From Heart Failure to Cardiomyopathy

William Harvey—a London physician—described the normal circulation in his classic monograph “De Motu Cordis” (Movement of the Heart) in 1628. However, the link between the clinical manifestations of heart failure (HF) and structural changes in the heart was not made for 4 decades, when Richard Lower wrote that when “the parenchyma of the heart...suffers from inflammation, abscess or a wound” it may be unable to provide “a constant circulation of the blood.” Lower also recognized that the heart was enlarged in patients with HF. Since then, efforts to understand the causes of HF have been central to both clinical cardiology and cardiovascular science.

In the 18th century, HF was attributed largely to valvular heart disease, which was common at the time. Because physicians related the clinical manifestations of HF to the findings at autopsy, they described an ever increasing number of patients with HF without an apparent cause. In 1891, Krehl—a physician in Leipzig—discussed idiopathic diseases of cardiac muscle. In 1901, Josserand and Galvardin introduced the term “primary myocardial disease” to describe such patients. Because the specialty of cardiology emerged with its new diagnostic tools, a growing number of patients with unexplained HF were encountered.

A turning point came in 1957, when Wallace Brigden—a London cardiologist—published an article...
Classification of Cardiomyopathies

John F. Goodwin, also a London cardiologist, developed a classification based on structural and functional changes.\(^6\) These included congestive cardiomyopathy, now referred to as dilated cardiomyopathy (DCM), hypertrophic cardiomyopathy (HCM), and constrictive (now referred to as restrictive) cardiomyopathy (RCM). A fourth category, arrhythmogenic right ventricular cardiomyopathy, now referred to as arrhythmogenic cardiomyopathy, was added more recently.\(^7\) Each of these categories was further subdivided by pathogenesis, such as secondary to a systemic disorder, an infection, inflammation, or an inherited disorder. In many patients, no pathogenesis could be identified, and these were termed idiopathic cardiomyopathies. Following Brigden’s lead, heart muscle disease secondary to ischemia was excluded, and the term nonschismic cardiomyopathy is frequently used.

Cardiomyopathies received increasing attention as the causes were clarified and as sensitive imaging and genetic testing became available. Periodically, the World Health Organization\(^8\) and national and continental cardiac societies provided definitions and classification schemes. In 2006, the American Heart Association proposed the following definition:\(^9\)

> “Cardiomyopathies are a heterogeneous group of diseases of the myocardium associated with mechanical and/or electric dysfunction that usually (but not invariably) exhibit inappropriate ventricular hypertrophy or dilatation and are due to a variety of causes that frequently are genetic. Cardiomyopathies either are confined to the heart or are part of generalized systemic disorders.”

In a departure, this panel added cardiac ion channel disorders (channelopathies) to the cardiomyopathies. In 2008, the European Heart Association did not accept this addition.\(^10\) The diagrams illustrating the classifications developed by these 2 panels are shown in Figures 10 and 11 in the article by McKenna et al.\(^11\) This war of words was averted when the Heart Rhythm Society (an American society) and the European Heart Rhythm Association prepared a consensus statement on genetic testing of the channelopathies and cardiomyopathies.\(^12\)

Oncologists have developed a staging system for cancer that has been successfully used for many years. It is the so-called TNM system, in which T refers to the tumor extent, N refers to the nodal status, and M refers to metastasis. In 2013, Arbustini et al\(^13\) proposed the MOGE(S) classification for cardiomyopathy, endorsed by the World Heart Federation.\(^13\) M refers to the phenotype (eg, DCM and HCM), O refers to organ involvement (eg, with/without extracardiac involvement), G refers to genetic transmission (eg, autosomal dominant or recessive), E refers to pathogenesis (eg, genetic with disease gene and mutation, if known), and S refers to disease stage. Each letter in the MOGE(S) classification has well-defined subscripts, which provide details.\(^14\)

It is the purpose of this compendium to review the current understanding of the clinical features and scientific bases of what remains a vibrant and growing area of clinical cardiology and cardiovascular science.

