gene, which leads to dilated cardiomyopathy when disrupted.[74] This protein, which interacts with α-actinin 2, disrupts the actin cytoskeleton when mutated. The titin gene, encoding for the giant sarcomeric cytoskeletal protein, titin, contributes to maintenance of the sarcomere organisation and myofibrillar elasticity, and interacts with these proteins at the Z disc/I band transition zone.[75] Furthermore, mutations have been identified in familial dilated cardiomyopathy.[76] Mutations in ANKRD1 cause both dilated and hypertrophic cardiomyopathy, lending support to the idea that sarcomere and Z-disk encoding genes can have variable phenotypes.[40,77]

Dilated cardiomyopathy that is associated with atrioventricular block or skeletal myopathy, or both, is most frequently associated with mutations in lamin A/C.[78,79] Lamins are located in the nuclear lamina at the nucleoplasmic side of the inner-nuclear membrane, and lamin A and C are expressed in heart and skeletal muscle. Mutations in this gene were first reported to cause the autosomal-dominant form of Emery-Dreifuss muscular dystrophy,[78] which has skeletal myopathy associated with dilated cardiomyopathy and conduction-system disease. These mutations also cause a form of autosomal-dominant limb-girdle muscular dystrophy, which is associated with conduction-system disease.[78,79] Mechanisms that are responsible for the development of this disease, conduction-system abnormalities, and skeletal myopathy are being established.

Immune system and heart failure

Myocarditis is characterised by pathological inflammation of the myocardium, leading to chronic heart failure in a substantial number of patients younger than 40 years.[80] Diagnosis for both viral and non-viral causes is based on well-established histological, immunological, and immunohistochemical criteria for endomyocardial biopsy samples. A subset of patients with myocarditis from various causes develop a chronic form of the disease that can be viral, post-infectious immune, or organ-specific immune in genetically predisposed individuals.[3,81] Autoimmune-mediated chronic myocarditis is characterised by autoantibodies to cardiac myosin and other heart antigens.[82] Results of clinical and experimental data[83] suggest that, of these antibodies, those that are directed against the cardiac β_1-adrenergic receptor induce cardiac dysfunction and cardiomyopathy, and might modulate severity of disease. However, whether patients develop heart disease because they possess harmful antibodies against this receptor or whether they develop these antibodies as a result of cardiac tissue injury remains unclear.

Results of other studies have implicated other autoantibodies; such as a group of autoantibodies against cardiac cellular proteins, including G-protein-linked receptors such as the muscarinic cholinergic receptor, myosin, mitochondrial proteins (eg, adenine nucleotide translocator and keto-acid dehydrogenase), actin, tubulin, heat-shock proteins, the sarcoplasmic reticulum ATPase, myosin, and the troponins.[84] Clinical aspects of these autoantibodies remain unclear. However, circulating cardiac autoantibodies are identified in dilated cardiomyopathy and myocarditis patients at a higher frequency than in patients with non-inflammatory heart disease. Furthermore, in healthy relatives of dilated cardiomyopathy patients, serum antiheart autoantibodies are an independent predictor for development of this disease.[85] Both innate and adaptive aspects of the immune system could have a role in affecting outcomes for experimental animals and people with viral myocarditis.[86]

Genetic mechanisms associated with autoimmune-mediated myocarditis remain poorly understood. Most genetic studies in people have suggested a relation between MHC class II antigens and dilated cardiomyopathy.[87] However, this relation, especially with *HLA-DRB4*, existed in a small patient population. Other studies[88] have not supported these findings. Such reported discrepancies could be secondary to differences in patient backgrounds, such as ethnic origin.[89] A recent report by Taneja and colleagues[90] of a non-obese diabetic mouse model developing spontaneous myocarditis also implicates a possible role of sex-related genes. The role of MHC class I in autoimmune myocarditis in animals or people has not been well established. Potential gene-specific mutations that cause autoimmune myocarditis have been investigated but rarely defined. Autoimmune diseases, such as diabetes and systemic lupus erythematosus, have overlapping loci with myocarditis, suggesting shared genetic traits. This finding could help to explain the susceptibility to autoimmune myocarditis across different populations.

The failing myocardium also provides signals to assist in leukocyte infiltration via upregulation or secretion of cell-adhesion molecules. The endothelium in the microvasculature of the failing heart increases expression of these molecules such as P-selectin, e-selectin, intracellular cell adhesion molecule-1, and vascular cell-adhesion molecule-1, which allows transendothelial migration of a range of immune cells into the myocardium, including B cells, T cells, natural killer cells, monocytes, and platelets.[91,92]

