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Current Perspectives on Cardiomyopathies

Edited by Angelos Tsipis

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Notice

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Meet the editor

Dr. Angelos Tsipis holds a diploma in Medicine (MD) from the Medical School at University "TorVergata", Rome, Italy and also received a PhD from the National and Kapodistrian University of Athens, Greece. He is a cardiologist at Onassis Cardiac Surgery Centre, Athens, Greece, and a research scientist of the 1st department of pathology at the Medical School, University of Athens, Greece. His interests cover cardiomyopathies and specifically cardiovascular pathology and molecular cardiology and he received prizes (6) for best research achievement in international and national congresses. Dr. Tsipis has published more than 120 scientific papers in international and national journals, conference proceedings and edited 2 monographs and textbooks. He is a member of the editorial board of 6 scientific journals, reviewer of 10 journals, and member of international and national medical societies.

Contents

Preface

Advances in the understanding of cardiomyopathies and the growth of cardiology have paralleled one another. The new concepts and events that have occurred in cardiology generally and in cardiomyopathies specifically are sufficient changes to justify this book. The material in this book encompasses and blends the knowledge recently acquired in genetics, pathology and physiology with the practical matters of diagnosis and treatment. Developments in cardiomyopathies have advanced at a rapid rate, largely because of the progress that has been made in instrumental analysis and the integration of clinical cardiology with other fields of basic research. Over the years, many classification methods have been developed for cardiomyopathies based on aetiology, structural models and the functional approach. The cardiologist who deals with cardiomyopathies has the following problems: to recognise myocardial disease per se; to develop skills in clinically identifying the numerous subgroups; to develop a systematic approach to finding a cause; to make sense of the many confusing terms; and to keep an open mind. The content of this edition was influenced by inheritance and environmental forces.

Mitochondria are dynamic organelles that can change in number and morphology in healthy cells. Despite their critical role, how their diverse functions are precisely coordinated in a cell is largely unknown. Mitochondrial dysfunction is increasingly being recognized as the basis of a wide variety of human diseases, including seizures, strokes, optic atrophy, neuropathy, myopathy, cardiomyopathy, hearing loss, diabetes mellitus, and common age-related disorders, such as Parkinson's and Alzheimer's disease. Myocardium is one of the most frequently affected tissues in mitochondrial diseases because of its high energy demand. Since cardiac involvement is an independent predictor of morbidity and early mortality, careful and accurate examination of cardiac damage is required. The authors of the first chapter review the aetiology of mitochondrial disease, clinical manifestations of mitochondrial cardiomyopathy, evaluation modalities for cardiac involvement and treatment options.

A genetic approach to identifying the specific genetic cause in individuals with hypertrophic cardiomyopathy (HCM) is summarized in the second chapter. Hypertrophic cardiomyopathy is an important genetic heart muscle disease characterized by left ventricular hypertrophy (LVH) in the absence of an underlying systemic condition or other cardiac disease. Major advances have been made with the discovery of several mutations that have demonstrated marked genotypic and phenotypic heterogeneity of this disease. Genetic testing is available and invaluable for optimal management of patients with HCM.

The mainstay of therapy for hypertrophic cardiomyopathy has been the combination of lifestyle changes and medical therapy including beta blockers or calcium channel blockers. For patients who are against medical treatment, the surgical septal reduction therapy, called septal myectomy, is indicated. Surgical mortality doubles when concomitant mitral procedures are done at

the time of septal myectomy. Careful decision-making should be done in treating concomitant mitral regurgitation. The authors of the third chapter examine the appropriate surgical approach and the technique that should be applied.

Arrhythmogenic right ventricular dysplasia (ARVD) is an inherited cardiomyopathy mostly due to mutations in both desmosomal and non-desmosomal genes. It is characterized by an abnormality in the development of the right ventricular (RV) musculature. ECG changes may have occurred long before the development of gross wall motion abnormalities. Therefore, it may be important to focus on electrical abnormalities to diagnose suspected ARVD rather than on structural changes alone. Epsilon waves are considered to be one of the major diagnostic criteria of ARVD and appear to better correlate with the extent of ARVD and arrhythmic risk. The fourth chapter focuses on the Epsilon wave, discusses the electrogenesis and analyses the shape and distribution of various methods recording Epsilon waves. Importantly, it provides evidence to help better understand the pathological changes underlying ARVD, thus promoting the management of these patients.

Takotsubo syndrome (TTS) is an increasingly recognised acute reversible form of heart failure that is typically seen in post-menopausal women following emotional or physical stress. Increased awareness among physicians led to a great number and variety of conditions associated with TTS and played a key role for development of new diagnostic criteria. A multi-disciplinary approach and additional research in the context of aetiology, pathophysiology, triggering factors and optimal treatment seem essential for better understanding Takotsubo syndrome.

Non-compaction cardiomyopathy (LVNC) is a rare, hereditary disease that may manifest as an isolated myocardial disorder or in relation with congenital heart defects, for example pulmonary atresia, defects in the atrial and ventricular septum, obstructions of the outflow tract of the left or right ventricle, or Ebstein anomaly. The aim of the sixth chapter is to provide an updated and detailed overview of the isolated form of LVNC.

Ischemic cardiomyopathy, a disease of the heart muscle due to coronary artery disease, is the most common cardiomyopathy. Ischemic cardiomyopathy most often presents with a dilated morphology often with wall motion defects and a history of previous myocardial infarction or confirmed coronary artery disease. Mechanisms of myocardial depression in ischemia are necrosis of myocardial cells resulting in irreversible loss of function or reversible damage, either short-term through myocardial stunning or long-term through hibernation. The final chapter offers a definition of ischemic cardiomyopathy and describes its epidemiology, pathophysiology, diagnosis, evaluation and treatment. It aims to help clinicians who treat patients with ischemic cardiomyopathy, researchers, and other professionals with an interest in the field and also patients and their relatives.

I wish to thank the authors who have contributed so generously to this book. They are all experts in their fields of interest, but they have taken time to write on their subjects in order to make this as comprehensive a work as possible.

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Chapter 1

Mitochondrial Cardiomyopathy

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Additional information is available at the end of the chapter

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Abstract

Mitochondrial diseases are multisystem disorders, resulting from mitochondrial electron transport chain dysfunction and oxidative phosphorylation due to pathogenic variants in mitochondrial or nuclear DNA. The clinical presentations are variable in the age of onset, symptoms, and range and severity of organ involvement. Diagnosis requires a multidisciplinary approach and is based on clinical symptoms, laboratory tests, histopathological findings, and genetic analysis. Due to the multi-organ involvement, the evaluation of mitochondrial diseases should include a systemic screening for all targeted organs, including neuroimaging, ophthalmology, and hearing examinations. Cardiac involvement should be evaluated at the time of diagnosis, as cardiac involvement is an independent predictor of morbidity and early mortality, even in asymptomatic cases. Hypertrophic cardiomyopathy is the most common cardiac manifestation; however, mitochondrial cardiomyopathy might also present as left ventricular non-compaction (LVNC) or as dilated, histiocytoid, or restrictive cardiomyopathy. The precise evaluation of cardiac involvement is of clinical use in predicting future cardiac events and prognosis. Despite advancements in molecular biology, no satisfactory treatments for mitochondrial diseases exist. Treatment remains largely symptomatic and does not significantly alter disease progression.

Keywords: mitochondrial disease, electron transport chain dysfunction, genetic variants, cardiomyopathy, multimodality imaging

1. Introduction

Disruption of the mitochondrial respiratory chain results in a diverse and variable group of multisystem disorders, known as mitochondrial diseases, which are progressive in nature. Since mitochondrial diseases comprise multi-organ system disorders, the clinical

manifestations are nonspecific. The varied and nonspecific nature of the early symptoms often renders the diagnosis of mitochondrial diseases difficult for physicians. Furthermore, the myocardium is one of the most affected tissues in mitochondrial cardiomyopathy because of its high energy demand. As cardiac involvement can be life-threatening and cause sudden death, cardiac assessment at diagnosis is necessary, even in asymptomatic cases.

Herein, we review the etiology and clinical manifestations of mitochondrial diseases, with a focus on cardiac symptoms. In addition, we review the evaluation modalities for cardiac involvement and treatment options.

2. Etiology

Mitochondria are rod-shaped organelles found in nearly all eukaryotic cells. Mitochondria play multiple roles in cellular processes, including calcium signaling, the generation of reactive oxygen species (ROS), and apoptosis [1–3]. The principal function of mitochondria is adenosine triphosphate (ATP) synthesis via aerobic metabolism. Mitochondria are responsible for the production of energy through the breakdown of carbohydrates and fatty acids via oxidative phosphorylation (OXPHOS). OXPHOS generates energy by coupling electron transport (complexes I, II, and IV) with ATP synthesis (complex V) through the electrochemical gradient [1–6]. Alterations in mitochondrial structure and function can impair OXPHOS, which in turn can reduce energy production, alter the cellular redox state, increase the ROS production, and dysregulate Ca^{2+} homeostasis, and apoptosis [1–6]. OXPHOS disturbance can destabilize the mitochondrial DNA (mtDNA), leading to a progressive accumulation of mtDNA mutations and deterioration of mitochondrial function [3, 6].

The transfer of electrons among respiratory chain enzyme complexes I–IV drives proton transfer across the inner mitochondrial membrane, forming an electrochemical gradient utilized by complex V to generate ATP. The mitochondrial genome encodes all of the ribosomal RNAs (mt-rRNAs), and most of the transfer RNAs (mt-tRNAs), needed for the translation of these protein-coding sequences within the mitochondria. The majority of mitochondria proteins is encoded in the nuclear DNA (nDNA), thought to have been transferred to the nucleus from the ancestral mitochondrial genome. However, the mtDNA encodes 13 polypeptides that are critical components of the OXPHOS enzyme complexes, 2 rRNAs (16S and 12S), and 22 tRNAs, which are required for the translation of the proteins encoded by the organelle genome [3, 6].

Mitochondria have their own genetic system, as mitochondria are thought to have evolved from bacteria. Mitochondrial genomes are usually circular DNA molecules, like those of bacteria, which are present in multiple copies per organelle. Since almost all of the mtDNA in fertilized eggs are contributed by the oocyte rather than by the sperm, germline mutations in the mtDNA are transmitted to the next generation in the maternal line [3, 6]. Although mtDNA mutations are exclusively maternally inherited, nuclear mutations may be transmitted as autosomal dominant, autosomal recessive, or X-linked traits [3, 6]. Approximately, 15% of mitochondrial diseases are caused by a mutation in the mtDNA; most mitochondrial diseases are caused by mutations in the nDNA.

The multi-copy nature of mtDNA gives rise to heteroplasmy, a unique aspect of mtDNA-associated genetics, which occurs when there is coexistence of mutant and wild-type mtDNA molecules. The mtDNA in cells can be identical (homoplasmy) or a mixture of variable copies (heteroplasmy) [3]. Heteroplasmic mutations often engender variable mutation thresholds (i.e., the level to which the cell can tolerate defective mtDNA mutations). Furthermore, the threshold level varies among different organs and tissues, depending on their energy requirements. Quality control can occur by fission/fusion, allowing the segregation of damaged mitochondria, mitophagy for the removal of damaged mitochondria, and, ultimately, cell death when the damage is too severe [7]. Thus, phenotypic variability is, at least in part, due to heteroplasmy, with varying proportions of mutant and wild-type mtDNA in different tissues. In addition, the tissue-specific mtDNA mutation load and threshold may affect the onset and extent of the clinical manifestations. Moreover, some nuclear genetic mutations can result in clinical phenotypes that are similar to those due to mtDNA variants.

3. Mitochondrial diseases associated with cardiomyopathy

Mitochondrial diseases comprise a clinically heterogeneous group of disorders that arise as a result of mitochondrial respiratory chain dysfunction. The clinical presentations are variable in terms of the age of onset, symptoms, and range and severity of organ involvement. While some mitochondrial disorders only affect a single organ, multiple organ systems are generally involved. High-energy-demanding tissues, such as the cardiac muscles, kidneys, liver, and central nervous system, are the most commonly affected tissues. Cardiomyopathies associated with defects in the electron transport chain (ETC) complex subunits and their assembly factors, mt-tRNAs, mt-rRNAs, ribosomal proteins, translation factors, mtDNA maintenance factors, and CoQ10 synthesis frequently manifest in mitochondrial diseases, as reviewed below (**Table 1**).

3.1. Deficiencies in the ETC complexes

ETC complex I deficiency accounts for approximately 30% of all cases of childhood-onset mitochondrial diseases and is clinically and genetically heterogeneous [8]. ETC complex I deficiency can present with hypertrophic cardiomyopathy, which might be isolated or associated with multi-organ disease [8]. ETC complex II is entirely nuclear-encoded and functions within the OXPHOS chain [9]. Hypertrophic and dilated cardiomyopathies, and left ventricular non-compaction, have been reported in patients with ETC complex II deficiency [9]. ETC complex III deficiency is one of the least common respiratory chain defects and is generally caused by mutations in the nDNA encoding the *BCS1L*, *UQCRB*, and *UQCRQ* genes and the mtDNA encoding the *MTCYB* gene, which encodes cytochrome b [9, 10]. Mutations in cytochrome b are associated with histiocytoid cardiomyopathy [10]. Mitochondrial complex III deficiency can be fatal in childhood; however, individuals with mild signs and symptoms can survive into adulthood [10]. ETC complex IV, or cytochrome c oxidase (COX), is the terminal enzyme of the respiratory chain and catalyzes the transfer of the reducing equivalents from cytochrome c to molecular oxygen. COX deficiency often leads to early-onset severe neuromuscular disease, and hypertrophic cardiomyopathy is the most common cardiomyopathy.

Syndrome	Clinical feature	Cardiac manifestation	DNA mutation, Mode of inheritance
MELAS	Myopathy, Encephalopathy, Lactic acidosis, Stroke-like episodes, Diabetes mellitus, Short stature, Sensorineural hearing loss	Hypertrophic cardiomyopathy, bundle branch block	t-RNA gene mutation (m.3243A>G), Maternal inheritance
MERRF	Myoclonus, Epilepsy, Ataxia, Muscle weakness, Sensorineural hearing loss, Short stature, Lactic acidosis	Dilated and histyocitoid cardiomyopathy, WPW syndrome	t-RNA gene mutation (m.8344A>G), Maternal inheritance
Coenzyme Q10 deficiency	Encephalopathy, Myopathy, Ataxia, Nephrotic syndrome	Hypertrophic cardiomyopathy	Mutations in gene involved in CoQ10 biosynthesis (CoQ2,4,6 etc)
Kearns-Sayre syndrome	External opthalmoplegia, Pigmentary retinopathy	Conduction defects, Dilated cardiomyopathy	single, large-scale mtDNA deletions
Friedreich ataxia	Ataxia, Dysarthria, Peripheral sensory neuropathy, Diabetes Mellitus	Hypertrophic cardiomyopathy	Defects in iron-sulfur cluster (FXN), Autosomal recessive inheritance
Barth syndrome	Myopathy, Growth retardation, Neutropenia	Non-compaction and dilated cardiomyopathies, supraventricular and ventricular tachycardia	3-Methylglutaconic aciduria type 2(TAZ), X-linked

MELAS: mitochondrial encephalopathy, lactic acidosis and stroke-like episodes
MERRF: Myoclonic epilepsy and ragged-red fiber

Table 1. Mitochondrial diseases associated with cardiomyopathy.

Mitochondrial mutations in the *MT-CO*$_2$ and *MT-CO*$_3$ genes, which encode complex IV, have been reported in dilated cardiomyopathy [11]. In addition, multiple OXPHOS complex deficiencies can result in mitochondrial dysfunction. Mutations in mt-tRNAs, mitochondrial ribosomes, and posttranscriptional modifications of mt-tRNAs may result in mitochondrial translation defects and multiple OXPHOS deficiencies [2, 4].

3.2. Mt-tRNA genes

Mutations in several mt-tRNA genes (e.g., *MTCK* and *MTTL1*) have been reported to cause mitochondrial diseases or isolated cardiomyopathies [12–17]. Cardiomyopathies associated with variants in genes encoding mt-tRNAs are usually hypertrophic but can also be dilated or histiocytoid [12–17].

Mitochondrial encephalopathy, lactic acidosis, and stroke-like episode (MELAS) is a multisystem syndrome that is often devastating. The syndrome is genetically heterogeneous; however, approximately 80% of patients with MELAS syndrome harbor a heteroplasmic A-to-G transition in the tRNALeu-encoding gene at base pair 3243 in the mtDNA (3243A > G) [12, 13]. The signs and symptoms of MELAS most often appear during childhood, and early symptoms may include muscle weakness and pain, recurrent headaches, loss of appetite, vomiting, and seizures. [18–20]. Most affected individuals experience stroke-like episodes before the age of 40 years [18–20]. These episodes often involve temporary muscle weakness on one side of the body, altered consciousness, vision abnormalities, seizures, and severe headaches, resembling migraines. Repeated stroke-like episodes can progressively damage the brain, leading to vision loss, movement problems, and loss of intellectual function [18–20]. Most patients with MELAS have a buildup of lactic acid in their bodies, known as lactic acidosis. Increased

acidity in the blood can lead to vomiting, abdominal pain, extreme tiredness, muscle weakness, and difficulty breathing [14, 15].

Myoclonic epilepsy and ragged-red fibers (MERRF) is a multisystem disorder characterized by myoclonus (often the first symptom), followed by generalized epilepsy, ataxia, weakness, and dementia [16, 17]. Common findings include hearing loss, short stature, optic atrophy, and cardiomyopathy with Wolff-Parkinson-White (WPW) syndrome. Pigmentary retinopathy and lipomatosis are occasionally observed. The mtDNA gene, *MT-TK,* which encodes tRNALys, is the gene most commonly associated with MERRF. The most common pathogenic variant (present in 80% of affected individuals) is an A-to-G transition at nucleotide 8344 (m.8344A > G). Pathogenic variants in *MT-TF*, *MT-TL1*, *MT-TI*, and *MT-TP* genes have also been described in a subset of patients with MERRF [3, 6].

3.3. CoQ10 deficiency

Coenzyme Q10 (CoQ10) shuttles electrons from complexes I and II to complex III. CoQ10 is also an antioxidant and is involved in the regulation of apoptosis and pyrimidine synthesis [21–26]. Defects in CoQ10 biosynthesis result in primary CoQ10 deficiency, which is a phenotypically and genetically heterogeneous condition with various clinical presentations, including encephalomyopathy, isolated myopathy, cerebellar ataxia, nephrotic syndrome, and infantile multisystem mitochondrial disease [21–26]. Hypertrophic cardiomyopathy has been reported with mutations in genes involved in CoQ10 biosynthesis (*COQ2*, *COQ4*, and *COQ9*) [21–26]. Although the response is variable, primary CoQ10 deficiency is treatable with CoQ10 supplementation.