Dilated Cardiomyopathy

The European Cardiac Society has defined DCM as dilatation of the left or both ventricles that is not explained by abnormal loading conditions or coronary artery disease.\(^10\) DCM is characterized by cardiac enlargement with ventricular walls of approximately normal thickness and varying extents of fibrosis (Figures 2 and 3 in the article by McKenna et al\(^11\)). The patients develop progressive HF with reduced ejection fraction, tachyarrhythmias, and an increased risk of sudden death. Echocardiography and other imaging modalities typically show dilatation of all 4 cardiac chambers, with increased end-systolic volumes of both ventricles.\(^15\) Mitral and tricuspid regurgitation because of annular dilatation are frequent and intensify the hemodynamic burden.

It has been recognized for >2 centuries that cardiac dysfunction can occur in the presence of many infections. In 1806, Corvisart—a French Professor—asked a prophetic question: “Is the inflammation of the heart always sharp and acute or does it not sometimes affect an insidious, hidden progress?”\(^16\) In 1948, the Coxsackie virus was isolated and shortly thereafter its role and that of other viruses, including influenza A and B, herpesviruses, and human immunodeficiency virus were all recognized as causes of acute carditis. In most cases, these infections are associated with transient electrocardiographic changes, and patients recover uneventfully, although a small percentage succumb to acute cardiovascular collapse\(^27\) (Figure). By 1968, a condition referred to as postcardiotic cardiomyopathy was established as a cause of DCM,\(^18\) thereby answering Corvisart’s question affirmatively. It now seems that many patients with DCM may have experienced an unrecognized acute viral myocarditis several years earlier (Figure). The relationship between viral myocarditis and DCM is also discussed in other articles on inflammatory cardiomyopathic syndromes in the compendium.\(^19,20\)

Cardiac toxins are also an important cause of DCM. The most common of these is alcohol\(^21\)—a cardiodepressant. Many substances including the prolonged use of cocaine and amphetamine have also been incriminated. Many cancer
Chemotherapeutic agents have been identified as cardiac toxins, which, like viral myocarditis, may cause acute ventricular dysfunction and lead to DCM years later. Other causes of DCM include peripartum cardiomyopathy and prolonged tachycardia-related cardiomyopathy. The familial aggregation of DCM in some cases has become apparent. McNally and Mestroni provide an important summary of familial DCM in this compendium. The mode of inheritance is usually autosomal dominant, but autosomal recessive and sex-linked transmission have also been described. Familial DCM is genetically heterogeneous; mutations in >50 genes have been identified, and the number continues to grow. The involved genes encode proteins in the sarcomeres, ion channels, cytoskeleton, nuclear envelope, and mitochondria. There is allelic heterogeneity as well, with mutations occurring at several positions of many of the involved genes. The gene that encodes titin—the giant protein that controls the stiffness of the sarcomere—is the most common and is responsible for ≈20% of cases of familial DCM.

Treatment of DCM is similar to that of other forms of HF with reduced ejection fraction. In 1979, Swedberg et al demonstrated improved survival in these patients when a beta blocker was added to their regimen. However, once clinical evidence of HF develops, a progressive downhill course often occurs, requiring chronic mechanical support or cardiac transplantation.

**Hypertrophic Cardiomyopathy**

**Early Years**

Knowledge about HCM has evolved in 3 phases. The first was the initial description of the condition. The unique pathophysiology was recognized almost a century before Brigden introduced the term cardiomyopathy. French physicians described several patients in the late 1860s. One patient described in 1869 was a 75-year-old woman with severe dyspnea and a systolic murmur. Liouville described the heart at autopsy as follows: “The left ventricle is enlarged and very thick. It has considerable concentric hypertrophy. When I insert my index finger from the ventricle toward the aortic outflow tract, my finger becomes tightly pinched in the myocardium, 1 cm below the aortic valve. When I try to insert my thumb backward through the aortic valve toward the ventricle, it cannot reach my index finger that I have inserted from the opposite direction. This is due to the obstruction that is caused by the myocardial thickening that is situated below the level of the aortic valve (my emphasis).” Amazingly, >8 decades before left ventricular pressure could be measured, this clinician–pathologist accurately described the key feature of this condition—ventricular hypertrophy—and deduced that it caused intraventricular obstruction!
During the first half of the twentieth century, several individual patients with idiopathic left ventricular hypertrophy were recorded. In 1944, 10 patients were described by Levy and von Glahn, who wrote: “These cases appear to form a clinical group of which the chief features are: marked cardiac hypertrophy, symptoms of cardiac insufficiency and occurrence of various types of arrhythmia. The hearts, at autopsy, all show hypertrophy of the muscle fibers”.27 In 1949, Evans reported that idiopathic ventricular hypertrophy may, in some instances, be familial.28 In 1958, Donald Teare—a pathologist—studied the hearts of 9 patients with left ventricular hypertrophy, 8 of whom had died suddenly; he reported that the hypertrophy was asymmetrical and most severe in the ventricular septum29 (Figure 4 in the article by McKenna et al11). Thus, by 1958, the condition now termed HCM had the following characteristics: asymmetrical left ventricular hypertrophy causing obstruction to ventricular outflow, a familial association in some patients and an increased risk of arrhythmias, and sudden cardiac death.