Left ventricular non-compaction

Left ventricular non-compaction has previously been regarded as a rare disease, and has been identified by various names—spongy myocardium, fetal myocardium, and non-compaction of the left ventricular myocardium.[93] The abnormality is thought to represent an arrest in the normal process of myocardial compaction, the final stage of myocardial morphogenesis, resulting in persistence of many prominent ventricular trabeculations and deep intertrabecular recesses. Left ventricular non-compaction can be difficult to diagnose unless the physician has a high level of suspicion during echocardiographic assessment. With careful review of echocardiograms and other clinical data, this disorder seems to be common in children, and is also reported in adults.[94] About 9% of all cases of cardiomyopathy are diagnosed as left ventricular non-compaction, with only dilated cardiomyopathy and hypertrophic cardiomyopathy being more common. In the most recent American College of Cardiology/American Heart Association (AHA/ACC) cardiomyopathy classification, left ventricular non-compaction was recognised for the first time as a formal form of cardiomyopathy.[4] A substantial percentage of these patients have a dilated left ventricle with systolic dysfunction, mimicking dilated cardiomyopathy. Signs, symptoms, and outcomes of these patients mirror those of patients with pure dilated cardiomyopathy, but in young children, outcomes are worse than for those with dilated cardiomyopathy.

Treatment

Therapy of dilated cardiomyopathy is mainly directed at treatment of heart-failure symptoms and prevention of disease progression and related complications, such as end-organ dysfunction and stroke. Revised guideline recommendations have been published.[95] Diagnosis, severity of disease, and, if possible, cause of the dilated cardiomyopathy should be known so that therapy can be as precise as possible. To improve diagnosis and grading of disease severity, a new method of staging patients who are developing heart failure with accompanying recommended therapies has been developed.[95] This new classification system, replacing the New York Heart Association (NYHA) classification, emphasises development and progression of heart failure and identifies patients who are at risk of heart failure and those with structural disease, both in symptomatic and asymptomatic states. On the basis of these recommendations, initial assessment should consist of standard serological testing, transthoracic echocardiography, and, in adults, coronary angiography to assess for possible revascularisation when appropriate. Additionally, testing for secondary or specific causes that mimic dilated cardiomyopathy is suggested—with clinical suspicion of haemochromatosis, sleep-disordered breathing, HIV infection, rheumatological disease, amyloidosis, or pheochromocytoma. MRI can also be helpful for identification of structural and functional abnormal findings, especially in the assessment of myocardial viability and scar tissue.[96]

Use of serological testing has been widely reported. In patients with heart failure, activation of the neurohormonal axis and inflammatory markers takes place. This activation can be measured and could aid in diagnosis and prognostic assessments. Braunwald[7] reviews the present understanding of biomarkers in heart failure. The most widely used biomarker is BNP. A rise in BNP is associated with reduced left ventricular systolic function, hypertrophy, raised filling pressures, and myocardial ischaemia.[97] This peptide is also useful in paediatric populations with chronic systolic dysfunction for prediction of high risk of death, need for hospitalisation, or need for cardiac transplantation.[11] Much research about NT-proBNP has been done, with hopes that this peptide is a better biomarker than is BNP, secondary to differences in renal clearance. However, van Kimmenade and co-workers[98] reported no difference in renal clearance between BNP and NT-proBNP.

Medical therapy remains the mainstay in patients with dilated cardiomyopathy and heart failure. Present oral regimen recommendations are outlined elsewhere,[99–102] and have led to significant improvements in survival and symptom relief. In short, inhibition of angiotensin-converting enzymes and β-blockade with or without diuretics continue to be standard options. Treatment of decompensated heart failure is focused on diuresis with loop diuretics for volume overload and afterload reduction. Modulation of afterload can be accomplished with use of vasodilator therapy such as nitroglycerin, nitroprusside, or nesiritide. In patients with heart failure and clinical evidence of hypotension associated with hypoperfusion and raised filling pressures, intravenous inotropic support or vasopressor therapy, or both, should be considered. We prefer to avoid inotropes that increase mechanical stress, such as dopamine and dobutamine, in children, with milrinone continuing to be the most popular therapy. Once the need for other inotropic agents becomes clear because of deterioration in blood pressure and perfusion, we consider placement of an assist device. Some institutions use balloon pumps regularly in this instance. A comprehensive list of therapeutic strategies with supportive evidence is provided elsewhere.[95]

Several clinical trials[103,104] have assessed use of implantable cardioverter-defibrillators in patients with

low left ventricular ejection fractions, with results showing reduced mortality.[103,104] For patients who have a left ventricular ejection fraction of less than 30% and symptomatic heart failure for which they are receiving optimum medical therapy, use of implantable cardioverter-defibrillators is a class I indication, as outlined by the ACC/AHA guidelines.[95] Despite the guideline recommendations, such devices have not been used as extensively as suggested, with great variation between hospitals. Additionally, results seem to vary by ethnic origin and sex with these devices.