3.4. Kearns-Sayre syndrome (KSS)

KSS is most commonly due to a 1.1–10 kb mtDNA deletion [26–28]. The KSS triad comprises external ophthalmoplegia, pigmentary retinopathy, and cardiac conduction defects [26–28]. KSS usually presents before the age of 20 years. Approximately 60% of patients with KSS have cardiac involvement, including recurrent syncope, bundle branch block, and fascicular block [26–28].

3.5. Friedreich ataxia

Friedreich ataxia is an autosomal recessively inherited disease caused by triplet expansion in FXN gene which encodes frataxin [29–31]. Exact function of frataxin has not been determined; however, previous studies showed frataxin is involved in the biosynthesis of Fe-S clusters [29–31]. Patients typically develop progressive ataxia at childhood [29–31]. Cardiac involvement is also frequently seen in patients with Friedreich ataxia and hypertrophic type of cardiomyopathy is most frequently observed [29–31].

3.6. Barth syndrome

Barth syndrome is an X-linked disorder characterized by cardiomyopathy, with skeletal myopathy, growth retardation, neutropenia, and urinary excretion of 3-methylglutaconic acid [32–34]. Barth syndrome is caused by mutations in the *TAZ* gene at Xq28, which encodes tafazzin, a phospholipid transacylase in the mitochondrial membrane [32–34]. Cardiac

manifestation is most common [35, 36]. Left ventricular non-compaction (LVNC) and dilated cardiomyopathies are common, while hypertrophic cardiomyopathy is rarely observed [35, 36]. Other cardiac manifestations of Barth syndrome include ventricular tachycardia and sudden death [35, 36]. Barth should be considered for male patients with severe cardiac failure. However, the prognosis after 5 years of age is favorable because cardiac function gradually recovers during infancy.

4. Diagnosis

Mitochondrial diseases constitute a broad spectrum of disorders that affect multiple organs. A maternal inheritance pattern or the presence of extra-cardiac features may raise suspicions regarding the diagnosis. Although extra-cardiac manifestations include common or nonspecific features, the particular pattern of organ involvement should alert the physician to the possibility of mitochondrial disease. Due to the multi-organ involvement, the evaluation of mitochondrial diseases should include a systemic screening of all targeted organs, including neuroimaging, hearing and ophthalmologic examinations, laboratory tests, histopathological analysis, and genetic testing (**Table 2**) [37, 38].

4.1. Laboratory tests

Laboratory tests should include serum creatine kinase (CK), serum fasting glucose, and hemoglobin A1c. Serum CK may be normal or mildly elevated in mitochondrial diseases. Patients with very high values in the thousands should first be evaluated for other types of myopathies like polymyositis. Diabetes mellitus is common in patients with mitochondrial diseases.

Lactic acidosis is the most recognized laboratory abnormality. The measurement of plasma or cerebrospinal fluid (CSF) lactate concentration is indicated in individuals with features of myopathy or central nervous system involvement. Markedly, elevated levels of lactate (>3 mm/L in blood or > 1.5 mm/L in cerebrospinal fluid) support a diagnosis of mitochondrial disease [39]. It is important to note that the elevated lactate level in plasma and/or CSF is neither specific nor sensitive [40, 41]. Thus, it is important to exclude other causes of lactic acidosis, such as ischemic stroke and seizures.

4.2. Neuroimaging

The brain is one of the most affected organs in mitochondrial diseases. In mitochondrial encephalopathy, central nervous system structures are affected differentially in their distribution and severity [42, 43]. Gray matter lesions are prevalent in MERFF and MELAS (**Figure 1A**, **B**), while white matter involvement is typically observed in KSS. Computed tomography may show basal ganglia calcification and diffuse atrophy of the cortex or cerebellum. Magnetic resonance (MR) imaging may show focal atrophy of the cortex or cerebellum, or high-intensity

Symptoms	Examination
Systemic	
short stature	Laboratory test: lactic acidosis
fatigue	Genetic testing: mtDNA or nDNA mutation
vomiting	Genetists examination
growth failure	
lactic acidosis	
Brain and nerve	
developmental delays	CT and MRI: basal ganglia calcification, atrophy of cortex and cerebellum , ischemic lesion, lactate peak in MR sepectroscopy
mental retardation	
dementia	
seizures	
stroke-like episodes	
migraines	
ataxia	
spasticity	
Muscles	
weakness	Skeletal muscle biopsy: ragged-red fibers, COX/SDH staining
cramping	Neurologists examination
hypotonia	
Ears and Eyes	
visual loss and blindness	Visual assessment by opthalmologist
ptosis	Hearing assessment by nasopharygiologists
visual field defects	
opthalmoplegia	
hearing loss	
Heart	
heart failure	Chest X-ray: cardiac enlargement, congestive heart failure
conduction problems	Electrocardiogram: AV block, WPW syndrome
ventricular pre-exciation	Echocradiography: various types of cardiomyopathy (hypertrophic is the most common type)
	CMR: late gadolium enhancement
	^{99m}Tc-MIBI, ^{123}I-BMIPP: perfusion and metabolic abnormality
Gastrointestinal	
constipation	Laboratory tests: hepatic dysfunction, hypoglycemia
dysphagia	
pseudo-obstruction	
Endocrine	
diabetes mellitus	Laboratory tests: Fasting glucose, HbA1c, Ca, PTH,FSH, LH, PRL
hypoparathyroidism	
gonadal failure	
kidney	
renal tubular acidosis	Laboratory tests: renal impairment
proximal tubule nephropathy	

CT: computed tomography, MR: magnetic resonance, CMR: cardiac magnetic resonance
^{99m}Tc-MIBI: ^{99m}Tc-sestamibi, ^{123}I-BMIPP: ^{123}I-labeled 15-(p-iodophenyl)-3-R,S-methylpentadecanoic acid

Table 2. Clinical symptoms and examination to diagnose mitochondrial diseases.

signals on T2-weighted scans, particularly in the occipital cortex. Cerebellar atrophy is also a prominent feature. MR spectroscopy may also be of use for the detection of an elevated lactate level (**Figure 1C**) [44]. Elevated central nervous system signals on MR spectroscopy may be detected, which is associated with a shorter survival duration [45].

4.3. Visual and hearing assessments

Various eye signs may accompany mitochondrial disease, including bilateral optic atrophy, chronic progressive ophthalmoplegia, pigmentary retinopathy, and loss of vision [46]. Bilateral optic atrophy is typically seen in Leber's hereditary optic neuropathy (LHON) [47]. Chronic progressive external ophthalmoplegia (CPEO) is the most common ocular manifestation in mitochondrial diseases. Acute or subacute vision loss typically occurs in early adult life. Pigmentary retinopathy occurs in MELAS, Leigh syndrome, and CPEO. Retrochiasmal visual pathway and visual cortex impairments can cause homonymous hemianopia and cortical blindness. Visual loss due to retrochiasmal visual pathway impairment is most frequently seen in MELAS.

Hearing impairment is common in patients with mitochondrial disorders, affecting half of the cases over the course of the disease [38]. Hearing assessments using audiograms or brainstem auditory-evoked potentials are necessary when hearing symptoms are present. Hearing impairment is usually peripheral, with cochlear or auditory nerve dysfunction; however, the central auditory system, including the brainstem and auditory cortex, can also be affected. Peripheral hearing loss typically affects high frequencies first, followed by intermediate frequencies. The preferential involvement of high frequencies may be related to the high-energy requirements of the basal cochlea.

4.4. Muscle biopsy

As discussed above, the laboratory investigation of suspected mitochondrial disease is complex. Although mitochondrial disorders are characterized by a wide spectrum of clinical presentations, skeletal muscles are one of the frequently affected tissues. Whenever possible, the presence of mitochondrial disease should be assessed in the affected tissues, such as the liver, heart, or skeletal muscle. However, in vivo access to these tissues is often not possible, and muscle biopsies must serve as an alternative, even when there is no evidence of myopathy.

The histology of the affected muscles typically shows ragged-red fibers (**Figure 2A**, **B**), which can be demonstrated using modified Gomori trichrome stains, and contains a peripheral and intermyofibrillar accumulation of abnormal mitochondria. Electron microscopy can sometimes reveal subsarcolemmal and enlarged, swollen mitochondria, with irregular cristae and paracrystalline inclusions (**Figure 2C**). The histochemical analysis of COX and succinate dehydrogenase is standard for assessing mitochondrial respiratory chain function in muscle samples [48, 49].

Establishing a biochemical phenotype is not only important for candidate gene selection but also provides important information required to interpret the genetic test results. The biochemical examination of a muscle biopsy to evaluate the functional state of the mitochondria

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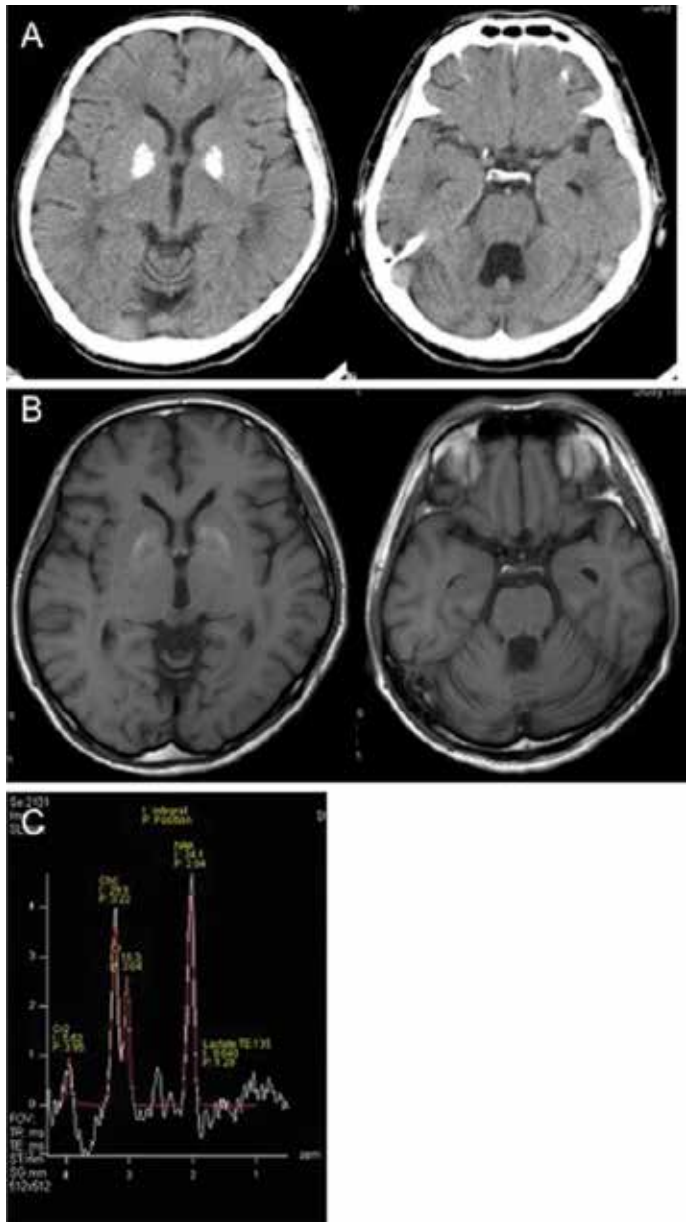

Figure 1. Neuroimaging: Brain computed tomography (A) and T1-weighted magnetic resonance imaging (B) show calcification in the bilateral basal ganglia and cerebellar atrophy. There is no lactate peak on magnetic resonance spectroscopy in this case (C).

is still regarded as a critical examination for patients with mitochondrial diseases. Activity measurements of oxidative phosphorylation enzymes and analyses of mitochondrial respiration, substrate oxidation, and ATP production can unveil an aberrant mitochondrial energy-generating system [50].

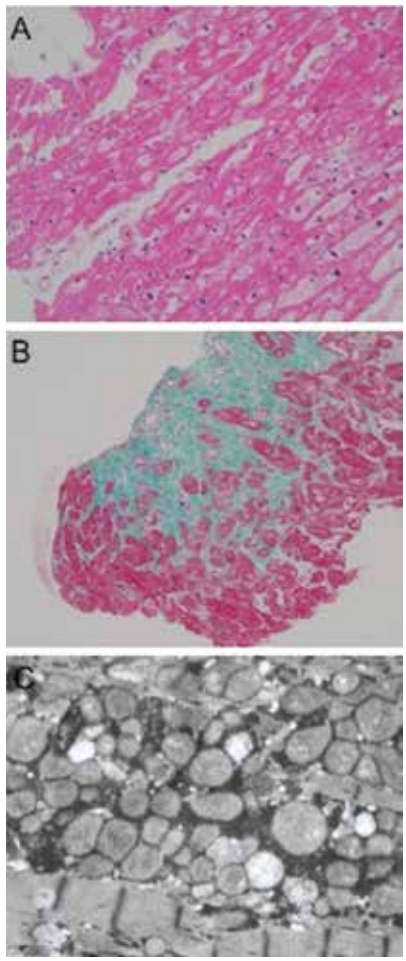

Figure 2. Histopathological findings: A myocardial biopsy from the endometrium of the right ventricles was performed. Hematoxylin-eosin staining shows a loss of cardiomyocytes and the enlargement of the remaining cardiomyocytes, with vacuoles (A). Elastica-Masson staining shows interstitial fibrosis (B). Electron microscope shows an increased number of mitochondria, with variable size and shape (C).

4.5. Molecular genetic analysis

A three-generation family history can suggest the mode of transmission, aid in the diagnosis, and direct the molecular genetic testing. Many individuals with mtDNA mutations display a cluster of clinical features that fall into a specific clinical syndrome, such as MELAS or MERRF [12]. When the presentation is classic for a maternally inherited mitochondrial syndrome, such as MELAS and MERRF, mtDNA studies should be obtained first. However, there is often considerable clinical variability, and many affected individuals do not fit into one particular category. Genotype-phenotype correlations are often obscure, and genetic analyses are frequently required for a definite diagnosis. Molecular genetic testing may be carried out on genomic DNA extracted from the blood or muscle. The ordering of molecular genetic tests and the interpretation of results require the support of an experienced clinical geneticist.

5. Cardiac manifestations

Because cardiac muscles are a high-energy-demanding tissue, cardiac involvement occurs in a large proportion of cases of mitochondrial diseases. Natural history studies have demonstrated that cardiac involvement is an independent predictor of morbidity and early mortality in mitochondrial diseases [2, 4, 51]. When mitochondrial disease is known or suspected, the cardiac examination should be directed toward eliciting signs of heart failure, including cardiac enlargement, elevated jugular venous pressure, auscultation of gallop, bilateral lung crackles, pitting edema, and hepatomegaly. Mitochondrial cardiomyopathies can vary in severity, from asymptomatic to severe manifestations, including heart failure, arrhythmias, and sudden cardiac death.

Patients with MELAS are particularly prone to cardiomyopathy [4, 52–54]. Hypertrophic cardiomyopathy is the most common cardiac manifestation, occurring in approximately 40% of cases [4]. However, mitochondrial cardiomyopathies might also present as LVNC or as dilated, histiocytoid, or restrictive cardiomyopathy [2, 4, 51]. In addition, the conduction system can be affected.

5.1. Hypertrophic remodeling

Hypertrophic remodeling is the most common form of cardiomyopathy and can mimic hypertrophic cardiomyopathy (HCM) [2, 4, 51]. Patients diagnosed as HCM may include those with mitochondrial abnormalities, especially in cases of atypical HCM. There are some differences between HCM and hypertrophic remodeling in mitochondrial cardiomyopathy. Left ventricular outflow tract obstruction is rarely observed in mitochondrial cardiomyopathy, while a progression to ventricular dilation and heart failure is more frequent than HCM [2]. A longitudinal study demonstrated that the degree of left ventricular hypertrophy (LVH) is correlated positively with left ventricular end-diastolic volume and negatively with ejection fraction in patients with MELAS [53]. These findings are unique in mitochondrial cardiomyopathy, not seen in hypertrophic cardiomyopathy due to mutations in sarcomeric proteins.

5.2. Dilated remodeling

Dilated remodeling, leading to heart failure, has also been occasionally reported in patients with mitochondrial diseases; however, it is less common [54]. Dilated remodeling is reported in KSS, MELAS, MERRF, and Light encephalomyopathy [54–56]; however, most of the dilated remodeling in mitochondrial diseases represents the progression from hypertrophic remodeling accompanying chamber dilation and systolic dysfunction.

5.3. Rare types of remodeling

LVNC is a rare finding in mitochondrial cardiomyopathy. However, among patients with LVNC, mitochondrial diseases are highly prevalent [57, 58]. Research using next-generation sequencing has revealed that mtDNA mutations, with subsequent mitochondrial dysfunction, may be key players in the etiology of LVNC. Furthermore, recent research has demonstrated

that a loss of mitochondrial intermediate presequence proteases results in LVNC [59]. LVNC is generally more frequent in male patients and tends to develop during pregnancy in female patients. Occasionally, it may disappear during the disease time course in some patients with mitochondrial diseases.

Histiocytoid remodeling is histologically characterized by morphological and functional abnormalities of the cardiomyocytes and Purkinje cells, with a cytoplasm similar to that in histiocytoid foam cells, containing glycogen and lipids [60]. This type of remodeling has been reported exclusively in mitochondrial diseases.

5.4. Conduction system abnormalities

Conduction system dysfunction commonly occurs in patients with mitochondrial diseases. The diagnostic criteria for KSS include atrioventricular block, given its high prevalence rate in KSS [61–64]. Conduction system disease occurs, albeit less commonly, in 5–10% of patients with other forms of mtDNA disease, with atrioventricular or intraventricular conduction disturbances reported in association with m.3243A > G and m.8344A > G mutations [2, 4, 51–53, 65].

In patients with mitochondrial diseases, progression to lethal atrioventricular block is often unpredictable, which requires the recognition of any conduction system abnormalities and consideration of intervention at early phase. Early deaths in patients with KSS may be attributable to infranodal heart block. Furthermore, WPW syndrome and conduction block are common in patients with mitochondrial diseases [66].