**Hemodynamic Era**

In the second phase, the development of left heart catheterization, echocardiography, and open heart surgery enhanced diagnosis and treatment. In 1959, Sir Russell Brock—the leading British cardiac surgeon of the era—described patients with subaortic pressure gradients caused by acquired aortic subvalvar stenosis found at operation.30 In the same year, Morrow and Braunwald described 2 patients in whom significant subaortic pressure gradients were demonstrated preoperatively “The hemodynamic evidence of obstruction to left ventricular outflow is unequivocal…a systolic pressure difference between left ventricle and aorta…was definitely localized to an area within the ventricle… the obstruction can only be explained by muscular hypertrophy of the left outflow tract of sufficient severity that flow is actually impeded during contraction…the left ventricular cavity appeared to be encroached upon and almost divided by an intrinsic mass, presumably hypertrophied cardiac muscle.”31

With the proliferation of catheterization laboratories and cardiac surgical programs in the 1960s, the number of patients in whom HCM was diagnosed increased rapidly. The obstruction to left ventricular outflow was found not to be constant, as in valvular aortic stenosis, but dynamic and variable.32 Interventions that reduce left ventricular volume and presumably narrow its outflow tract (such as assuming the erect posture, β-adrenergic agonists, tachycardia, and exercise) increased obstruction, whereas interventions that increase ventricular volume had the opposite effect. Three categories of HCM patients emerged33,34: (1) patients with obstruction at all times, (2) patients without obstruction in the basal state in whom obstruction could be provoked, and (3) patients without obstruction in whom obstruction could not be provoked. Diastolic dysfunction was present in most patients with HCM, irrespective of the presence or severity of obstruction.35 The development of echocardiography resulted in a major step forward.36 It helped to confirm or refute the diagnosis, was useful in family screening programs, and allowed repeated follow-up examinations of individual patients.

During this phase, both pharmacological and invasive therapies were developed. The former consisted of beta adrenergic blockers,37 with nondihydropyridine calcium antagonists as back up drugs. In 1961, Morrow developed left ventricular myectomy for symptomatic patients with severe obstruction.38 In 1995, Sigwart described the less-invasive technique of alcohol septal ablation,39 in which a catheter is inserted into a branch of the left anterior descending coronary artery; alcohol is injected through the catheter to cause infarction localized to the obstructing septal myocardium. Ventricular fibrillation is the most common cause of death in HCM. It can be prevented by implantation of a cardioverter defibrillator into patients who are at high risk of this complication.40 A much less frequent cause of death is intractable HF, which may require cardiac transplantation.

**Genetic Era**

The third and current phase of progress is the genetic phase. Although familial occurrence was described in 1949,28 it was subsequently shown that inheritance was through an autosomal dominant mechanism.32,41 In 1990, C. Seidman and J.G. Seidman discovered a molecular cause of HCM with a missense mutation in the myosin heavy gene.42 This work was extended and multiple mutations in 9 genes that encode sarcomeric proteins have been shown to be responsible for HCM.43 Ongoing genetic studies of HCM are advancing the understanding of the molecular basis of cardiac contraction and relaxation. Whole exome sequencing is useful in identifying mutation-positive patients with or without phenotypic expression. The latter are at risk of expressing the phenotype later in life; others never develop the phenotype. Mutation-negative patients in families with HCM do not appear to be at risk.