Use of cardiac resynchronisation therapy has expanded the therapeutic options for both paediatric and adult patients with advanced heart failure and ventricular-conduction delay. This therapy is designed to eliminate the delay in activation of the left ventricular free wall, a finding often seen in adults with left ventricular systolic dysfunction. Hence, cardiac resynchronisation therapy improves mechanical synchrony, which in turn increases left ventricular filling time, decreases mitral regurgitation, and reduces septal dyskinesis, which is frequently reported in adults. This therapy has been shown to restore coordination and relaxation of cardiac chambers, results in favourable cardiac remodelling, and improves survival in this population.[105–107] However, up to a third of patients do not have any clinical benefit with present recommended criteria.[108] These patients could have identifiable reasons for a poor response and might benefit from further treatment optimisation.[109]

Surgical management of dilated cardiomyopathy with congestive heart failure is one of the most rapidly expanding areas of cardiovascular surgery, with a goal to improve the biophysics of the left ventricle and reduce the stimulus for unfavourable remodelling.[110] Although much of the research has been in patients with ischaemic disease, many of the strategies used could apply to the dilated cardiomyopathy population. Use of palliative surgical procedures as a bridge to transplant in this disorder has had little success. The Batista procedure,[111] or partial left ventriculotomy, is useful in patients with end-stage dilated cardiomyopathy. Other interventions include surgical ventricular restoration by recreation of the elliptical shape of the left ventricle by volume reduction with a sizing balloon, achieving a volume of 55–60 mL per m^2 body-surface area.[112] Long-term results[113] of the CorCap Cardiac Support Device (Acron Cardiovascular, St Paul, MN, USA), which reduces left ventricular wall stress, have been reported, suggesting favourable effects on left ventricular size and shape. This device could also improve quality of life and has a similar safety profile to mitral-valve annuloplasty. Surgical mitral-valve annuloplasty is feasible[114] and decreases functional mitral regurgitation. Results of the AMADEUS[115] and CARILLON[116] trials also show feasibility of percutanoues mitral-valve annuloplasty, with a decrease in functional mitral regurgitation.

Cardiac transplantation is needed in extreme cases. At present, transplants are reserved for patients with the most severe disease—those needing inotropes and usually mechanical ventilatory and mechanical device support. Waiting times for organs remain a significant restriction. Use of ventricular-assist devices has significantly improved survival of adults and children with dilated cardiomyopathy with end-stage disease who are awaiting heart transplant.[117,118] Such devices[119] are highly effective in heart-failure populations that are ineligible for cardiac transplant. We have shown[120] that N-terminal dystrophin is reduced or absent in hearts of patients with all forms of dilated cardiomyopathy (ischaemic, acquired, genetic, and idiopathic) and that reduction of mechanical stress by use of these devices reverses remodelling of dystrophin and of the heart itself. Various ventricular-assist devices exist at present—some are stationary, others ambulatory, and some are fully implantable. The total artificial heart is the most aggressive of these devices and is used for destination therapy (use of long-term mechanical circulatory support in patients with endstage heart failure, without the intention of eventual heart transplantation).

Controversy continues about therapy for myocarditis. In view of the chronic inflammatory nature of the disease and the effects of the immune system, immunomodulatory therapy might be beneficial. However, non-selective therapy has not proved useful.[121] Prospective data with combined therapy of steroids and azathioprine show[14] long-term benefit in dilated cardiomyopathy patients with evidence of HLA upregulation on biopsy samples. Cooper and co-workers[15] reported usefulness of immunomodulation in giant-cell myocarditis. Frustaci and colleagues[13] reported a beneficial immunosuppressive effect in patients with active lymphocytic myoarditis, circulating cardiac autoantibodies, and no viral genome detected with endomyocardial biopsy sample. Some researchers[121,122] support use of intravenous gamma globulin. However, McNamara and co-workers[123] did not show a benefit from intravenous gamma globulin in myocarditis on the basis of Dallas criteria. A trial[124] is in progress to test the efficacy of interferon gamma in Europe. These reports all suggest that non-specific therapy might be of no benefit. However, immunomodulatory or antiviral therapy could be of some benefit in very well-defined populations.

Interest in the use of stem-cell therapy as a treatment for end-stage dilated cardiomyopathy has increased during the past decade. Several studies[125] have documented beneficial effects of stem-cell transplantation in patients who have depressed left ventricular systolic dysfunction after myocardial infarction. However, concern has grown that this approach might only result in paracrine growth-factor stimulation or improvement in myocardial scaffolding without generation of new myocardium. Much debate[126] has taken place about the optimum cell source for myocardial regeneration. However, a substantial research effort in both paediatric and adult populations is in progress to improve definition of this therapeutic option.

Although improved outcomes in dilated cardiomyopathy and heart failure have been achieved, improving outcomes for patients with non-ischaemic disease remains problematic. For these reasons, gene-based therapies such as gene therapy,[127] stem-cell therapy,[128,129] and targeted treatments are being investigated. The next decade will probably further define causes and mechanisms of this disease, and result in breakthroughs in treatment that will hopefully improve the outcome for these patients.

Contributors
Both authors contributed equally to the literature search and writing of this Seminar.

Conflicts of interest
We declare that we have no conflicts of interest.

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