5.5. Rare manifestations

Pulmonary artery syndrome has been observed in patients with MELAS syndrome, as well as in patients with hyperuricemia, pulmonary hypertension, renal failure in infancy, and alkalosis (HUPRA) syndrome. HUPRA syndrome is associated with mutations in *SARS*, which encodes mitochondrial seryl-tRNA synthetase [66]. Furthermore, congenital cardiac abnormalities are observed in microphthalmia with linear skin lesions, which is associated with holocytochrome-c-type synthetase and *COX7B* mutations [67].

6. Evaluation of the cardiac manifestation severity

Multiple imaging modalities exist for differentiating viable myocardium from scar tissue in territories with contractile dysfunction [67]. Cardiac involvement should be evaluated at the diagnosis in all patients with mitochondrial diseases, irrespective of their symptoms, as the cardiomyopathy can remain asymptomatic until reaching an advanced stage. Because of the heterogeneous and variable manifestation of mitochondrial cardiomyopathies, the evaluation of the extent and severity of the cardiac damage is rather difficult. However, the evaluation and follow-up of cardiac involvement are quite important, as cardiac involvement is the major cause of death in mitochondrial diseases. Below, we review here the current status of each relevant imaging modality for the assessment of mitochondrial cardiomyopathy.

6.1. Cardiac MR (CMR) imaging

With tissue characterization using late gadolinium enhancement (LGE) and T1 and T2 mapping, the underlying etiology of the heart failure can be readily established [68, 69]. Gadolinium is extracellular and resides in the interstitial space. LGE refers to the discrimination of regions of scar tissue, necrosis, and/or inflammation from normal tissue by the prolonged retention of gadolinium-based contrast agents (**Figure 3A**, **B**) [69, 70]. CMR is a noninvasive tool that accurately identifies and quantifies myocardial fibrosis. Nonischemic cardiomyopathy can be distinguished from ischemic cardiomyopathy, as a subendocardial or transmural LGE pattern concordant with the coronary artery supply is indicative of ischemic cardiomyopathy (necrosis begins in the subendocardium and progresses toward the epicardial area). However, nonischemic cardiomyopathies, including sarcoidosis, amyloidosis, and Fabry's disease, show various LGE patterns [71–74]. Extensive amounts of LGE can be predictive of subsequent remodeling and an evolution toward the end stage [75, 76]. In addition, the presence and extent of LGE in cardiomyopathies are associated with adverse cardiovascular outcomes and a poor response to standard medical and interventional therapies [75, 76]. Furthermore, abnormal myocardial perfusion reserve and fibrosis occur before cardiac damage becomes symptomatic in patients with Friedreich ataxia [77]. Thus, CMR may be useful in detecting trivial myocardial damage in the early stages of mitochondrial cardiomyopathy and in evaluating the extent of cardiac damage and assessing the prognosis in cardiomyopathies.

6.2. ^{99m}Tc-MIBI cardiac scintigraphy

^{99m}Tc-sestamibi (MIBI) is a lipophilic cation. Myocardial uptake and the retention of ^{99m}Tc-MIBI involve passive diffusion across the plasma and mitochondrial membranes. Cellular influx of the tracer is driven by the inside negative plasma and mitochondrial inner membrane potentials, which concentrate the tracer within the cytosol and mitochondria [78, 79]. The retention of ^{99m}Tc-MIBI in the mitochondria is related to mitochondrial function (**Figure 3C**). The washout rate of ^{99m}Tc-MIBI is calculated from the segmental counts in the early and delayed images. Recent human studies on patients with congestive heart failure have shown that the myocardial washout rate of ^{99m}Tc-MIBI is a novel marker for the diagnosis of myocardial damage or dysfunction, providing prognostic information [80, 81]. ^{99m}Tc-MIBI is commonly used as a myocardial perfusion imaging tracer for the detection of significant coronary artery disease. Furthermore, an impaired ^{99m}Tc-MIBI washout may predict mitochondrial dysfunction, and the impairment of myocardial contractile and relaxation reserves during dobutamine stress in patients with HCM or dilated cardiomyopathy [81]. In patients with MELAS, decreased ^{99m}Tc-MIBI uptake and increased MIBI washout are observed, which correlate inversely with the left ventricular ejection fraction [82–88]. Thus, the ^{99m}Tc-MIBI washout rate and a disturbed uptake of ^{99m}Tc-MIBI are indicators of the severity of mitochondrial damage in mitochondrial cardiomyopathy.

6.3. ^{123}I-BMIPP scintigraphy

As free fatty acids are the main energy source of the heart under aerobic conditions, the evaluation of myocardial fatty acid metabolism is useful in understanding the pathophysiological

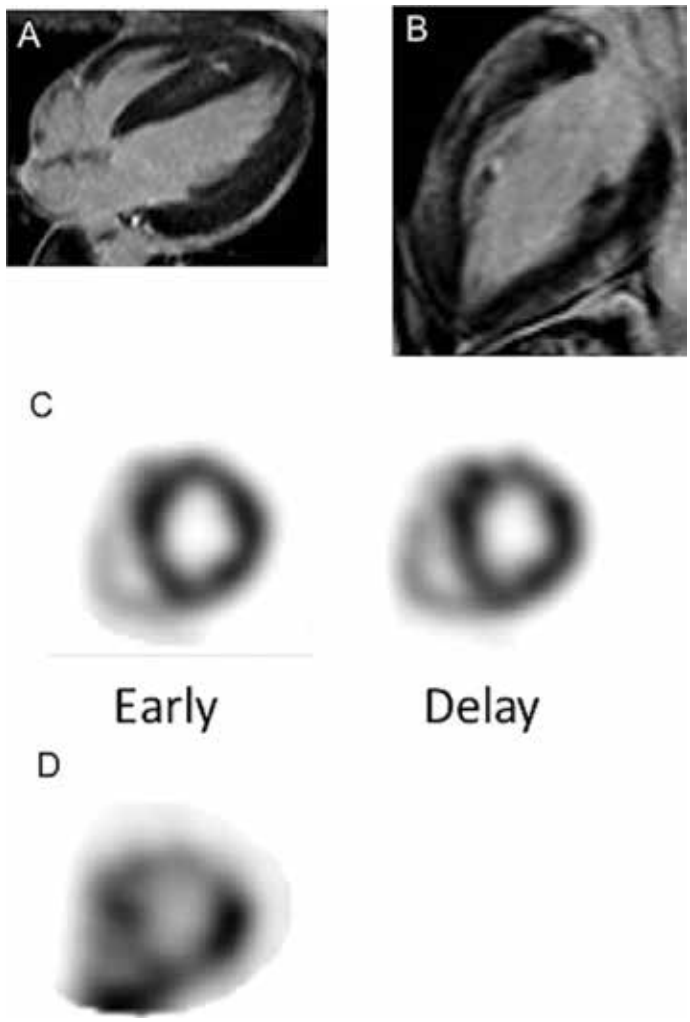

Figure 3. Multimodality imaging: Cardiac magnetic resonance reveals regional wall motion abnormalities, with thickening of both the left and right ventricular walls (A). Late gadolinium enhancement is observed in the middle layers of the anterior and interventricular septum and inferior walls, partially extending into the epicardium (B). Decreased uptake of ^{123}I-labeled 15-(p-iodophenyl)-3-R,S-methylpentadecanoic acid (^{123}I-BMIPP) is observed in the anterior and interventricular septum and inferior walls (C). Preserved uptake of ^{99m}Tc-sestamibi (MIBI) in the early phase is shown (D). Global ^{99m}Tc-MIBI washout rate is increased, which is one of characteristic features of mitochondrial cardiomyopathy (24.74% vs. control 11 ± 5%).

conditions of various heart diseases [85]. ^{123}I-labeled 15-(p-iodophenyl)-3-R,S-methylpentadecanoic acid (BMIPP) is a radiolabeled fatty acid tracer that can be used with single photon emission tomography (SPECT) to evaluate fatty acid metabolism [86–88]. Areas of the myocardium with reduced BMIPP uptake, relative to that for myocardial perfusion following revascularization for acute myocardial infarctions, suggest the presence of metabolically dysfunctional myocardium, which may indicate a lower likelihood of functional recovery [89–92].

Myocardial metabolism abnormalities on ^{123}I-BMIPP scintigraphy are related to the severity of heart failure. ^{123}I-BMIPP scintigraphy can detect minor metabolic abnormalities, even when echocardiography fails to show any abnormality (**Figure 3D**) [93]. Many previous case reports have demonstrated that increased uptake of ^{123}I-BMIPP in mitochondrial cardiomyopathy is a consequence of suppressed fatty acid metabolism due to enhanced glucose utilization.

6.4. Multimodality evaluations

Current imaging methods focus on the evaluation of myocardial anatomy and function. However, the detection of perfusion and metabolic abnormalities using SPECT may aid in understanding the extent and severity of the myocardial damage.

Although previous case reports suggest that a decreased uptake of ^{99m}Tc-MIBI and increased uptake of ^{123}I-BMIPP are characteristic patterns in mitochondrial cardiomyopathies [82, 83], our group reported a unique case demonstrating a non-decreased ^{99m}Tc-MIBI/^{123}I-BMIPP mismatch pattern [84]. In this previous report, we also compared the findings on scintigraphy, CMR imaging, and histopathology. Inhomogeneous LGE intensity reflects scattered viable myocytes and surrounding fibrosis, while preserved uptake of ^{99m}Tc-MIBI may reflect preserved blood flow and a volume effect of the left ventricular wall from the histopathological investigation. Although the ^{99m}Tc-MIBI/^{123}I-BMIPP mismatch pattern in our case may reflect a nonspecific phenomenon in patients with dilated cardiomyopathy, the diverse patterns of myocardial damage may reflect different stages or diverse manifestations of mitochondrial cardiomyopathies.

Multimodality studies with cardiac scintigraphy, CMR imaging, and histopathology may unveil the current status of metabolic and perfusion abnormalities, myocyte damage, and the severity and future progression of mitochondrial cardiomyopathies. Comparisons between imaging modalities and histopathological findings may also aid in the understanding of the underlying etiology; however, further studies and an accumulation of data are required. Furthermore, molecular imaging might provide a perspective on the investigation of mitochondrial function of the myocardium in vivo, noninvasively and quantitatively, in the near future. Moreover, the response to therapeutic interventions could be monitored using these methods.

7. Treatments

Currently, there are no satisfactory therapies available for mitochondrial diseases. Treatment remains largely symptomatic and does not significantly alter the progression of the disease [94–96].

Exercise can be helpful for patients with mitochondrial disease. In healthy individuals, a lack of exercise leads to an overall reduction in mitochondrial ETC activity, whereas endurance training can improve ETC activity, and resistance training can stimulate the incorporation of satellite cells into existing muscle fibers. Resistance training might also improve

mitochondrial function. Although no specific dietary manipulation has shown a consistent benefit for individuals with mitochondrial diseases, pharmacologic strategies include the use of various dietary supplements. Therapeutic strategies for mitochondrial diseases include the use of agents that enhance ETC function and mitochondrial biogenesis, agents that act as an energy buffer, antioxidants, and gene therapy [78, 79, 97]. However, most attempted strategies have turned out to be failures [98–100]. CoQ10 and its synthetic analogues are the only agents which have shown therapeutic benefits for mitochondrial diseases with CoQ10 deficiency [101–103]. Oral CoQ10 supplementation may alleviate the progression of encephalopathy.

Gene therapy has shown promising results in treating LHON. Approximately, 70% of individuals with LHON have pathogenic variants in the mtDNA gene encoding subunit 4 of complex IV (*MT-ND4*). The adeno-associated virus (AAV) can carry the mitochondrial and mitochondrial targeting genes, and the viral capsid, VP2, can be fused with an AAV mitochondrial-targeting sequence to the mitochondria, achieving ND4 expression. Wild-type ND4 expression in cells with an ND4 mutation leads to the restoration of defective ATP synthesis [104]. In addition, clinical studies have shown an improvement in the average acuity for patients with LHON and bilateral vision loss with the use of this therapy [105].

It is usually difficult to improve cardiac function once deterioration in cardiac function occurs. In patients with cardiomyopathy, early intervention with beta-blockers and an angiotensin-converting enzyme (ACE) inhibitor is thought to delay cardiomyopathy progression, as it does in other causes of heart failure. Recommendations for the management of hypertrophic remodeling in mtDNA diseases are reliant on clinical studies in HCM and LVH. Calcium channel antagonists and beta-blockers are recommended in symptomatic patients or in those with symptomatic LVH and HCM. Beta-blockers, ACE inhibitors, and angiotensin receptor blockers have been demonstrated to reduce LVH in the general population [106]. Given the progressive nature of hypertrophic remodeling in mitochondrial diseases, these drugs are often started with the first appreciation of LVH in mitochondrial cardiomyopathy.

American and European guidelines recommend permanent pacemaker implantation at an early stage of conduction system dysfunction in patients with mitochondrial diseases, due to its unpredictable progression. Rarely, heart transplantations have been performed in patients with mitochondrial cardiomyopathy when the clinical manifestation was limited to the myocardium and extra-cardiac manifestations were relatively mild and nonprogressive [107–119].

8. Conclusion

Myocardium is one of the most frequently affected tissues in mitochondrial diseases because of its high energy demand. The clinical presentations are variable in terms of the age of onset, symptoms, and range and severity of organ involvement. Since cardiac involvement is an independent predictor of morbidity and early mortality, careful and accurate examination of cardiac damage is required. Current imaging methods focus on the evaluation of myocardial anatomy and function; however, the detection of perfusion and metabolic abnormalities using SPECT may aid in understanding the extent and severity of the myocardial damage in each patient.

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Conflict of interest

The authors have no conflicts of interest to declare.

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Chapter 2

Genetic Evaluation of Hypertrophic Cardiomyopathy

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Additional information is available at the end of the chapter

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Abstract

Hypertrophic cardiomyopathy (HCM) is defined as left ventricular hypertrophy in the absence of abnormal loading conditions. In 50–60% of adolescents and adults with HCM, the disease is inherited as an autosomal dominant trait caused by mutations in cardiac sarcomere protein genes. The most cases are due to mutations in genes which determine the synthesis of myosin-binding protein C (MYBPC3) and beta-myosin heavy chain (MYH7). More rarely involved genes are those encoding myosin light chain 3 (MYL3), tropomyosin alpha-1 chain (TPM1), and cardiac troponins I and T (TNNI3, TNNT2). Mutations in genes encoding Z-disc or calcium-handling proteins account for less than 1% of cases. Multiple sarcomeric protein mutations are present in up to 5% of individuals. A further of 5% of patients have inherited metabolic or neuromuscular diseases, chromosome abnormalities, and genetic syndromes. HCM is characterized by a highly heterogeneous phenotype, highly variable intra- and interfamily expressivity and incomplete penetrance, therefore by a genotype-phenotype plasticity.

Keywords: autosomal dominant, mutations, sarcomere proteins genes, incomplete penetrance, phenotype

1. Introduction

Hypertrophic cardiomyopathy (HCM) is an important genetic heart muscle disease characterized by left ventricular hypertrophy (LVH) in the absence of an underlying systemic condition or other cardiac disease, such as valvular heart disease or arterial hypertension. HCM is a global disease characterized by a prevalence of 1:500 [1, 2]. HCM is the most frequent genetic heart disease and the most important etiology of sudden death not due to trauma in adults of young age and trained athletes in the United States [3]. The onset of HCM disease can occur at any age, from infants to old people, and symptoms usually are not present before teen age in

carriers of the specific genetic mutation [3]. HCM is the first autosomal dominant genetically transmitted condition, with clinical variability and incomplete penetrance in many cases. Clinical picture of HCM covers a large spectrum, from asymptomatic disease to evolving heart failure in years and dramatic sudden cardiac death (SCD) triggered by electrical or mechanical disorders. The most used tools for diagnosis are cardiac imaging methods, such as cardiac echography and magnetic resonance imaging. Asymmetrical hypertrophy involving the septum represents a frequent finding [4].

Histopathologic characteristics include myocyte hypertrophy and disarray and increased myocardial fibrosis [4], these lesions leading to impaired diastolic function [5]. In ~5–10% of patients, cardiac systolic function decreases over time, leading to progressive left ventricle (LV) dilatation, heart failure and, finally, burnt-out HCM, morphologically similar to dilated cardiomyopathy (DCM) [6].

2. Mechanism of disease

HCM is commonly defined as a sarcomere disease. The variants with pathogenicity were found in almost all proteins of the sarcomere [7]. The pathways of molecular alteration are augmented actin-activated ATPase activity, fragmentation of interaction between actin and myosin and force developing, and modified intramyocyte calcium signaling in cardiac cells [8]. Also, some studies found that LVH can be triggered by troubles in CaMKII Mef2 signaling pathways and transforming growth factor b (TGF-b) [9].

Phenocopies of HCM are syndromes characterized by multiorgan alteration that can also present only LVH or like a dominant trait. These syndromes are storage or metabolic diseases (cardiomyopathies), like Danon disease and Wolff-Parkinson-White syndrome [10], and Fabry disease, which is a lysosomal storage condition [11]. These disorders are characterized by vacuolar accumulation in the myocytes of glycogen or glycosphingolipids, not by cardiomyocyte disarray and fibrosis [10]. LVH can also be found in the phenotype of patients with Noonan syndrome [12] and Friedreich ataxia [13].

Almost three decades ago, mutations in the beta-myosin heavy chain gene (MYH7) [14] were discovered to cause HCM, and since then, hundreds of different disease-causing mutations have been identified in genes that encode proteins of the sarcomere, the contractile unit of the cell. [15]. This molecular etiology is involved in the most familial diseases [16] and an important part of not yet explained hypertrophy sporadically found in childhood and adult age [17, 18]. There is still need for describing other genetic causes for unexplained LVH transmitted as a Mendelian or common trait in the population.

The mechanism of disease is the modification of a unique nucleotide belonging to a protein of the sarcomere. Clinical manifestations appear later in life, even if the mutant protein is present from birth. Studies on experimental models carrying human HCM mutations uncovered the mechanisms of this disease. These models demonstrate typical features of HCM found in humans like cell increasing, cardiomyocyte disarray, and interstitial fibrosis clinically

evolving similarly with those found in humans: absence of disorder in young people and progressive expression of histopathological findings in older age.

3. The genetic background of HCM

Most HCMs are caused by a dominant gene mutation. Half of all descendants of the affected individuals will inherit the HCM gene mutation and pose a very high risk for this disease. Young carriers of the mutation often have no clinical manifestations, and the symptoms develop insidiously, comprising a hypertrophic remodeling that occurs with aging [6]. Because HCM have an age-related penetrance, the absence of disease in one assessment cannot rule out further development. Sequential clinical assessments or genetic testing of family members at risk for HCM are very important.