Two articles in the compendium are devoted exclusively to HCM.44,45 In addition, the article on cardiac imaging deals with echocardiographic findings in HCM,15 whereas the article on pediatric cardiomyopathies discusses HCM in this age group as well.20

**Arrhythmogenic Cardiomyopathy**

In 1736, in a remarkable treatise entitled “De Motu Cordis et Aneurysmatibus” (on the movement of the heart and aneurysm), the great Italian anatomist Giovanni Maria Lancisi described a family with aneurysmal dilatation of the right ventricle, HF, palpitations, and sudden death occurring in 4 generations.46 René Laennec, inventor of the stethoscope, described the combination of fatty replacement of right ventricular myocardium and sudden death.47 More recently, Dalla Volta et al48 demonstrated absence of normal right ventricular contraction in this condition. In 1982, Marcus et al49 described 24 patients with recurrent tachycardias, right ventricular dilatation, and failure. Ventricular postexcitation waves, described as small undulations in the ST segment, were observed in one third of the patients (Figure 6 in the article by McKenna et al11).

Nava, Thiene, and their collaborators tied these strands together by recognizing that this disorder, initially referred to as arrhythmogenic right ventricular cardiomyopathy, was an important cause of death in patients <35 years.50 Ultrastructural analyses revealed that the abnormalities in intercellular adhesion molecules, desmosomes, cause cell death and fibrofatty
replacement. These abnormalities are caused by mutations in genes, such as PKP2 and DSP, encoding plakophilin 2 and desmoplakin, respectively. Inheritance in most cases is by Mendelian dominant transmission. Less commonly, autosomal recessive forms of arrhythmogenic right ventricular cardiomyopathy are responsible. The epsilon wave of delayed repolarization following the QRS complex is helpful in diagnosis. Contrast-enhanced cardiac magnetic resonance (CMR) and bipolar electroanatomic mapping allow determination of the severity of this abnormality. Reports of dysplastic involvement of the ventricular septum and left ventricular wall have been reported in some patients who have survived to midlife and beyond. The increasing recognition of left ventricular involvement has been responsible for the change in designation from arrhythmogenic right ventricular cardiomyopathy to arrhythmogenic cardiomyopathy.

Treatment consists of the cessation of heavy physical exertion and competitive athletics. For patients with recurrent ventricular tachycardia, epicardial catheter ablation may be effective. Implantation of a cardioverter/defibrillator is indicated in patients who have experienced ventricular fibrillation or refractory ventricular tachycardia. Patients with intractable HF may require cardiac transplantation. Genetic screening should be performed in family members.

An important advance has been the development of a transgenic mouse model expressing a desmoglein-2 mutation, which reproduced the disease, including ventricular aneurysms (initially described in patients by Lancisi46) with fibrous replacement of the ventricular myocardium, prolonged ventricular activation, arrhythmia inducibility, tachyarrhythmias, and sudden death.53

### Restrictive Cardiomyopathies

#### Amyloid Cardiomyopathy

In 1860, in his classic textbook, the German pathologist Rudolf Virchow described tissue deposits of a substance that resembled starch in its response to iodine and sulfuric acid. He named it amyloid, resembling the Latin word for starch, amylosum.44 In 1922, cardiac amyloidosis was described,55 followed by the discovery of familial amyloid heart disease (Figure 14 in the article by McKenna et al41). In 1948, the clinical and hemodynamic similarities between cardiac amyloidosis and chronic constrictive pericarditis were noted.57 Hetzel et al58 reported that pressure pulse tracings were almost identical in patients who have experienced ventricular fibrillation or refractory ventricular tachycardia. Patients with intractable HF may require cardiac transplantation. Genetic screening should be performed in family members.

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CMR is a sensitive diagnostic technique for amyloid cardiomyopathy. Late gadolinium enhancement (LGE) has been shown in >80% of patients, including patients without evidence of this disorder by echocardiography.59 Marked elevations in T1 and extracellular volume may be useful for diagnosis and monitoring response to therapy. Encouraging results of treatment have been reported by Pilebro et al60 using the tracer C-Pittsburgh compound B, which has been shown to detect cardiac amyloid by positron emission tomography (PET).61 A definitive diagnosis of this condition still requires histological verification.

Therapy of light-chain amyloidosis includes autologous bone marrow stem cell transplantation and drugs that include dexamethasone, melphalan, immunomodulatory agents, and the proteasome inhibitor bortezomib. In wild-type transthyretin amyloidosis, orthotopic liver transplantation has been reported to be beneficial. Early-stage (phase I) clinical trials with RNA interference have shown promising results in suppressing production of the mutant and wild-type transthyretin in patients with transthyretin amyloidosis. Much additional work is required to understand the fundamental mechanism(s) responsible for the protein misfolding. Then the task will be to identify the optimal treatment for each subtype. Because few centers have access to large numbers of these patients, a multinational registry will be needed to gather experience with various therapeutic approaches leading ultimately to clinical trials.

#### Endomyocardial Fibrosis

In 1893, Reinbach described a patient with eosinophilia and mural thrombi.64 Almost a half century later, Lööfier reported 2 patients with eosinophilia, fibrous endocarditis, and progressive HF.65 Subsequently, idiopathic hypereosinophilic syndrome—a leukoproliferative disorder with eosinophilic infiltration of multiple organs—became apparent; in Lööfier endocarditis, the heart is the target organ and generally presents as an acute febrile illness. CMR is useful for showing ventricular thrombi and for assessing the obliteration of the ventricular cavities.66 Endomyocardial biopsy usually shows hyaline thickening of the endocardium and mural thrombosis. Interleukin 5 is important in the development of eosinophils, which play a key role in the pathogenesis. Mepolizumab—an anti-interleukin 5 monoclonal antibody approved for the treatment of eosinophilic asthma—may prove effective in the treatment of Lööfier endocarditis.67

In 1946, Bedford and Konstam described a fibrotic disorder leading to fatal HF in African soldiers.68 In Uganda, Davies described an endomyocardial fibrosis that was frequently associated with fibrous thickening of the mitral and tricuspid valves causing regurgitation associated with mural thrombosis which interfered with ventricular filling.69 This condition, the most common form of RCM, remains endemic in East Africa, but has also been described in Southern India and equatorial South America; it is often referred to as tropical endomyocardial fibrosis.70 This RCM can be detected in its
early, asymptomatic stage by echocardiography. CMR may show apical thrombi in one or both ventricles and subendocardial LGE. In late stages, it causes intractable HF.

The pathogenesis of tropical endomyocardial fibrosis is not clear. Eosinophilia, diet, infections and genetic factors, or some combinations of these have been incriminated. There has been considerable debate whether Löffler eosinophilic endocarditis and tropical endomyocardial fibrosis are pathogenetically related or are different stages of the same disease; the best available evidence indicates that the latter is unlikely. Therapy of tropical endomyocardial fibrosis includes the several measures used in the treatment of HF. In advanced cases, endocardial resection with replacement of the mitral and tricuspid valves may be performed and may improve cardiac function. Efforts should be directed to selecting patients for operation earlier in the course of the disease.

Future research should focus on defining the pathogenesis. It is possible that tropical endomyocardial fibrosis is a syndrome composed of several unrelated conditions. If this turns out to be correct, their delineation could lead to more specific therapies.

Inflammatory Cardiomyopathies

Myocarditis

Infection, inflammation, and immune reactions are involved in the pathobiology of many cardiomyopathies, and these are discussed in an excellent article in the compendium by Trachtenberg and Hare. In 2013, the European Society of Cardiology published a position article on myocarditis that included the progression of myocarditis to DCM (Figure). Noninfectious, immune-driven causes of myocarditis include allergic reactions to drugs, Kawasaki disease, systemic lupus erythematosus, and Löffler endocarditis. CMR provides a powerful tool in the recognition and assessment of myocarditis. This technique can reveal regions of myocardial edema, represented by elevated T2 relaxation times; hyperemia/capillary leak, which can be detected by early gadolinium enhancement; and irreversible cell injury with fibrous tissue replacement as LGE. Endomyocardial biopsy with histology, immunohistochemistry, and viral genome analysis remain the gold standard for providing the definitive diagnosis in high-risk patients with suspected myocarditis.

Kühl et al. have shown in endocardial biopsies in patients with myocarditis that prolonged persistence of virus is associated with progressive deterioration of cardiac function. Biopsies in many patients with DCM have shown a chronic intramyocardial inflammatory process with immune activation of endothelial and interstitial cells, consistent with an active, chronic autoimmune process. Both innate and adaptive immune mechanisms are involved in the acute inflammatory response to cardiac tissue injury, irrespective of pathogenesis. Although immune suppression with prednisone and azathioprine or cyclosporine failed, treatment with interferon-β improved hemodynamic indices and survival of patients with myocarditis and persistent enteroviral or adenoviral genome in the myocardium.