Mutations from 13 single genes cause HCM [15] and represent about 75% of familial HCM [18]. Mutations occur predominantly in genes encoding sarcomere proteins [19], the contractile unit of myocytes. The typically mutation sarcomere proteins are those of thick and thin filament [20] and the less commonly affected are proteins who influence or transmit sarcomere forces (sarcomere-associated or Z-disc). Most mutations described in HCM are "private," appearing only in that patient and his family. Families with HCM without any correlation have different mutations in most situations [21]. Some mutations are common for specific populations. For example, 4% of people with South Asian origin have a unique HCM mutation [22]. For diagnosing the causal mutation in every patient, we usually need an accurate sequencing of all HCM genes [23]. This issue can be realized through DNA sequencing strategies which are recently developed. The HCM genetic diagnosis is possible at several registered molecular diagnostic laboratories, listed at the National Center for Biotechnology Information GeneTests website.

Defining the pathogenic mutation in an affected family member allows for further defining and low-cost assessing of mutation in all relatives. Mutation carriers have an increased risk of developing HCM, while people with negative mutations are at no risk for the disease and do not need clinical serial evaluation.

3.1. Mutations in genes that encode sarcomere proteins

Genetic etiology of HCM covers a wide spectrum, existing approximately 900 different mutations reported in the genes that encode 8 sarcomere proteins: the beta-myosin heavy chain (MYH7), cardiac myosin C-related protein (MYPBC3), cardiac troponin T (TNNT2), cardiac troponin I (TNNI3), cardiac actin (ACTC), alpha-tropomyosin (TPM1), the essential myosin light chain (MYL3), and the regulatory myosin light chain (MYL2) [18]. Mutations in MYH7 and MYPBC3 occur most frequently and represent about 50% of HCM cases. The mutations in TNNT2, TNNI3, ACTC, TPM1, MYL3, and MYL2 represent totally less than 20% of HCM cases [24]. Mutations within these genes correlate with the disease status in the HCM families and are absent from the control populations. Mutations modify highly conserved residues throughout evolution, which means that changing each specific amino acid is deleterious—this

has been confirmed by animal models that carry mutations in the sarcomeric gene. These experimental models develop cardiac remodeling similar to human HCM. Mutations in other genes reported as causing HCM are based on weaker evidence for HCM etiology.

Gene encoding for troponin C (TNNC1) represents a sarcomere protein gene that has not been definitely involved in HCM [25]. Studies which analyzed over 1000 HCM patients described four variants of TNNC1 sequences, although genetic criteria for a pathogenic role remain unknown. Experimental models analysis of another gene variant highlighted the augmented Ca^{2+} sensitivity of force transmission and ATPase activation [25, 26], similar to the biophysical changes presenting in already defined genes for HCM.

3.2. Mutations in genes encoding Z-disc proteins

Genes encoding molecules that interact with sarcomeric proteins have also been investigated for HCM mutations. Many of these analyses focus on proteins located in the Z disc, which bind sarcomere units. Other variants have been discovered in genes encoding titin (TTN) [27], LIM muscle protein (CSRP) [28, 29], telethonin (TCAP) [30] and myozenin 2 (MYOZ2) [31]. Analysis of sequence was referring only to the subsets of the 363 exons encompassing titin, which represents a giant molecular structure in the sarcomere laying from the Z-disc to the M-line, but the screening for other mutant proteins in the Z-disc is more complete. Functional studies of newly identified variants indicate that they alter protein-protein interactions. For example, the modified titin residues that have been identified have increased binding affinity for actinin [27, 32] or for cardiac ankyrin repeat protein [33]. The pathogenic role of some variants in HCM remains inconsistent because sequence variants in Z-disc proteins identified in some HCM families are not large enough to provide statistically significant analyses.

3.3. Storage cardiomyopathies simulating HCM

Patients with left ventricular hypertrophy (LVH) of unknown etiology and atypical clinical manifestations from those with HCM helped identify storage cardiomyopathy and disorders that have distinct molecular etiologies. Mutations in the gamma-subunit of the AMP-dependent protein kinase gene (PRKAG2) cause LVH that is inherited as a dominant feature, in which cardiac histopathology shows a marked accumulation of glycogen in myocytes and not myocyte disarray [10]. Patients with PRKAG2 mutations also have electrophysiological disorders and develop progressive disease of the conduction system. Mutations in the X-linked lysosome-associated membrane protein 2 (LAMP2) cause early and important LVH in boys and male teenagers, severe ventricular arrhythmias, and rapid evolution to cardiac failure. LAMP2 mutations demonstrate at histopathological examination accumulation of vacuoles filled with non-degraded cellular products resulting from autophagy [10]. Fabry disease is produced by mutations in a gene located on X chromosomes, which encodes alpha-galactosidase (GAA). These patients commonly demonstrate ventricular hypertrophy in addition to systemic involvement. The most patients develop myocardial disease [34], while renal, neurological, and cutaneous changes are subclinical.

All these storage cardiomyopathies are accompanied by cardiac hypertrophy. Considering histopathological differences with HCM, distinct clinical phenotypes, and different functions of mutated molecules, these disorders are considered distinct from HCM.

4. Clinical gene-related diagnosis of HCM

An important clinical progress resulting from the discovery of the genetic causes of HCM is gene-based diagnosis. Given the overlapping clinical phenotype of unexplained LVH that arises from various cardiomyopathies and the lack of clinical manifestations to accurately predict the implication of a particular HCM gene, gene-based diagnostic platforms required the general query of all sarcomere genes, sarcomere-related genes, and genes causing storage cardiomyopathies; this technically difficult task is, until recently, very expensive and laborious. With the next-generation sequencing development, many obstacles have diminished.

Contemporary sequencing strategies have the ability to query millions of nucleotides at a reasonable cost. An additional advantage is that these platforms define the genetic sequence and also the dose of genes. Recent findings indicate that mutations that modify the number of gene copies can lead to conditions like congenital heart diseases, neurological and cognitive diseases, and neoplasia [35, 36]. A few HCM may appear from an abnormal number of genetic copies (by increasing or decreasing the dosage of the gene). The absence of a specific mutation in some patients with HCM could be explained by existence of mutations that modulate gene dose in HCM and thus a leakage of detection by classical sequencing methods. This concept that HCM might be provoked by modified dosage of sarcomere protein genes is particularly challenging due to the fact that some mutations in the MYPBC3 gene have been shown to cause disease by decreasing protein levels [37, 38]. Another cause of HCM might be mutations that modified the quantity of the MYPBC3 gene and perhaps other sarcomere protein genes which could significantly affect protein levels.

5. Links between genetic testing and phenotype in HCM

One of the many advances that may result from large-scale genetic testing in HCM is better assessment of genotype relevance in the phenotype. HCM genetic testing, recognized to accurately predict disease progression in at-risk relatives, cannot predict the clinical course for each patient. It is possible that the number of HCM genotyped patients remains too modest to explore these correlations, particularly based on genetic heterogeneity and the influence that modifiers such as background genotypes [39], gender [40], and the environment [41]. Clinical course is recognized as more adverse in patients with HCM with an identified mutation than patients without mutation [42]. Some specific mutations can affect the evolution. Sudden cardiac death appears more frequently in MYH7 specific mutations (R403Q, R453C, G716R and R719W) [43], and progression to heart failure is more commonly seen in MYH7 (R719W), TNNI3 (deletion Lys183), and MYPBC3 (intron 32 mutations deletion) than in other HCM mutations [22, 44]. Understanding of the full range of HCM genes together with the molecular genetic analysis of well-investigated patient cohorts can contribute to develop these links and improve knowledge of clinical differences in HCM.

The age at which the signs and symptoms of HCM appear are influenced by causal gene mutation [15, 19]. Clinical manifestations of HCM caused by mutations in the heavy β-myosin or troponin T chain usually begin in adolescence [21, 45]. In contrast, myosin-linked protein C

mutations, especially those that inhibit the protein, trigger HCM after a prolonged period of clinical quiescence that can extend to middle age [46, 47].

The various genetic causes of HCM do not correlate with the size or distribution of hypertrophy, with some notable exceptions. Troponin T mutations generally generate much lower hypertrophy than other HCM genes, and genetic diagnosis is useful in determining the status of individuals at risk of inheriting these mutations [45]. The different morphological models of HCM hypertrophy (asymmetric, concentric, or apical) do not refer to the underlying genotype, except for a single actin mutation that produces uniform apical hypertrophy [48]. Factors that involve morphological pattern remain unknown.

The natural history of HCM includes dyspnea and progressive angina. These symptoms reflect a noncompliant myocardium, increased ventricular diastolic pressure, and impaired diastolic filling [6, 41, 49, 50]. The anatomy of coronary artery tree is normal in HCM but mechanism of myocardial ischemia in HCM consists of decrease of blood flow in diastole due to intramural arterial remodeling and impaired myocardial relaxation [51]. Approximately 5% of patients with HCM appear severe diastolic dysfunction which can be accompanied in time by contractile insufficiency of the myocardium [52].

Patients with a genetic mutation of the defined sarcomeric protein have lower cardiac output than those whose HCM etiology remains unknown [42]. In addition, it was shown that HCM specific mutations [53], compound mutations [54], and a mutation that is predominant among patients of Indian origin [22] substantially increase the risk of developing heart failure.

6. Cardiac hypertrophy mechanisms in HCM

6.1. Alteration in sarcomere function

Several models have been proposed for mechanisms of myocardial hypertrophy by mutations of the sarcomere genes. Recent analyses in human cardiac samples and experimental models show that concentration of myosin-binding protein C is reduced in the myocardium of patients with MYBPC3 missense amino acid residues and truncation mutations [37, 38]. This information indicates that MYBPC3 haploinsufficiency or a decrease in the quantity of functional protein due to a dominant gene mutation that inactivates an allele acts as a pathological mechanism for HCM. In contrast, studies on most other sarcomere mutations indicate that these influence on the fact that protein levels are normal, but its function is disturbed. The biophysical properties of sarcomeres carrying MYH7 mutations indicate an increase in function. Myosines containing HCM mutations improved the ATPase activity of myosines, increased the force generated, and accelerated the actin filament gliding [55]. Analyses of human TNNT2 mutations indicate that these anomalies show an increase in contraction [56] and ATPase activation [57].

The consequences of changes in the biophysical properties of contractile proteins could significantly influence sarcomere performance, myocardial cell biology, and myocardial energy.

Due to the presence of both mutant and normal proteins within sarcomeres, regulated contractions would become discoordinated, as shown with HCM myosin mutations: HCM mutation MYH7 R403Q is attached to the actin at angles highly variable compared to the normal myosin [58]. Biophysical changes of mutant sarcomeres are also expected to modify the calcium cycling and contribute to increased susceptibility to arrhythmia in experimental and human HCM [59]. The increase in ATPase activity by sarcomere mutations can also cause a higher consumption of myocardial energy, which may accelerate the death of cardiomyocytes and may contribute to focal fibrosis and scarring described in HCM [60].

6.2. Activation of Ca^{2+}-dependent signaling in HCM

Dysregulation of intracellular Ca^{2+}, a pivotal modulator of myocardial contraction and relaxation, can trigger hypertrophy and failure in this stressed myocardium [61]. Experimental models of HCM myocytes exhibit abnormal intracellular Ca^{2+}, including low sarcoplasmic reticulum levels and elevated diastolic Ca^{2+} concentration [56, 62]. In HCM models, Ca^{2+} disorders precede hypertrophic remodeling. Some longitudinal studies demonstrate that initial pharmacological therapy that normalized Ca^{2+} abnormalities has decreased the development of hypertrophy [62]. An important yet unclarified idea raised by this is which hypertrophic mechanisms are stimulated by Ca^{2+} dysregulation in HCM cardiomyocytes?

In experimental studies on hypertrophy induced by pressure overload, intracellular Ca^{2+} triggered activation of calmodulin and calcineurin, its phosphatase, which produce dephosphorylation, and activated NFAT (nuclear factor of activated T cell) transcriptional factor, a known molecule involved in hypertrophic remodeling [63]. Calcineurin inhibitors, like cyclosporin, inhibit hypertrophy induced by overexpression of calcineurin in the hearts [64]. However, cyclosporin administered to HCM mice has a very different effect: rapidly evolving pathological remodeling and cardiac insufficiency [65]. The pathways which provoke the stimulation of calcineurin in HCM are not yet understood and some studies have shown a critical role for Ca^{2+}-dependent signaling in HCM pathogenesis. These data have promoted studies of prevention addressed to normalizing Ca^{2+} dysregulation in HCM models. Young HCM mice (myosin R403Q), without any proof of hypertrophy, were treated with L-channel type Ca^{2+} blocker, diltiazem. This resulted in intracellular Ca^{2+} levels normalization and important inhibition of development of cardiac hypertrophy [62], suggesting that targeting key intracellular events in the development of HCM pathology could prevent the development of the disease.

6.3. HCM enhances myocyte stress

Modified biophysical forces and intracellular Ca^{2+} in HCM myocytes, as well as increased energy demands, promote increased stress on HCM myocytes. Moreover, microvascular dysfunction, demonstrated by positron emission tomography (PET) and cardiovascular magnetic resonance (CMR) in HCM patients [66, 67], may cause ischemia in HCM. In addition, factors that increase myocardial stress are supposed to promote death of myocytes and lead to myocardial scarring in HCM [68].

Molecular analyses also support increased myocyte stress in HCM. In HCM models [69] and human HCM hearts, fetal heart genes are found. These genes are normally repressed after embryonic development but are re-expressed with myocyte stress [70]. Lipid peroxide levels, indicating oxidative stress, are also elevated in HCM models [71]. Studies of mechanism implicated in oxidative stress in HCM hearts exhibit thio-responsive pathways, an observation that determined the study of N-acetylcysteine in HCM models. High concentration of this substance decreased biochemical markers of oxidative stress and surprisingly demonstrated the reversal of fibrosis in HCM models [60, 72]. The potential favorable effect of antioxidants in human HCM requires further studies.

7. Clinical testing and genetic etiology

Pathogenic variants for HCM were originally described in eight genes encoding sarcomere proteins, with most (~80%) present in the MYH7 and MYBPC3 genes [3, 73]. Typically for these structural proteins, most sarcomere variants act in a dominant negative way (by negatively affecting the normal gene product). Loss-of-function variants that lead to haploinsufficiency appear less frequently, predominantly in the MYBPC3 gene [74]. Sarcomeric variants are identified in up to 60% of HCM patients with a family history and in approximately 40% of patients with sporadic HCM [75]. Storage cardiomyopathies that mimic HCM are caused by mutations in GLA (Fabry disease), LAMP2 (Danon disease), and PRKAG2 (Wolff-Parkinson-White syndrome).

The HCM-associated gene spectrum has been developed in nonarrhythmic genes and includes genes encoding Z-disc proteins and proteins localized in the plasma membrane and sarcoplasmic reticulum. Variants in these genes are rare, with limited studies supporting evidence of a role in the disease. Some genes are associated with strong genetic evidence such as segregation with disease or functional data in vivo (e.g. CSRP3) [29], but many genes (e.g. MYH6, MYLK2, and TCAP) are only supported by the presence of variants in affected individuals and the absence from controls. These genes are better considered candidate genes. Almost 1000 HCM variants have been diagnosed so far [75], most of which being unique or private, and can only be identified through a comprehensive genetic evaluation. A small number of recurrent variants are detected at larger population frequencies; the most frequent being a 25 bp deletion in the intron 32 of MYBPC3 gene, which is predominant in Southeast Asian populations (~4%) and increases risk of heart failure with an odds ratio of ~7 [45].

With few exceptions, genotype-phenotype correlations for HCM are incompletely defined. Some, but not all, TNNT2 mutations are associated only with minor hypertrophy, but with an appreciable risk of arrhythmia [45]. MYH7 variants generally appear to promote significant LVH that is evident in the second decade of life and are believed to be associated with an increased risk of heart failure and SCD [76]. Pathogenic variants in MYBPC3 are believed to be associated with a later onset [47]. These variants were also identified in a significant proportion of patients with early onset LVH in childhood [18]. Most variants of MYBPC3 in the pediatric population were missense mutations that contrasted with the high prevalence of

identified loss-of-function variants in HCM adult patients and suggest that missense variants may have worse functional consequences [18].

The US HCM Guidelines recommend complete testing for five HCM genes (MYBPC3, MYH7, TNNI3, TNNT2, and TPM1) [77]. Sequencing diagnostic panels, including these genes, are offered by several laboratories around the world.

In fact, genetic testing for HCM is mainly used to identify families with a detectable genetic cause of the disease and to examine family members at risk. Testing can also help to exclude nongenetic conditions, such as the heart of the athlete, though in case of an identification of a pathogenic variant [75, 78]. Due to the absence of clear genotype-phenotype links, the genetic test results in clinical management guidance have limited usefulness. The exception is enzyme replacement treatment for storage diseases that may have isolated LVH [79, 80].

An area under development is the use of genotype analysis to guide treatment decisions in preclinical HCM patients. Experimental animal studies suggest that some calcium channel blockers, such as diltiazem, may influence by delaying the clinical progression of HCM [62].

Studies in animals have also led to a link between sarcomeric HCM and increase in transforming growth factor b signaling. An anti-transforming growth factor b antibody and losartan (a type 1 angiotensin II receptor antagonist) prevented cardiac fibrosis and hypertrophy in sarcomere mutation-positive mice, which may suggest additional therapeutic possibilities [9].

Since the discovery that pathogenic variants in sarcomeric genes cause HCM [7], much progress has been made to define the genetic etiology of inherited cardiomyopathies. The high risk of SCD in patients with this disorder has encouraged interest in clinical genetic testing. All cardiomyopathies are characterized by a high heterogeneity linked to the great number of loci and allele that require sequential analysis of the entire coding region of several genes, which has been an expensive and long-lasting process using classical technologies. Genetic and phenotypic overlapping between different cardiomyopathies is increasing and this assumes more difficulties, often leading to testing more cardiomyopathy-specific gene panels when the diagnosis is not entirely known. The next-generation sequencing technologies (NGS) have eliminated these problems and allowed the concomitant investigation of a multitude of genes. A negative effect of this possibility of sequencing any gene is an increased likelihood of detecting variants of unclear clinical significance (VUSs). This disadvantage requiring a strict review of the proofs supporting the signs of disorder association as variants in poorly studied genes can be difficult to estimate. There were described variants in >50 genes to be causal for various inherited cardiac muscle diseases, but a comprehensive review shows that only half of them meet the criteria to be considered a definitive gene of the disease.

Current practice guidelines and expert opinions on clinical approach and genetic diagnosis for inherited cardiomyopathies recommend taking a detailed family history that includes at least three generations, clinical screening of at-risk family members, counseling patients about the possibility of an inherited cause, and examining by genetic testing the most obvious affected persons in the family [77]. The recommendations of specific or comprehensive genetic testing are established by the guidelines for only a small number of genes [77], in opposition to the growing use of large gene panels in clinical practice.

For inherited cardiomyopathies, the treatment possibilities are very few and the clinical utility of genetic testing is based on the capacity to confirm the etiology of the disease in proband (when a known pathogenic variant is identified). Subsequent genetic testing of at-risk family members can eliminate the risk of disease (when negative) or identify those members who require monitoring or clinical intervention to reduce the risk of morbidity or mortality (when positive). The spectrum of pathogenic variants present in the population is incompletely characterized, even in well-known disease genes, with a high probability of detecting a new VUS sequence that can create emotional stress for patients [80].

8. Genotype-phenotype overlap between inherited cardiomyopathies

Cardiomyopathies were classically classified only based on clinical features, including ventricular morphology and function. Although HCM, DCM, and arrhythmogenic right ventricular cardiomyopathy (ARVC) are distinct clinical diseases, there is an increasing observation of substantial genetic and phenotypic overlapping. There are phenotypic overlaps between HCM in the final stage and DCM [81] and between DCM and ARVC (which may be manifested by ventricular dilatation and VS involvement) [82]. Also, left ventricular noncompaction (LVNC) features may overlap with those of HCM, DCM, and restrictive cardiomyopathy (RCM) [83].

The genetic etiologies underlying these conditions are clarified and the overlapping results increase substantially. Pathogenic sarcomere variants have been identified first in HCM patients, but also in patients with DCM, LVNC, and RCM [80].

Z-disc mutation genes were involved in DCM and HCM [84]. Desmosomal protein genes were originally thought to be involved only in ARVC, and the evidence suggests that variants in these genes can also lead to DCM [85]. The phenotypic spectrum of variants in the desmin gene includes DCM, RCM, and, most recently described, ARVC [86–88]. Variants of the cardiac troponin T (TTN) gene have recently been shown to be a frequent etiology of DCM, but growing evidence also associates this gene with ARVC [89].

Although it is established that variants in a particular gene may lead to more than one cardiomyopathy, it has been investigated whether the responsible variants are different. Some studies have discovered the same variant in patients with HCM and in patients with DCM, this fact being attributed to phenotypic plasticity [90, 91]. However, the background molecular mechanisms of HCM (high contractility) and DCM (low contractility) are extremely different, which raises questions as to whether the same variant can indeed cause both diseases [80]. Functional characterization of several HCM and DCM variants revealed opposite fundamental properties, supporting distinct variants [92–94]. Assuming nonoverlapping variants, identification of HCM variants in patients with marked LV dilatation and impaired systolic function may reflect remodeling in the final phase of HCM rather than primary DCM. Another explanation for identifying one and the same variant in disorders with distinct molecular mechanisms is that they are not the principal or initial cause of the disease but act as modifiers

or are completely benign. We have now the possibility to evaluate the spectrum of rare benign variations since we are able to query thousands of sequenced genomes and exomes (1000 Genomes Project, National Heart, Lung and Blood Institute Exome Sequencing Project). A disadvantage was the fact that many studies in the past have inferred gene pathogenicity based on insufficient proofs. This has recently been demonstrated for a lot of published variants that have been reported to determine DCM [95]. One example illustrating the temporal evolution of a variant is the Ala833Thr variant of MYBPC3, which was originally reported in four HCM probands and 1 in 400 control individuals [74, 96, 97]. Its presence in a single control person was considered insufficient to exclude a pathogenic role because low penetration is quite frequent in HCM. It is already discovered that this variant is present in 12 of 6952 chromosomes (0.17% Exome Sequencing Project from the Heart, Lung and Blood National Institute), demonstrating the importance of extensive genomic sequencing studies and clearly suggesting that there is a low probability for this variant to be a primary cause of HCM.

In conclusion, it seems probably that the individual variants are most commonly specific to one cardiomyopathy presentation, and new studies that include more precise phenotypic testing and classification of the genetic variants can be useful to prove this with certainty (**Table 1**).

Gene	Location	Inheritance	Muscular component	Gene product
MYH7	14q11.2	AD	Thick filament	β-Myosin heavy chain
MYL3	3p21.31	AD	Thick filament	Essential myosin light chain
MYL2	12q24.11	AD	Thick filament	Regulatory myosin light chain
TTN	2q31.2	AD	Thick filament	Titin
MYH6	14q11.2	AD	Thick filament	α-Myosin heavy chain
TNNT2	1q32.1	AD	Thin filament	Cardiac troponin T
TNNC1	3p21.1	AD	Thin filament	Cardiac troponin C
TNNI3	19q13.42	AD	Thin filament	Cardiac troponin I
ACTC		AD	Thin filament	α-Cardiac actin
TPM1	15q22.2	AD	Thin filament	α-Tropomyosin
MYBPC3	11p11.2	AD	Intermediate filament	Cardiac myosin-binding protein C
CASQ2	1p13.1	AR	Calcium handling	Calsequestrin
JPH2	20q13.12	AD	Calcium handling	Junctophilin 2
MYOZ2	4q26	AD	Z-disc	Myozenin2
ACTN2	1q43	AD	Z-disc	α-Actinin2
VCL	10q22.2	AD	Z-disc	Vinculin/metavinculin
TCAP	17q12	AR, AD	Z-disc	Telethonin
CSRP3	11p15.1	AD	Z-disc	Muscle LIM protein

Table 1. Genes having pathogenicity for hypertrophic cardiomyopathy [98–100].

9. Conclusions

For an optimal approach of patients with HCM, genetic testing is available and very useful. Major progresses have been made with the finding of several mutations that have demonstrated marked genotypic and phenotypic heterogeneity of this cardiac muscle disorder. This genetic testing must be performed in certified diagnostic laboratories. The first indication is for testing patients who have completed the diagnostic criteria for HCM, allowing further screening of the family members. Some other potential advantages are confirming or infirming the diagnosis in ambiguous situations and allowing a better understanding of this polymorphic disease.

Conflict of interest

None.

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Chapter 3

Contemporary Surgical Treatment for Hypertrophic Cardiomyopathy

Takashi Murashita

Additional information is available at the end of the chapter

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Abstract

Hypertrophic cardiomyopathy is the most common cause of sudden death in young athletes. Surgical septal myectomy is highly effective for the patients with hypertrophic obstructive cardiomyopathy, which is refractory to medical treatment. The perioperative mortality rate for isolated septal myectomy is less than 1% in high volume centers. The long-term outcomes have been reported to be outstanding with >90% of patients being free of significant symptoms and most being able to return to a normal lifestyle. There is a documented survival benefit after surgical septal myectomy. There is a wide variation of pathophysiology in hypertrophic cardiomyopathy including diffuse midventricular obstruction or subvalvular abnormalities. Several surgical approaches have been applied in accordance with the pathophysiology, such as transaortic, transapical, and transmitral septal myectomy. There is a controversy how to manage concomitant mitral valve regurgitation. The most recent Society of Thoracic Surgeons database showed that operative mortality of concomitant septal myectomy and mitral valve operations was double compared with isolated septal myectomy.

Keywords: hypertrophic cardiomyopathy, septal myectomy, surgical outcomes

1. Introduction

Hypertrophic cardiomyopathy is a genetic disorder of the heart muscle, resulting in a small left ventricular cavity and marked hypertrophy of the myocardium [1, 2]. Although many patients remain asymptomatic throughout life, some patients develop symptoms such as dyspnea,

angina, and syncope. Hypertrophic cardiomyopathy is the most common cause of sudden death in trained athletes [3].

The mainstay of therapy for hypertrophic cardiomyopathy has been the combination of lifestyle changes and medical therapy including beta blockers or calcium channel blockers. However, there remain patients who are refractory to medical treatment. For these patients, surgical septal reduction therapy, called septal myectomy, is indicated with class I indication [4]. When surgery is contraindicated because of serious comorbidities or advanced age, alcohol septal ablation is recommended with class IIa indication [4]. Dual-chamber pacing has also been used for the relief of outflow tract obstruction in patients whom both surgical septal myectomy and alcohol ablation are considered to have unacceptable risk. The treatment algorithm for the management of hypertrophic cardiomyopathy patients is shown in **Figure 1**.

Given the duration of experience and documented evidence of long-term outcomes, surgical septal myectomy is the preferred treatment for most patients who need invasive therapy. Operator and institutional experience is a key factor of successful surgical outcomes. The guidelines suggested that surgical treatment should be performed only by experienced operators, which were defined as an individual operator with a cumulative case volume of at least 20 procedures or an individual operator who is working in a dedicated hypertrophic cardiomyopathy program with a cumulative total of at least 50 procedures [4].

Compared with surgical septal myectomy in which the hypertrophic muscle is directly visualized and resected, successful alcohol ablation is dependent on the variable septal artery anatomy, which may not supply the targeted are of the septum in up to 20–25% [4].

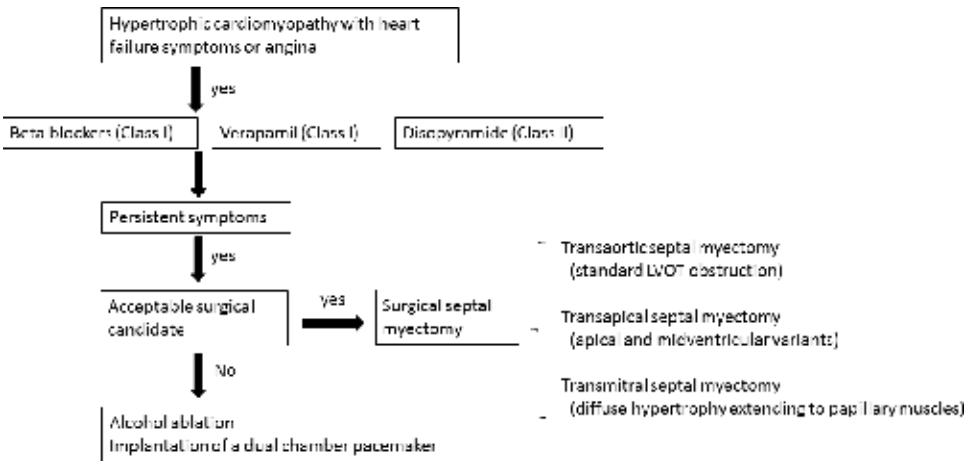

Figure 1. Treatment algorithm for the management of hypertrophic cardiomyopathy patients. LVOT, left ventricular outflow tract. **Figures 2–5** were cited from the study of Price et al, but **Figure 1** was not cited from them.

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2. Surgical septal myectomy

2.1. Historical perspective of septal myectomy

The attempts of surgical correction for HCM were started in the late 1950s. One of the earliest septal myectomy was performed by Cleland and colleagues in 1958. They reported a series of 12 cases of septal myectomy in 1964, and there were three operative deaths [5].

Septal myectomy is also called Morrow operation, as it was reported by Morrow and Brockenbrough in 1961 [6]. They reported two cases of successful subaortic ventriculomyotomy via a transaortic approach for severe symptomatic hypertrophic subaortic stenosis.

Kirklin and Ellis reported two cases of successful surgical relief of diffuse subvalvular aortic stenosis via a left ventriculotomy in 1961 [7].

2.2. Transaortic septal myectomy

The initial technique reported by Morrow and colleagues involved excising a rectangular segment of the septal myocardium beneath the right coronary cusp with approximately 3–4 cm long, 1 cm wide, and 1.5 cm deep [8].

In recent years, the standard transaortic procedure has evolved into an extended septal myectomy. Following the initiation of cardiopulmonary bypass, exposure of the left ventricle is obtained via an oblique aortotomy. The completed myectomy extends from the subaortic level, about 5 mm below the aortic annulus to the midventricular level, opposite the base of the anterior papillary muscle of the mitral valve, for a total length of about 7 cm (**Figure 2**).

Ashikhmina et al. reported the importance of direct intraoperative measurement of pressures in the left ventricle and aorta [9]. After cannulation of the aorta, a 2.5 inch, 22-gauge spinal needle is placed into the aorta close to the aortic cannula and another 3.5 inch, 22-gauge spinal needle is placed into the left ventricle through right ventricular free wall and septum.

Nguyen et al. reported that transaortic septal myectomy can be achieved for relatively thin ventricular septum (<18 mm) with low risk of iatrogenic ventricular septal defect (0.3%) [10]. Brown et al. reported that septal thickness or left ventricular mass was not associated with death [11].

2.3. Transapical septal myectomy

Apical hypertrophic cardiomyopathy is a relatively rare form of hypertrophic cardiomyopathy. Eriksson et al. reported that this type of hypertrophic cardiomyopathy is not associated with sudden cardiac death and has a benign prognosis; nevertheless, one of third of these patients experience cardiovascular complications such as myocardial infarction and arrhythmias [12].

For these patients, transaortic septal myectomy is not always effective. Schaff et al. described a technique for resection of hypertrophic apical myocardium via an apical ventriculotomy

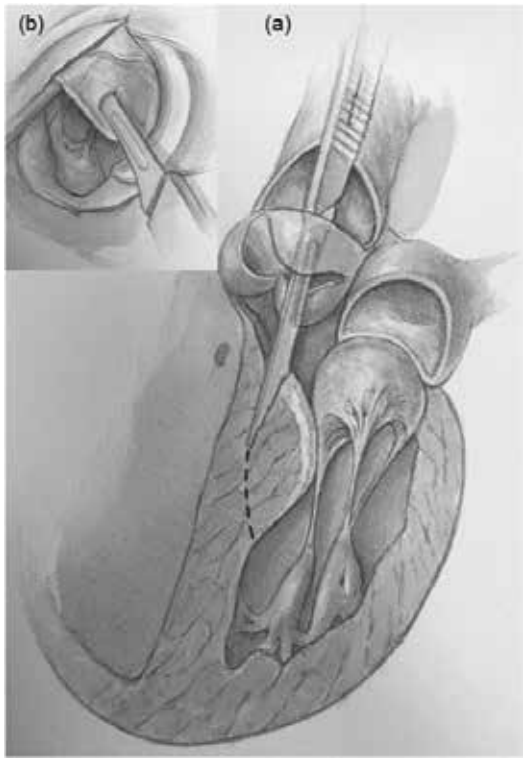

Figure 2. (a) Extended basal septal myectomy via supravalvular aortotomy. (b) Surgeon's view through the aortotomy, identifying the hypertrophic septum immediately inferior to the right coronary aortic valve cusp. Figure was cited from the study of Price et al. with their permission [49].

[13, 14]. A 6-cm longitudinal incision is made lateral to the left anterior descending artery beginning at the apical dimple. The goal of apical resection is to sufficiently enlarge the left ventricular cavity and shaving of the excess papillary muscle can be carried out if necessary (**Figure 3**).

Kunkala et al. reviewed 56 patients with midventricular obstruction [15]. Septal myectomy was performed through transaortic approach in 5, transapical approach in 32, and a combination of these in 19. There were no complications unique to the apical incision, and 5-year survival rate was similar to the expected one. Hang et al. also reported the effectiveness of combined transaortic and transapical approach to complex septal hypertrophy [16].

2.4. Transmitral septal myectomy

Transmitral septal myectomy was first described in 1963 by Lillehei and Levy [17]. This approach is indicated for patients with diffuse hypertrophy extending to or below the papillary muscles with mid-ventricular obstruction, which is not amenable to repair via a transaortic myectomy. Gutermann et al. reported 12 cases of transmitral septal myectomy with one mortality [18]. In the transmitral myectomy, the anterior mitral leaflet is widely detached

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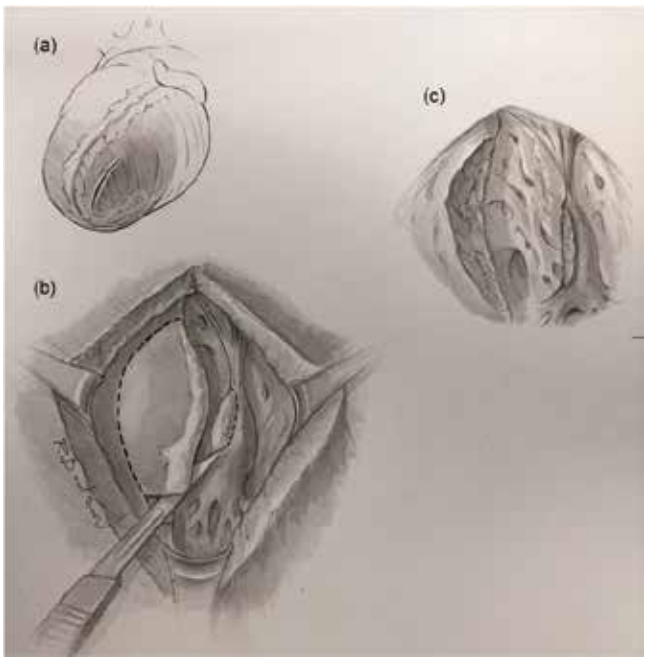

Figure 3. (a) Apical incision lateral to the left anterior descending coronary artery, ensuring there is enough myocardium remaining to leave the left anterior descending coronary artery uninvolved in the suture line. (b) Surgeon's view through the apical incision, identifying the hypertrophic myocardium and potentially hypertrophic papillary muscles. (c) Surgeon's view after resection, with an adequately resected left ventricular cavity. Figure was cited from the study of Price et al. with their permission [49].

from commissure to commissure, but the commissures are left intact. That allows an easy myectomy toward the base of the anterior papillary muscle, with mobility fully restored (**Figure 4**). The abnormal chordae from the septum to the anterior papillary muscle can be divided. After all intraventricular repairs are complete, the continuity of anterior mitral leaflet was restored either with continuous suture or with augmentation using an autologous pericardial patch.

Transmitral approach may provide excellent exposure to septal hypertrophy in patients with a narrow aorta which limits the transaortic view [19].

There are several case reports of minimally invasive transmitral septal myectomy through right thoracotomy, either with video-assisted methods or robotic platform [20–23].

2.5. Surgical outcomes and complications

Maron et al. reported the operative mortality data from five high-volume centers in North America [24]. Over the 15-year period, 3700 isolated septal myectomy operations were performed, and operative mortality was only 0.4%. In the meantime, it is expected that the surgical expertise of the high-volume centers would be passed down to regional multidisciplinary centers as well [25].