Chagas Disease

It is rare for a single individual to describe a major disease and to elucidate its pathogenesis. Carlos Chagas—a Brazilian physician—was such an exception. In 1909, he discovered, described, and named the etiologic agent—a protozoan (Trypanosoma cruzi)—for the disease that appropriately bears his name. He went on to elucidate the complex disease process involving its insect vector and described both the acute and chronic phases of the disease. The acute phase of Chagas myocarditis is usually asymptomatic and often is not recognized clinically. About one third of infected patients usually develop the chronic form, a biventricular DCM characterized by aneurysmal thinning of the cardiac apex, extensive ventricular fibrosis, conduction system abnormalities, and apical thrombosis, leading to HF, atrioventricular block, and systemic embolism.

Chagas disease remains a major health threat in South and Central America, and with increasing world travel and migration, it is being recognized with greater frequency in temperate climates. Globally, it remains the third most common parasitic disease. Control of the vector that is responsible for the transmission of T. cruzi in endemic regions has been reasonably successful in reducing the incidence of Chagas disease. However, millions of patients with the chronic phase of the disease persist. Their treatment remains unsatisfactory, and death may be sudden because of an arrhythmia or it may be caused by progressive HF.

Future research on Chagas disease could include more precise genotyping of the Trypanosome, which would throw light on the molecular epidemiology of the disease. It would also be helpful to identify biomarkers for disease progression. Two aspects seem to play important roles in the pathogenesis of HF in chronic Chagas disease: (1) sympathetic overactivity consequent to parasympathetic nerve damage and (2) autoimmune responses directed against the damaged myocardium. Both aspects can be addressed and could provide the basis for more successful therapies of this important condition.

Sarcoidosis

In 1899, Caesar Boeck—a Norwegian dermatologist—described a granulomatous disease that affects the skin and lymph nodes. He named it sarcoid because of its histological similarity to some forms of sarcoma. Early in the twentieth century, it was observed that sarcoidosis can involve the viscera, including the myocardium (Figure 13 in the article by McKenna et al) leading to HF. It frequently invades the conduction system and causes atrioventricular block and occasionally sudden death. Involvement of the pulmonary parenchyma and enlarged mediastinal lymph nodes are prominent.

Sarcoidosis is now recognized as an inflammatory condition in which noncaseating granulomas involve multiple organs, including the heart. Sarcoid cardiomyopathy is described in the articles by Muchtar et al. and by Trachtenberg and Hare. This cardiomyopathy presents significant challenges to and opportunities for both basic and clinical investigators. For the former, the pathogenesis and pathology still need to be more clearly defined. There are tantalizing clues to genetic, infectious, environmental, and immune-activating stimuli, which should be followed up. Sarcoidosis may actually represent several different disease processes. Current therapy involves glucocorticoids, supplemented by other immunosuppressive agents if necessary. However, this approach is based
Pediatric Cardiomyopathies

Although cardiomyopathies occur less frequently in pediatri
c than in adult populations, they represent a relatively more
common cause of HF in the former. Indeed, cardiomyopathies
are the most frequent cause of HF requiring cardiac transplanta
tion in children.\(^{20,84}\) In adults, cardiomyopathies are
often observed in middle age and beyond and are frequently
complicated by comorbidities, including complications of
atherosclerosis, diabetes mellitus, hypertension, chronic pulmonar
y, and renal disease. One of the adult cardiologists’ important
tasks in patients with cardiomyopathy and HF is to
determine whether the latter is caused by the cardiomyopa
thy, by a comorbidity, or by some combination of the two.
Cardiomyopathies in children are usually not accompanied
by the baggage of acquired comorbidities. However, pediatric
cardiologists are not infrequently confronted by mixed pheno
types, such as DCM and HCM, and a variety of other complex
disorders mentioned below.

The pediatric cardiomyopathy registry has provided an
enormous amount of information about these conditions.
Steven E. Lipshulz—the senior author of the article on pe
diatric cardiomyopathy in this compendium\(^{20}\)—has played a
key leadership role in this registry. The incidence of pediatric
cardiomyopathy phenotypes, as determined by this registry
are DCM –51%, HCM –42%, RCM –3%, and left ventricular
noncompaction –3% (Figure 9 in the article by McKenna\(^{11}\).\(^{85}\)\)

The most important causes of cardiomyopathies in children
(<18 years) are genetic, postmyocarditic, inborn errors of
metabolism, association with malformation syndromes, and
mitochondrial disorders.\(^{20,86}\) These causes can be identified in
about one third of children with cardiomyopathy; the remain
ning two thirds are still classified as idiopathic. The elucidation
of the causes of the latter remain a major challenge.