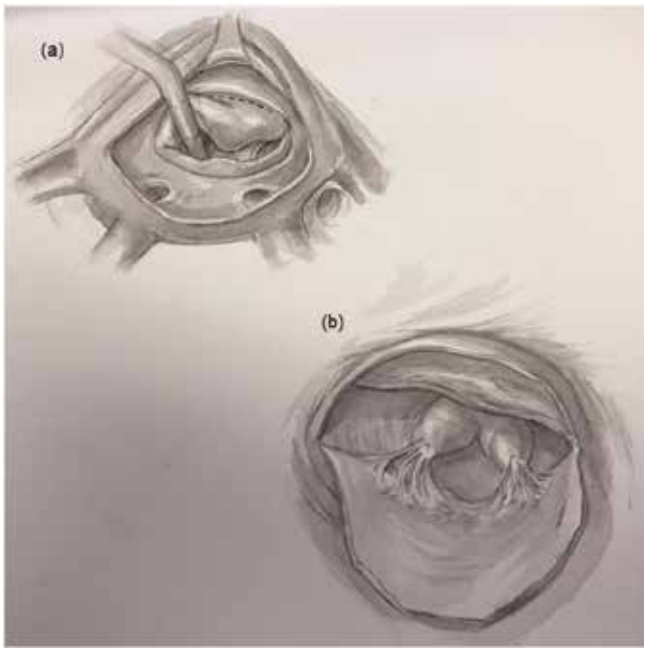

Figure 4. (a) View of the atrial surface of the mitral valve, with the dashed line representing the incision line in the anterior mitral valve leaflet. (b) Following incision and release of the anterior mitral valve leaflet, a broad view of the interventricular septum, down to the left ventricular apex, is obtained. Figure was cited from the study of Price et al. with their permission [49].

Kotkar et al. reviewed over two decades of surgical experience at Mayo Clinic [26]. More than 3000 patients underwent septal myectomy, and risk of hospital death after isolated septal myectomy was <1%. Postoperative complications such as iatrogenic ventricular septal defect and complete heart block requiring permanent pacemaker occurred infrequently (0.3 and 2%, respectively).

Parry et al. reviewed one surgeon's experience of septal myectomy for 211 patients at Toronto General Hospital [27]. The in-hospital mortality was 0.5% and 5-year survival rate was 98.1%.

According to the Society of Thoracic Surgeons database, 3452 septal myectomy operations were performed from July 2014 through December 2016, in the United States. Emergency status, endocarditis, aortic stenosis, and planned aortic valve operations were excluded, but concomitant coronary artery bypass was included. In the final cohort of 2038 patients, 1315 (65%) received septal myectomy alone, and 723 (35%) had septal myectomy with concomitant mitral operations. The median number of annual cases per center was 2 (range 1–435). Operative mortality and major morbidity were lower in isolated septal myectomy group than septal myectomy plus mitral operations (1.5% vs. 3.0%, $p = 0.03$; and 10.6% vs. 21.4%, $p < 0.001$, respectively). Postoperative iatrogenic ventricular septal defect and complete heart block requiring permanent pacemaker were rare (0.8 and 3.4%, respectively in isolated septal myectomy, and 1.8 and 4.1% in septal myectomy plus mitral operations) [28].

2.6. Long-term outcomes of septal myectomy and its impact on cardiac function

Ommen et al. reviewed the experience of Mayo Clinic and studied the impact of surgical septal myectomy on long-term survival [29]. The 1-year, 5-year, and 10-year survival was 98, 96, and 83%, respectively, and they did not differ from those of the general population. They also stated that myectomy significantly improved all-cause mortality, obstructive cardiomyopathy-related mortality, and sudden cardiac death.

Woo et al. reviewed 338 patients who underwent septal myectomy at Toronto General Hospital and reported the excellent long-term survival with 1-year, 5-year, and 10-year survival of 98, 95, and 83%, respectively [30].

Deb et al. studied the impact of septal myectomy to left ventricular remodeling after surgery [31]. They found a significant decrease in the left ventricular mass index which occurred early after surgery and persisted beyond 2 years of follow-up.

Geske et al. reported that septal myectomy is associated with improvement in pulmonary hypertension, and it was most pronounced in patients with moderate or severe pulmonary hypertension [32].

In patients with hypertrophic cardiomyopathy, latent left ventricular outflow obstruction, which is defined as gradient <30 mmHg at rest and that increases to >50 mmHg with provocation, has been recognized important recently. Schaff et al. suggested that surgery should be offered to these patients [33].

2.7. Management of concomitant papillary muscle abnormalities

There is a subset of patients in whom the mitral valve and subvalvular apparatus such as papillary muscles and chordae play a significant role in creating the dynamic obstructive process [34–36]. Klues et al. reported that 66% of the patients with hypertrophic cardiomyopathy had a constellation of structural malformations, including increased leaflet area and elongation of the leaflets or anomalous papillary muscle insertion directly into anterior mitral leaflet, in mitral valve [34].

Minakata et al. reviewed 291 patients who underwent septal myectomy, and 56 (19.2%) had anomalous mitral subvalvular apparatus [37]. These anomalies were successfully treated with resection of anomalous chordae or relief of papillary muscle fusion, and no patients required mitral valve replacement.

Several reports described other surgical techniques to treat subvalvular abnormalities.

Redaelli et al. reported good outcomes of septal myectomy combined with papillary muscle repositioning for patients with abnormal papillary muscle morphology [38].

Ferrazzi et al. reported good outcomes of septal myectomy combined with a secondary chordal cutting for patients with thickened anomalous chordae [39].

2.8. Management of concomitant mitral regurgitation

Mitral valve leaflets play an important role in the pathophysiology of left ventricular outflow tract obstruction. Systolic anterior motion of the mitral apparatus narrows left ventricular outflow tract, and in many patients, leads to mitral regurgitation. There is a controversy how to treat concomitant mitral regurgitation at the time of septal myectomy. Ideally adequate septal myectomy can get rid of not only systolic anterior motion, but also mitral regurgitation. However, some groups have advocated that mitral valve replacement is necessary when mitral regurgitation is severe [40, 41].

Hong et al. reviewed the experience of septal myectomy operations at Mayo Clinic and concluded that mitral regurgitation related to systolic anterior motion of the mitral valve is relieved by septal myectomy alone in most cases, therefore, concomitant mitral operation is not necessary unless intrinsic mitral valve disease is present [42].

Balaram et al. suggested adding anterior mitral leaflet plication to septal myectomy when patients have long anterior leaflet (≥3 cm) and systolic anterior motion [43–45]. They call their method as "resection-plication-release" method (**Figure 5**). They have reported excellent outcomes using their technique.

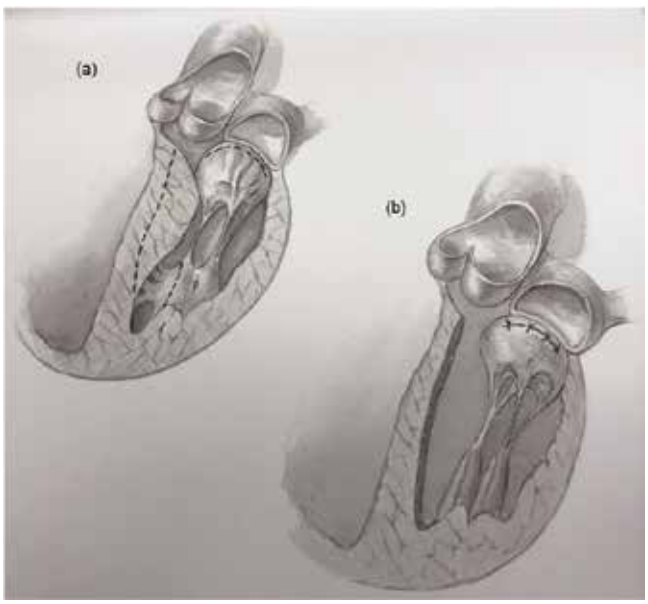

Figure 5. (a) The resection-plication-release method identifies areas of left ventricular outflow tract obstruction, including the hypertrophic septum, abnormal papillary muscle attachments, and an elongated anterior mitral valve leaflet. (b) Following the resection-plication-release procedure, the hypertrophic septum is resected, the abnormal papillary muscle attachments are released, and the elongated anterior mitral valve leaflet is plicated. Figure was cited from the study of Price et al. with their permission [49].

As the Society of Thoracic Surgeons database showed, concomitant mitral operations were performed in one-third of the cases in the United States. Operative mortality of concomitant septal myectomy and mitral operations was double compared with isolated septal myectomy (3.0% vs. 1.5%). However, postoperative grade 3–4 mitral regurgitation was found more frequently in isolated septal myectomy than combined septal myectomy and mitral operations (10.6% vs. 5.8%, $p < 0.0001$). Following risk adjustment, the odds ratio for composite mortality and morbidity was not significant for mitral valve replacement vs. repair at 1.43 [0.9–2.2] ($p = 0.0991$) [28].

2.9. Recurrent obstruction

The recurrent obstruction after surgical myectomy is reported to be rare.

Minakata et al. reviewed 610 septal myectomies at Mayo Clinic between 1975 and 2003, and 13 patients underwent redo septal myectomy [46]. The interval between initial myectomy and redo myectomy ranged from 13 months to 11 years. The mechanism for recurrent obstruction was limited myectomy at the initial operation in 11, septal hypertrophy at the midventricular level in 8, and anomalous papillary muscle in 3.

Cho et al. also reviewed the surgical series at Mayo Clinic and stated that inadequate length of septal excision was associated with residual and recurrent obstruction [47].

Smedira et al. reviewed 323 patients who underwent isolated septal myectomy at Cleveland Clinic, and there were 10 cardiomyopathy-related reoperations; 4 redo myectomy, and 6 mitral valve procedure [48].

3. Conclusions

Surgical septal myectomy provides a survival benefit to patients with drug-refractory hypertrophic cardiomyopathy. It also has a positive effect on patients' quality of life and cardiac function. According to the variation of pathology, appropriate surgical approach and technique should be applied. The recent study based on the national database showed surgical mortality doubles when concomitant mitral procedures are done at the time of septal myectomy. Careful decision making should be done in treating concomitant mitral regurgitation.

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Chapter 4

Epsilon Waves: The Gate to Understand Arrhythmogenic Right Ventricular Dysplasia

Guo Liang Li, Ardan M. Saguner and
Guy Hugues Fontaine

Additional information is available at the end of the chapter

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Abstract

Arrhythmogenic right ventricular dysplasia (ARVD), first recognized in 1977, is an inherited cardiomyopathy mostly due to mutations in both desmosomal and non-desmosomal genes. ARVD is considered as a leading cause of sudden cardiac death in the young and the athlete. It is characterized by an abnormality in the development of the right ventricular (RV) musculature. The final diagnosis of ARVD was pathologically based on the findings characterized by fibro-fatty infiltration and cardiomyocyte loss predominantly affecting the RV. Epsilon waves are a feature of ARVD reflecting postexcitation of the myocytes in the RV that are interspersed between fibrous and fatty tissue. Epsilon waves are considered to be one of the major diagnostic criteria of ARVD and appear to correlate with the extent of ARVD and arrhythmic risk. In this review, we will briefly review the discovery of ARVD and Epsilon waves, discuss the electrogenesis and various methods for recording Epsilon waves, provide evidence to assist in understanding the pathological and functional changes of the heart in ARVD, thus promoting the management of this disease in patients and family members.

Keywords: sudden cardiac death, mutation, ECG, Arrhythmogenic right ventricular dysplasia, epsilon waves

1. Introduction

Arrhythmogenic right ventricular dysplasia (ARVD) was recognized in 1977 during antiarrhythmic surgery to map and treat ventricular tachycardia in Paris [1]. This work demonstrated some male patients presenting with ventricular tachycardia (VT) originating in the right ventricle (RV)

(**Figure 1**) [2]. However, all of them had preserved left ventricular function [1, 3–5]. The term "dysplasia" was chosen because it was observed at this critical point that the remaining myocardium was thinner than normal and covered by a large amount of fat (**Figure 2**A). This pattern constantly observed on the first four cases led to conclude that this structural abnormality was the result of a "developmental deficiency". The same reasoning has been made 25 years before by Dr. Henry Uhl, a pathologist of the Johns Hopkins Hospital, who observed the eponym disease on a single pediatric heart without myocardium, mostly seen on the RV free wall [6, 7]. Based on the previous evidence, the dysplastic phenomenon preferentially involved the areas of the anterior RV infundibulum, the RV apex and the inferior or diaphragmatic aspect of the RV, which constitute the original "triangle of dysplasia" (**Figure 2**B).

The term "arrhythmogenic right ventricular cardiomyopathy (ARVC)" was introduced before the First International Symposium organized in Paris in 1996 to incorporate other diseases already known under a different name such as right ventricular outflow tract (RVOT) VT or Brugada syndrome (BrS), and has foreseen completely new subgroups based on clinics and/or genetics. Naxos disease and desmoplakin related RV diseases are examples demonstrating that this prediction was correct. Therefore, the term ARVCs (plural) looks appropriate to incorporate all the clinical forms of cardiomyopathies of the right ventricle, in which ARVD as described by Marcus and Fontaine in 1982 [3], remains the most frequent form of presentation. In addition, the notion of "dysplasia (trouble of development)" was strongly confirmed by the heart of an arrhythmic fetus (**Figure 3**) and by recent advances of reproducing the disease in-the-dish [8–11].

The final diagnosis of ARVD was pathologically based on the previous findings of the typical evidence, namely myocardium embedded in or bordered by fatty tissue or fibrosis (**Figure 4**)

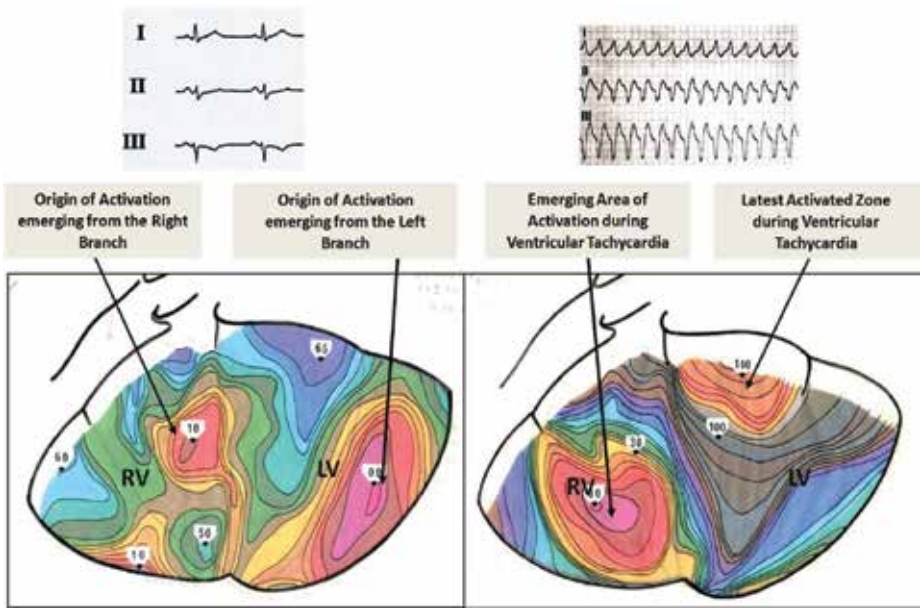

Figure 1. First ARVD patient, in whom the epicardial mapping during atrial overdrive pacing of sinus rhythm was performed. Note that the RV is activated 10 ms after the left ventricle (left); mapping after VT induction by burst stimulation (right). (With permission from Dr. Guy Hugues Fontaine) [2].

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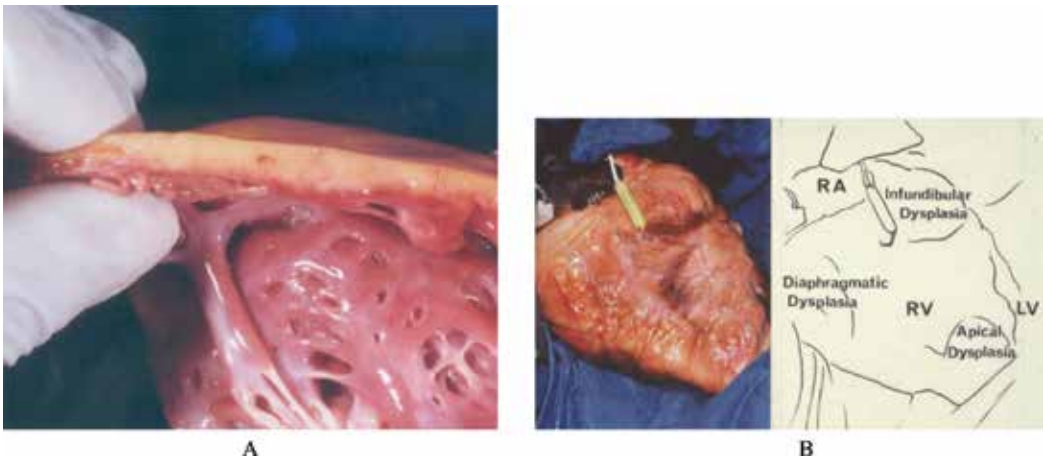

Figure 2. (A) Macroscopic findings in a patient with ARVD show a thinned endocardial layer of myocardium covered by a thicker than normal layer of fatty tissue. (Courtesy of Prof. Piccolo Venice). (B) The heart of a 50-year-old female ARVD patient during surgery. The most prominent areas of dysplasia are illustrated on the drawing. (With permission from Dr. Guy Fontaine) [3].

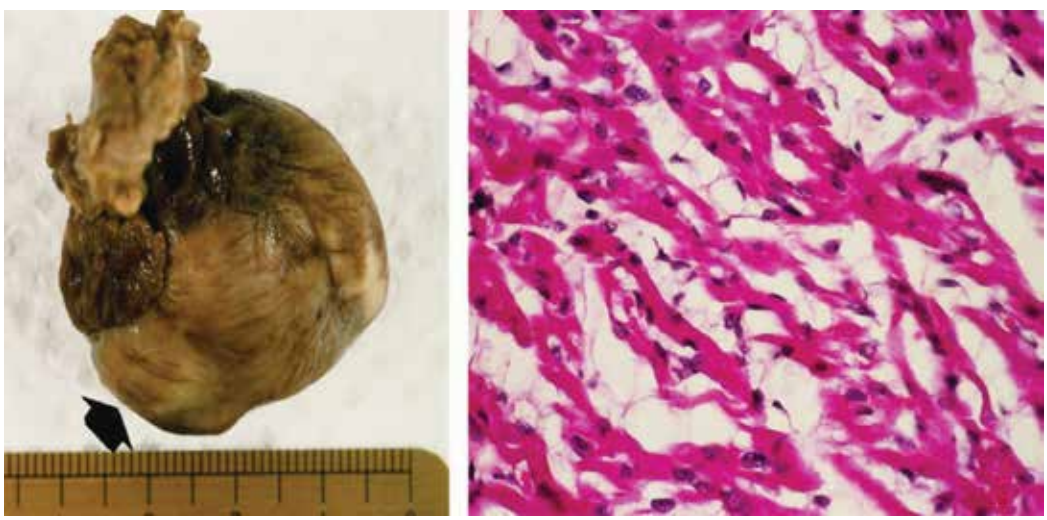

Figure 3. Evidence of a right lateral aneurysm of a 27-week-old fetal heart, arrhythmogenic in utero. Histology shows evidence of adipocytes interspersed with myocardial fibers. Minor fibrosis but no signs of inflammation were observed. Hematoxylin-phloxine-saffron stain; magnification ×400. (With permission from Dr. Guy Fontaine [10]).