DCM in children is postmyocarditic in about half of the
cases, more frequently than in adults with DCM.\(^{19}\) Parvovirus
B19 and Epstein-Barr virus are most frequently isolated by
cardiac biopsy in children.\(^{86,87}\) About one fourth of children
with DCM have underlying neuromuscular disorders, specifi
cally Duchenne and Becker muscular dystrophies.\(^{88}\) Overall,
DCM seems to have a worse prognosis in children than in adults.\(^{89}\) Among children with DCM, the prognosis seems to
be worse in patients >5 years, whereas more favorable in
children with familial DCM and postmyocarditic DCM.\(^{86,90}\)

Important areas for future research include enhancement of
understanding of the fundamental mechanisms by which viral
myocarditis and genetic mutations impair myocyte function
so as to result in the chronic DCM phenotype and whether
similar mechanisms are operative in both children and adults
with idiopathic DCM.

HCM is a relatively common disorder in adults\(^{44,45}\) but less
so in children.\(^{91}\) Although cardiac dilatation and HF are rela
tively rare in adults with HCM in whom the cause of death is
most commonly arrhythmic, in children <10 years HF may
be so serious as to require cardiac transplantation and is a
common cause of death. Patients with HCM diagnosed in the
first year of life often exhibit malformation syndromes, mito
chondrial diseases, inborn errors of metabolism, or neuro
muscular disorders.\(^{20,91}\) Inborn errors of metabolism, including
storage diseases,\(^{92}\) are responsible for about one fifth of car
diomyopathies in children—a much higher percentage than in
adults. Most are inherited in an autosomal recessive manner
and can be detected by newborn screening by the development
of hypoglycemic episodes, hyponatremia, and developmental
delays.

Left ventricular noncompaction (Figure 9 in the article by
McKenna et al\(^{11}\)) is frequently associated with DCM and with
HCM in children.\(^{86,87}\) Our understanding of this cardiomyopa
thy is still relatively primitive. It is not clear how often it repre
sents a congenital disorder based on an embryological defect
in children. Infants with isolated left ventricular noncompac
tion during the first year of life are at the highest risk of devel
oping arrhythmias and sudden death, whereas older children
without cardiomegaly seem to have a better prognosis.

Treatment of children with cardiomyopathy and HF is
similar to that in adults. For life-threatening HF in children
>2 years, orthotopic heart transplantation, when performed in
experienced, specialized centers provides early results similar
to those in adults.\(^{93}\) Because of the delays involved in procur
ing donor hearts in children, often even longer than in adults,
pediatric ventricular assist devices are being developed as a
bridge to transplantation; some success with the use of these
devices has been reported.\(^ {94}\)

Cardiac Imaging

Technological Development

Cardiac imaging represents one of the most profound ad
vances in cardiovascular medicine and science. It is generally
safe, noninvasive, or minimally invasive. Cardiac imaging en
hances diagnosis, aids in establishing prognosis, as well as
the response to therapy, and thereby has improved the care
of untold millions of patients worldwide. As a technology
based subspecialty, it relies on close collaboration between
clinicians and physicists, engineers, and radiation biologists.
The first imaging technique was roentgenography,\(^ {95}\) appropria
tly named after its discoverer, Wilhelm Roentgen, who was
awarded the first Nobel Prize in Physics in 1901. Early in the
20th century, cardiac enlargement was first clearly recognized
on a post-mortem by this technique. The development of fluoros
copy a few years later allowed an assessment of the extent and
rapidity of the heart’s motions during the cardiac cycle.