[1, 4]. At the same time, the potential of apoptosis was also appreciated in remodeling myocardium in ARVD (**Figure 5**) [4]. In addition, further evidence indicates that the RV progressively enlarges over long-term follow-up. Left ventricular involvement is very frequently observed at later stages. This progression is likely to result in congestive heart failure leading to death [3, 12, 13]. The notion of ARVD as a genetic disease was strengthened by the evidence of its genetical susceptibility to myocarditis, (**Figure 6**) [14–17]. This, in turn, indicates that environmental factors can trigger rapid progression of ARVD.

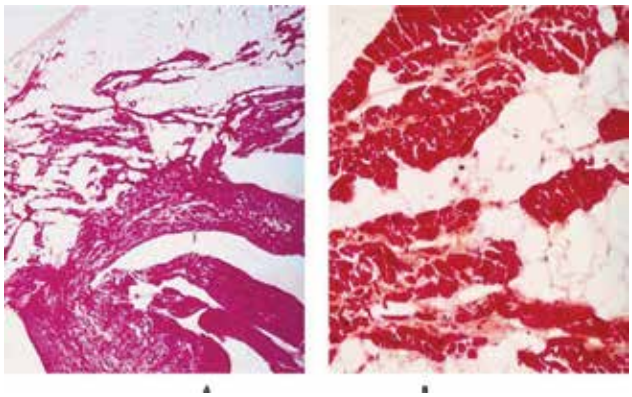

Figure 4. Free wall of the RV of a patient with ARVD. In panel a, there is a large amount of adipose tissue occupying the mediomural and subepicardial layers (hematoxylin-phloxine-saffron staining, ×10). In panel b, high magnification reveals surviving strands of myocardium bordered by or embedded in fibrous tissue. The presence of fibrous tissue is necessary for the diagnosis of ARVD. (With permission from Dr. Guy Fontaine [4]).

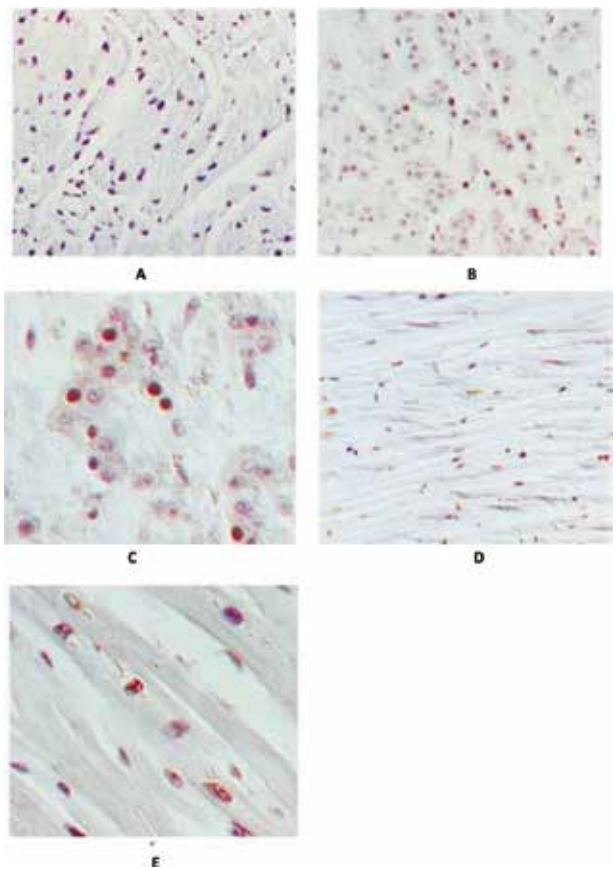

Figure 5. In situ end-labeling of fragmented DNA with TdT and biotinylated dUTP. Cells with fragmented DNA stained brown, whereas cells with normal nuclei stained blue (immunoperoxidase staining with hematoxylin counterstaining). In Panel A, a section from a normal human RV shows no apoptotic nuclei (×100). Transverse sections (Panels B and C) and longitudinal sections (Panels D and E) of RV myocardium from patients with lethal ARVD shows numerous myocardial nuclei with apoptosis. (Panels B and D, ×100; Panels C and E, ×400.) (With permission from Dr. Guy Fontaine [4]).

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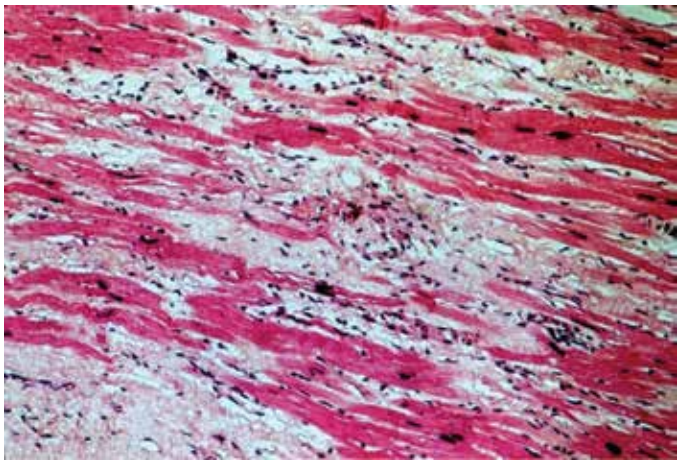

Figure 6. A 28-year-old male patient in whom the clinical course was illustrated by release of troponin and progressive decrease in left ventricular ejection fraction (LVEF), and finally heart transplant confirming the diagnosis of ARVD, but also showing a typical involvement of both ventricles by histological signs of lymphocytic myocarditis. A zone of chronic-active myocarditis in the LV in the same case indicated major loss of cardiac function leading to progressive deterioration of heart function and transplantation. (With permission Dr. Guy Fontaine [17]).

Major criteria
Epsilon waves or T wave inversions in leads V1-V3 and beyond in the absence of complete right bundle branch block
Minor criteria
Late potentials (signal-averaged ECG)
Inverted T waves in precordial leads (V1 and V2 or V4, V5 or V6) in absence of right bundle branch block
Terminal activation duration >=55ms in V1, V2 or V3

Table 1. ECG-based task force criteria for diagnosing ARV/D.

According to the 2010 Task Force criteria on ARVD [18], the fundamentals of ECG applications in the diagnosis of ARVD still remain unshakable. As an important noninvasive test, ECG provides useful information about disease evolution and the risk of VT/VF and SCD. ECG parameters for the diagnosis of ARVD were reviewed by several groups [3, 12, 19–24] and finally by the Task Force Criteria (**Table 1**) [18, 25]. The clinician needs to be aware of the ECG abnormalities reflecting the pathophysiology of ARVD to ascertain the likelihood of patients having this disease. This review focuses on the Epsilon wave, discusses the electrogenesis and various methods of assessing Epsilon waves. Importantly, it provides evidence to help better understand the pathological changes underlying ARVD, thus promoting the management of these patients.

2. Discovery of Epsilon waves

Epsilon waves (**Figure 7**), a reliable diagnostic ECG criterion of ARVD in the Task Force Criteria, were also reported in 1977 during surgery aforementioned [1]. We found that

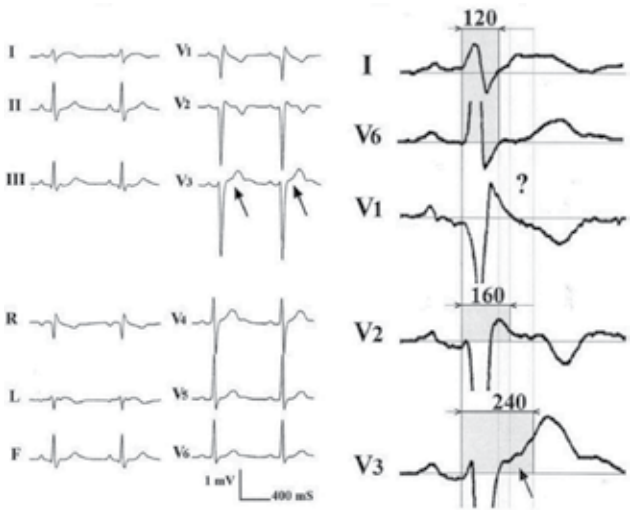

Figure 7. Typical ECG from a young man with ARVD with enlargement of some leads to stress the Epsilon wave in right precordials as opposed to the left. Also note fragmentation of the PR segment, which is in agreement with the possible risk of atrial arrhythmias. The '?' sign stresses the limit of Epsilon wave recognition on a single lead. (With permission from Dr. Guy Fontaine [28]).

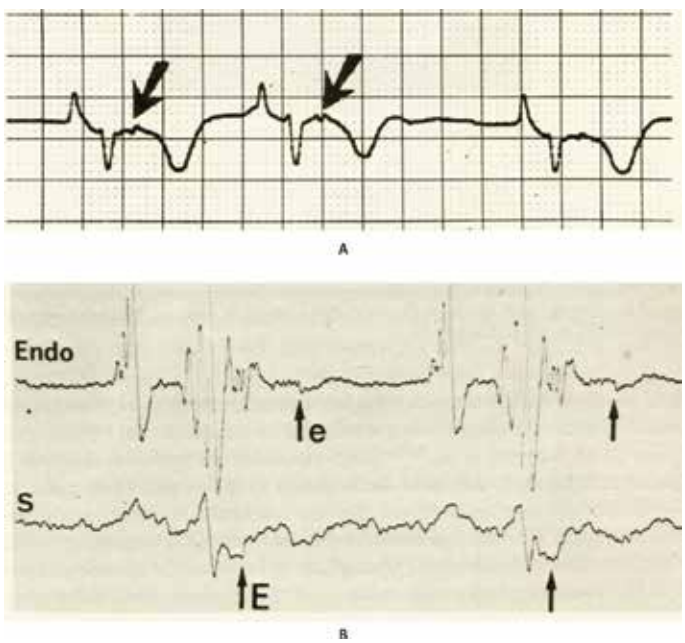

Figure 8. (A) Epsilon wave recorded from the body by two precordial electrodes positioned on both sides of xyphoid extremity. The Epsilon wave is indicated by an arrow. (B) on a bipolar thoracic lead (S), late potentials (indicated by an arrow) are seen in spite of considerable muscular activity. An intracavitary bipolar lead (electrodes located 6 cm apart) shows post-excitation waves, which occur much later than on the surface lead. (With permission from Dr. Guy Fontaine [1]).

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the origination of VT was in the RV rather than the usual left ventricular scar areas. Low-amplitude signals on the epicardium during mapping consistently following each QRS complex (QRS) on the surface ECG were observed (**Figure 8**) [1]. At the end of right precordial QRS of the surface ECG, tiny signals as a slurring were also detected. Both signals were named Epsilon waves. The name "Epsilon wave" was given because (1) it is small in amplitude, (2) it is a "postexcitation" phenomenon that mirrors the "pre-excitation" delta wave of the Wolff–Parkinson–White syndrome at the beginning of each QRS complex, (3) it is the next Greek letter after delta, and (4) it represents delayed activation of right ventricular myofibers [9, 26].

3. Electrogenesis of Epsilon waves

This ECG feature of ARVD can be explained by its underlying pathogenesis. Epsilon waves are typically detected in ARVD patients during sinus rhythm. Observations from gross pathology of ARVD hearts during surgery and later from histology of tissue samples taken at surgery proved that electrogenesis of Epsilon waves was because of a structural anomaly. Strands of myocardium embedded in fatty tissue or fibrosis could account for zones of slow conduction leading to abnormal depolarization as a sign of postponed activation and the electrogenesis of Epsilon waves [1, 3, 4]. Conclusive clinical abnormalities contributing to Epsilon waves were only obtained after we studied 24 ARVD patients with resistant VT [3].

Epsilon waves typically appear in sinus-rhythm ECGs in ARVD patients as tiny potentials or notches following or buried at the end of the QRS, respectively, in the right precordial leads rather than the left counterparts (difference of QRS duration often ≥25 ms) (**Figure 7**). Epsilon waves were rarely observed during VT because most of the tachycardias in arrhythmogenic RV dysplasia exit from the triangle of dysplasia with early activation occurring in the RV myocardium. However, under some rare situation, Epsilon-like waves may also be detected during VT probably indicating extremely slow activation in the RV free wall of extensive ARVD [27].

4. Methods of assessing Epsilon waves

Three types of Epsilon waves (**Figure 9**) in ARVD patients can be recorded by various methods, including the common recording method of standard 12-lead ECG (S-ECG), the Fontaine Lead System (FLS), signal-averaged ECG (SAECG), and sometimes right-sided precordial lead electrocardiography (R-ECG) [3, 5, 26]. Recently, we also demonstrated the potential of an insertable loop recorder (ILR) [28] and a 16-lead High-Definition ECG recorder to detect Epsilon waves [29].

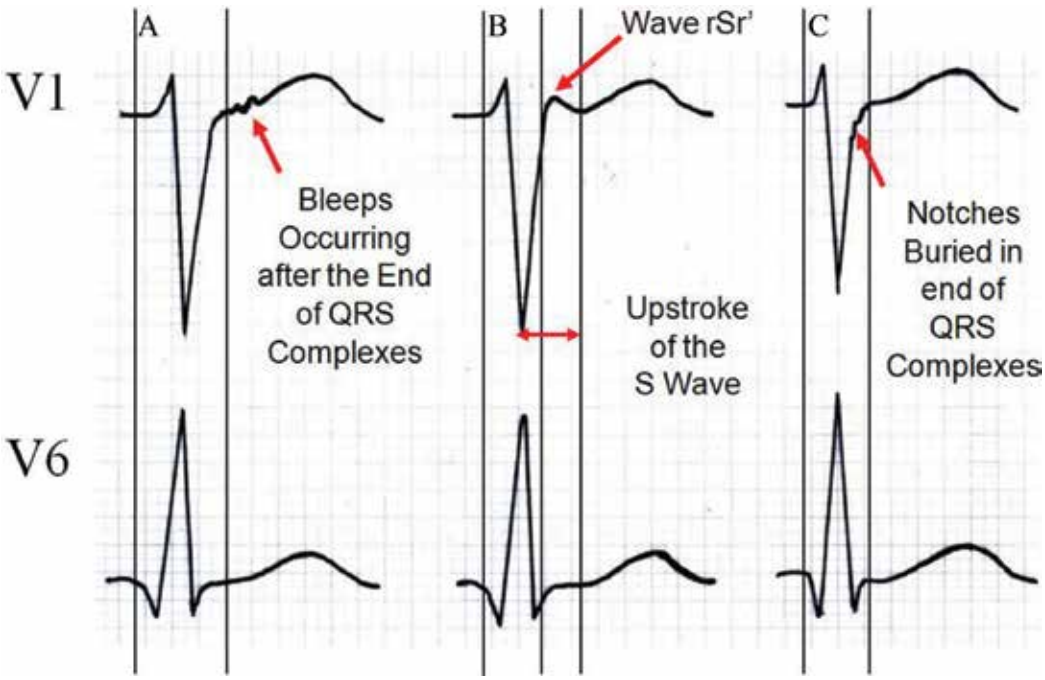

Figure 9. Patterns of Epsilon waves. Please note that our definition of Epsilon waves differs from the revised 2010 Task Force Criteria. The red arrows indicate the 3 patterns of Epsilon waves: (A) wiggle waves, (B) smooth potential waves with QRS duration in V_1 exceeding the duration in V_6 by 25 msec. (C) Small spike waves (With permission from Dr. Guy Fontaine). Please note that in the revised 2010 Task Force criteria these small spike waves within the upstroke of the S wave in leads V1-V3 are considered a minor depolarization criterion if the terminal activation duration is >=55ms (With permission from Dr. Guo-Liang Li) [29].

5. Standard 12-lead ECG

The detection rate of Epsilon waves was found to be up to 30% in S-ECG of ARVD patients evident in precordial leads V1 through V3 [5], and small spiked waves are the most common type observed [1, 5, 30]. When postponed activation of surviving strands of myocardium are present, an atypical prolonged R' wave of Epsilon waves can be detected in the right precordial leads. Therefore, the duration of any delayed signal in leads V1, V2 or V3 longer than the duration of the QRS in lead V6 by at least 25 ms can be regarded as Epsilon waves, indicating postponed activation of some RV myocardial fibers. Interestingly, the dynamic change of Epsilon waves was also addressed in the same individual [30]. Epsilon waves were seen in leads in V1 through V2 after the class 1C anti-arrhythmic drug propafenone to be administered intravenously for VT, but they disappeared after propafenone withdrawal. This dynamic change of Epsilon waves is not easy to explain; however, we can speculate that this is probably due to the effect of a rather large dose of propafenone I.V. The Epsilon wave is produced by a relative increase in conduction slowing in some, possibly more vulnerable, strands of RV myocardium. Also note that there is a "Presilon" wave, which disappears during propafenone administration due to a complete block of other strands of fibers.

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6. Fontaine lead system

The FLS is a bipolar-lead system ECG performed specifically to detect RV signals from the infundibulum to the region of the diaphragm. FLS is able to detect larger amplitudes and a longer duration of Epsilon waves than S-ECG, on which this phenomenon of conduction slowing in the epicardial layers of the inferior RV and LV is too weak to produce significant Epsilon waves (**Figure 10**). In FLS, Epsilon waves were detected by putting an electrode close to the right arm connection (negative) on the manubrium sternal and the left arm connection (positive) on the xyphoid [5]. This placement is performed to detect more specifically the signals caused by the postponed RV fibers, covering the involved areas of the RV (**Figure 10**). The potential to detect Epsilon waves may also be increased by enhancing the sensitivity of detection [3, 5, 26, 21–33]. The detection rate of Epsilon waves was increased to more than 70% by FLS [26]. Previous work indicated that the FLS is capable of detecting Epsilon waves in FI, FII, and FIII to help meet a definitive diagnosis of ARVD according to the Task Force Criteria (**Table 1**) [32, 34].