In 1925, Blumgart conducted the first test of cardiac func
tion in humans by determining the velocity of blood flow. He
injected radium C into an antecubital vein and detected it in
the opposite arm using a modified Wilson cloud chamber,\(^ {96}\)
thereby giving birth to nuclear cardiology. In 1954, Engler—a
cardiologist—and Hertz—a physicist—reported on the use of
ultrasoundography (echocardiography) for recording the contin
uous movement of the heart walls,\(^ {97}\) and soon thereafter, Edler
applied it to mitral valve disease, pericardial effusion, and a
variety of other cardiac disorders. Computed tomography
was introduced by Hounsfield in 1973,\(^ {98}\) for which he too was
awarded the Nobel Prize. In the same year, Lauterbuc showed
that nuclear magnetic resonance, another technique developed by physicists, could provide images of biological systems, leading to CMR imaging; this technological advance now provides high spatial and temporal resolution of cardiac structure and motion without requiring radiation.

**CMR Imaging**

The assessments of cardiomyopathies provided by cardiac imaging are well summarized in this compendium by Jan and Tajik. Although echocardiography has been for decades and currently remains the workhorse of cardiac imaging (Table), the ability of CMR imaging to assess myocardial tissue characteristics has become of intense interest. The oldest approach is LGE, which identifies focal deposition of collagen in the extracellular matrix, reflecting areas of fibrosis. Identification and sizing of LGE may be useful in patients with DCM in whom the extent of fibrosis is useful in estimating prognosis. Extensive LGE identifies patients with HCM at risk of sudden death, who may be candidates for implantation of an automatic cardioverter defibrillator.

Even more sensitive and precise methods of determining myocardial collagen content than LGE have become available. It has been shown that LGE-negative patients with DCM may have prolonged T1 relaxation times and excessive extracellular volume fraction. These measurements may reflect subclinical progression of myocardial fibrosis in DCM, HCM, and other cardiomyopathies. T1 relaxation time has also been shown to be prolonged in the hearts of patients with autoimmune carditis, and in the detection of myocardial involvement in patients with skeletal muscular dystrophies. In contrast, T1 relaxation times have been reported to be reduced in myocardial iron overload. T2 weighted images detect myocardial edema and inflammation in DCM.

PET with an uptake of a glucose analog occurs in inflammation and in many neoplasms. Hybrid CMR/PET scanning of the heart provides the combination of the detailed resolution provided by CMR with the metabolic information from PET and represents a significant advance in studying cardiomyopathies, such as cardiac sarcoidosis.

**Future Developments**

In the future, there is likely to be an increase in the availability of hybrid devices, including computed tomography/PET; the latter can be used to measure coronary blood flow and coronary flow reserve, allowing assessment of regional microcirculation, which will allow further noninvasive characterization of cardiomyopathies. Clinical cardiac imaging services are now being reorganized in many centers. Specialists in all modalities of cardiovascular imaging rather than proponents of single techniques are selecting the optimal single or combinations of modalities to address specific clinical problems.

The imaging techniques discussed by Jan and Tajik are now widely available in industrially developed nations. The modalities other than echocardiography are currently available to only a minority of patients in developing nations, where the bulk of the world’s patients with cardiomyopathy, such as endomyocardial fibrosis and Chagas disease, now reside. This major problem must be addressed, although its solutions are beyond the scope of the compendium.

**Concluding Comments**

We are at an especially interesting point in the history of nonischemic cardiomyopathies, which are now being recognized at an accelerating frequency and as an important cause of cardiac disease. Although these disorders are diverse and differ widely from one another, the paths taken to lead to our current understanding have actually been similar. The first clue has usually come from careful observations on a subgroup of patients with fatal or near fatal heart disease by brilliant clinicians who correlated clinical with postmortem or operative findings. Once recognized, efforts have been directed toward developing approaches, which would allow earlier diagnosis and assessment of severity of individual cardiomyopathies. This usually involved one or more imaging techniques, sometimes supplemented by endomyocardial biopsy.

Basic scientists, often working simultaneously, began to elucidate the pathogenesis and pathobiology of specific cardiomyopathies. In many instances, a genetic abnormality, infection, inflammation, or an immune response were identified as causal. As a consequence, the fraction of patients in whom the pathogenesis remains undefined is shrinking, whereas the fraction who are identified early in their course or with a mild form of the disease is expanding.

The recent advances that have led to an understanding of the natural history and to some effective therapies are based on collaborations between a large variety of clinical investigators and basic scientists. The goal of this compendium is to summarize some of these advances and to identify scientific opportunities so as to enhance further collaborative research and accelerate progress in this important field.

**Disclosures**

None.

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