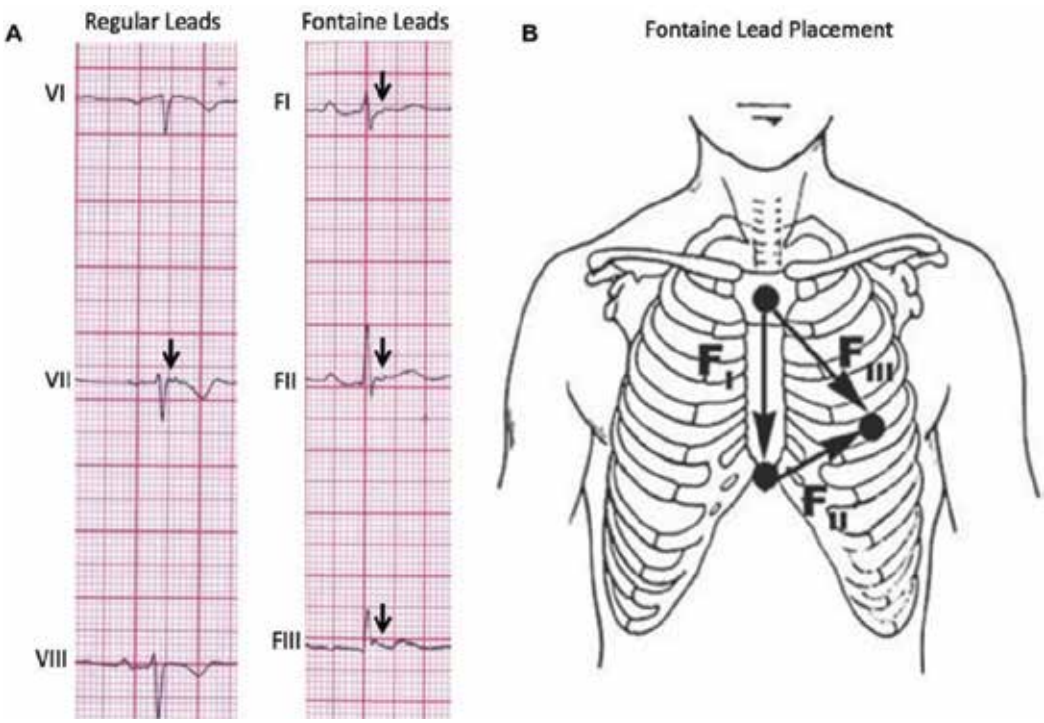

Figure 10. (A) Comparison of regular lead placement versus Fontaine Lead System in the ability to detect Epsilon waves (arrows). Using the Fontaine Lead System increases the sensitivity of detecting Epsilon waves so that they are detected in three leads (FI, FII, FIII) rather than one lead in the regular placement. (B), Fontaine bipolar precordial lead placement. In this modified technique, the ECG should be recorded at double speed (50 mm/s) and double amplification (20 mm/s) to improve the sensitivity for detection of Epsilon waves. (With permission from Dr. Guy Fontaine [32]).

Major
Regional RV akinesia or dyskinesia or dyssynchronous RV contraction and one of the following:
RV EDV/BSA ≥110 mL/m^2 (male) or ≥100 mL/m^2 (female)
RV ejection fraction ≤40%
Minor
Regional RV akinesia or dyskinesia or dyssynchronous RV contraction and 1 of the following:
RV EDV/BSA ≥100 to 110 mL/m^2 (male)or ≥90 to <100 mL/m^2 (female)
RV ejection fraction >40 to ≤45%

Table 2. CMR-based task force criteria for diagnosing ARVC/D.

7. Signal-averaged ECG

SAECG was performed to record late potentials (LPs). LPs provide a substrate for reentry presumably to initiate VT, especially after myocardial infarction. This is why LPs were frequently detected in individuals who are at risk of sustained VT or those affected by coronary artery disease and cardiomyopathy. The detection rate of LP in these patients ranges from 60 to 90%. The potentials detected by SAECG in ARVD have been better defined and systematically reviewed [3, 12, 23]. The prevalence of late potentials varied among ARVD patients ranging from 21 to 100%. SAECG has been performed to record low-amplitude and high-frequency signals in the terminal QRS of ARVD with high sensitivity, showing better correlation between the presence of LPs and the risk of VT as well as the extent of ARVD [3, 20, 35].

There is a direct relationship between SAECG variables and diffuse morphologic abnormalities as well as the regions of fibrous or fatty substitution of RV myocardium, further supporting the predictive value of SAECG for the extent of anatomical damage in individuals affected by ARVD [36, 37]. In addition, several studies were conducted to better define the potential of SAECG to evaluate progression of ARVD by recording LPs [12, 35, 37, 38]. Adults showed a higher prevalence of LPs on SAECG than the young, reflecting the gradually progressive course of ARVD [12, 36, 28]. During 8 years of follow-up conducted by Folino et al., [35] all parameters of SAECG showed a progression consistent with the evolution of LPs, particularly filtered QRS and high-frequency low-amplitude (HFLA) and root-mean-square (RMS).

8. Insertable loop recorder

ILR may constitute a sensitive method to detect Epsilon waves. The recording of Epsilon waves from ILR indicates a higher detection rate in ARVD due to the closer anatomic placement of ILR in relation to the RV than other methods. Recently, two cases of Epsilon waves detected by ILR were presented [28, 39]. In a case of a PKP2-mutation-positive carrier, we demonstrated for the first time the potential of an ILR to record Epsilon waves, absent on S-ECG. ILR displayed recurrent episodes of VT. In addition, fragmented potentials were detected before and after VT, indicating Epsilon waves undetectable by S-ECG (**Figure 11A**, **B**). The detectability of Epsilon waves

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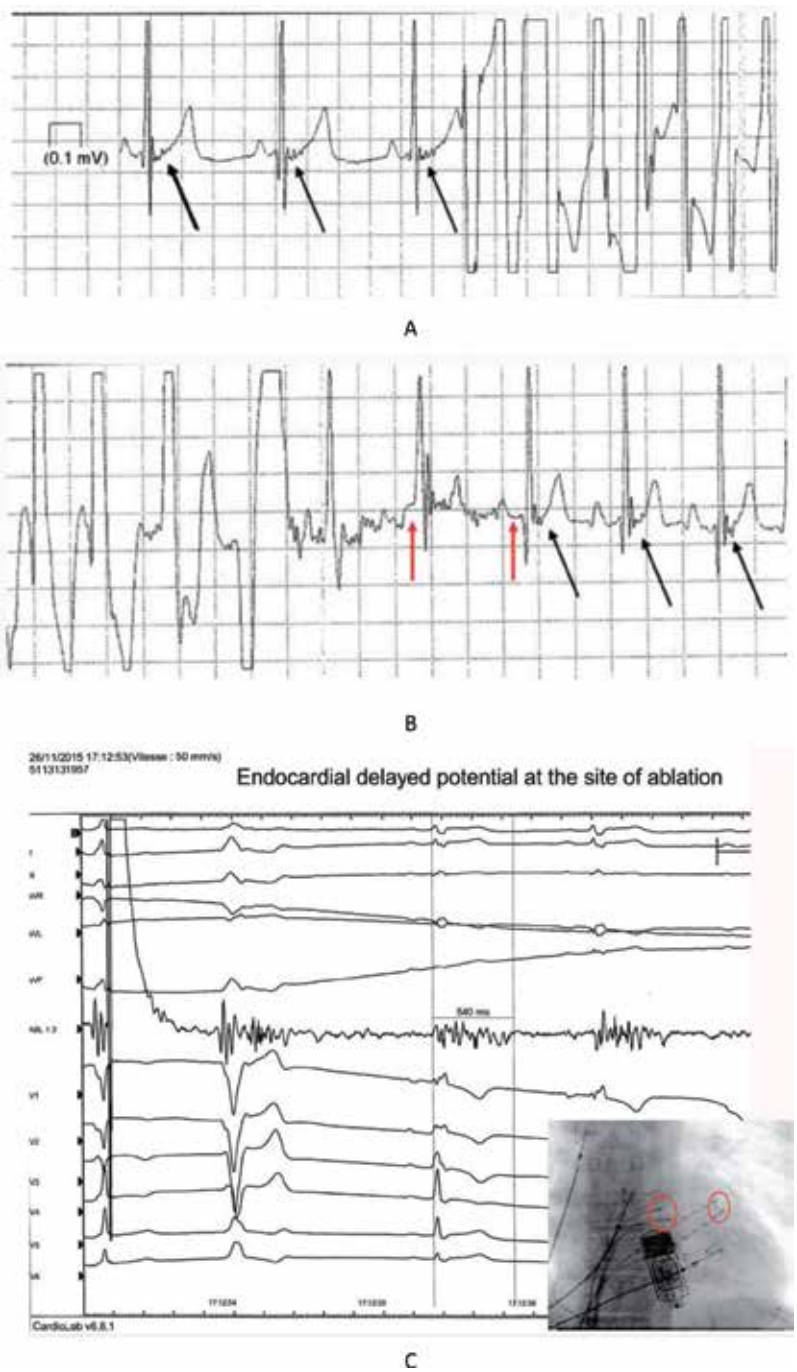

Figure 11. (A) Presence of Epsilon wave in the EGM of the ILR before the onset of VT (B) presence of Epsilon waves after EGM after spontaneous stop of VT (black arrows). Epsilon waves immediately after the VT interruption are able to occupy 80% of the basic cycle. Note that the two PR intervals show no fragmentation (red arrows). (C) Longest endocardial fragmented potentials in the infundibulum and X-ray image recorded during the ablation procedure (double catheter images is X-ray artifact). Position of the inserted loop recorder is close and almost parallel to the sternum. (With permission from Dr. Guy Fontaine [28]).

detected by ILR can be explained by its proximity to the RV free wall (if ILR are implanted in a classical position), where a 540 ms delay in conduction existed (**Figure 11C**). In addition, a host of myocardium encompassed by ILR systems may be another reason. Epsilon waves recorded by this system can help in the diagnosis of ARVD in individuals receiving ILR or similar devices. Recently, we also reported another case of ARVD in which the Epsilon wave is present on the surface ECG, but is also observed on the ILR confirming the previous description [28, 39]. However, a comparison of the potential of ILR to record Epsilon waves and other methods among ARVD individuals is lacking.

9. Combination of various methods

Multiple electrocardiographic recording methods are recommended to improve the potential to record Epsilon waves. Evidence from our and other groups confirmed the variability in distribution of involved regions from patient to patient and even within the same individual during the different stages of ARVD [30, 40]. Therefore, combined electrocardiographic recording methods are able to reinforce one another in the detection of Epsilon waves, especially after catheter ablation was introduced to treat ARVD related VT. The local-contact map in scar regions can clearly record delayed potentials, while Epsilon waves are not always visible upon surface ECG recordings [27, 41–43].

10. Cardiac magnetic resonance

Cardiac magnetic resonance (CMR) plays an important role in the detection of ARVD (**Table 2**). CMR can provide comprehensive information on cardiac morphology, function, and tissue characterization in a single investigation and help the physician toward the correct diagnosis, especially in distinguishing ARVD from other cardiomyopathies. [44, 45] As previously systematically reviewed [44–46], common findings of ARVD by CMR include global reduction in RV function and enlargement of the RV. In the revised TFC, the terms “akinesia,” “dyskinesia” and “dyssynchronous” contraction are used to describe CMR findings.

However, evaluation of cardiac structure and function using CMR is probably not necessary in the absence of baseline electrical abnormalities [47]. In one of the largest clinical studies, the value of CMR was evaluated in a prospective cohort of 69 ARVD mutation carriers without prior sustained ventricular arrhythmias [47]. Te Riele et al. have shown that electrical abnormalities based on their ECG and Holter monitors were more prevalent (61%) than structural changes on CMR (48%). Of note, only 1 (4%) patient without electrical abnormalities at initial evaluation had structural changes on CMR, further suggesting that electrical abnormalities may have occurred long before the development of obvious signals detected by clinical and cardiac imaging tools such as CMR. This lead the authors to conclude that evaluation of cardiac structure and function using CMR is probably not necessary in the absence of baseline electrical abnormalities. Therefore, the optimal strategy is to perform CMR in individuals with baseline electrical abnormalities, especially in those with a history of arrhythmic events,

but deferred use of CMR is recommended in patients with normal ECG and/or 24-h Holter monitoring and transthoracic echocardiography at initial evaluation.

11. Significance and conclusion

ARVD development is a concealed process at the early stage. Most patients during this period present with ECG abnormalities, and there are no validated signals detected by clinical and cardiac imaging tools, indicating that ECG changes may have occurred long before the development of gross wall motion abnormalities. Therefore, it may be important to focus on electrical abnormalities to diagnosis suspected ARVD rather than on structural changes alone. For those with known ARVD, electrical indexes may help evaluating the progressive extent of this disease. In addition, understanding the manifestations on the ECG and the extent of this disease would help assisting in clinical decision-making, namely antiarrhythmic drugs, ICD insertion, and endocardial/epicardial ablation. Over the past four decades of progress since 1977, the contribution of Epsilon waves is increasingly recognized and is always on the list of available ECG markers used as a criterion of ARVD diagnosis. There is emerging evidence that there is a good correlation of Epsilon waves with the extent of ARVD and the risk of arrhythmias. However, the definition of Epsilon waves remains difficult and its value is sometimes controversial though emerging technological methods are introduced to increase the detection rates of Epsilon waves. Therefore, more accurate methods are needed to improve the sensitivity and specificity of Epsilon wave detection. Moreover, prospective, multicenter and collaborative studies are needed to broaden or define the potential of Epsilon waves in the diagnosis and risk stratification of patients with ARVD, particularly in family members, since up to one-third of ARVD first-degree relatives will develop manifest ARVD [48]. Finally, the detection of Epsilon waves with new techniques such as the 16HD-lead ECG system and some other noninvasive markers similar to or better than new CMR sequences (high-resolution T1 mapping or feature tracking) to perform a non-invasive morphological and functional evaluation, as well as to evaluate the risk of arrhythmias and the extent of progression in ARVD are imperative, especially when predominant left ventricular involvement is increasingly recognized. This is a challenge we all face in the present era.

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Conflict of interests

Authors declare no conflict of interests.

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Chapter 5

Takotsubo Syndrome: Still Graveyard of Case Reports?

Gültekin Günhan Demir

Additional information is available at the end of the chapter

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Abstract

Takotsubo syndrome, or previously named as Takotsubo cardiomyopathy, is an increasingly recognized acute reversible form of heart failure, which is typically seen in postmenopausal women following emotional or physical stress. Although several mechanisms regarding pathophysiology had been proposed, the most common ones include catecholamine toxicity, diffuse epicardial coronary artery spasm and microvascular dysfunction. A vast majority of patients with TTS (>90%) have good prognosis as they regain normal left ventricular systolic function in 3–6 months after the acute phase. Increased awareness among physicians led to the recognition of a great number and variety of conditions associated with TTS and played a key role for the development of new diagnostic criteria. However, there are still big gaps in the management and treatment of this syndrome to be supported with further well-designed randomized controlled trials.

Keywords: Takotsubo syndrome, Takotsubo cardiomyopathy, apical ballooning syndrome, brokenheart syndrome, stress cardiomyopathy

1. Introduction

When Sato et al. [1] first described Takotsubo Cardiomyopathy (TTC) 28 years ago, they were probably unaware of carrying out a new area of debates in daily cardiology practice. The name "Takotsubo" was inspired from a Japanese octopus trap used by Japanese fisherman.

To date, more than 75 names were used for description of TTC in the literature with the most commonly used three names include *Takotsubo cardiomyopathy*, *Takotsubo syndrome* and *apical ballooning syndrome* [2]. 'Broken heart syndrome' definition was used in sarcasm to emphasize the close relationship between disease and stressful triggers; however, joyful incidents have also been shown to be associated with TTC thus called 'happy heart syndrome' [3].

Although diagnostic criteria of TTC were described long ago, recent debates focus on definition (rather than treatment) whether this form of heart failure is a cardiomyopathy or a syndrome [4]. Growing body of evidence including diseases, conditions, toxins or drugs associated with Takotsubo Syndrome (TTS) has provided a wide insight into disease pathophysiology. The authors favoring the use of TTS save the idea that patients with TTS suffer severe myocardial ischemia and show most of the indirect signs of ischemia (ECG changes, troponin rise, chest pain and wall motion abnormalities). The mechanism underlying TTS can not be solely explained with ischemia and vascular impairment via contemporary data. Nonetheless, Redfors et al. [5] demonstrated that myocardial perfusion at TTS onset is normal despite increased catecholamine levels. The definition of cardiomyopathy defined as '*myocardial disorder in which the heart muscle is structurally of functionally abnormal in the absence of coronary artery disease, hypertension, valvular disease and congenital heart disease sufficient to explain the observed myocardial abnormality*' qualifies and covers TTS as a cardiomyopathy but several controversial subjects need to addressed such as (1) transient nature of the disease, (2) lack of genetic origin, (3) presence of certain trigger factors, (4) close relationship with catecolamine excess, (5) lack of macroscobic fibrosis or significant necrosis in histopathological examination, (6) presence of intense myocardial edema in the acute phase of TTS. On the other hand, current evidence is not consistent with the authors suggesting classification of TTS in the context of acute coronary syndromes [4].

The most recent comprehensive assessment of TTS was performed in a position statement by European Society of Cardiology (ESC) which suggested the use of TTS definition instead of TTC. Therefore, it makes more sense to use TTS instead of cardiomyopathy in consistence with current data and ESC recommendations. Moreover, they subdivided TTS into primary and secondary forms [6].

The main characteristics of TTC include chest pain associated with ECG changes, which mimic ACS, transient left ventricular systolic dysfunction, modest elevated levels of cardiac troponin and the absence of obstructive coronary artery disease documented by coronary angiography [7].

It is hard to say that increased number and variety of case reports have contributed to a completely clear understanding of this disease. Just think of a disease that can be associated with coronary ischemia, heart failure, arrhythmia, sudden death and also usually transient and in benign nature. When all components of this syndrome are taken into account, a multidisciplinary approach and additional research in the context of etiology, pathophysiology, triggering factors and optimal treatment seem essential for better understanding.

2. Epidemiology

Although the exact incidence of TTs is not known, increasing number of case reports and associated conditions are added into the literature. In an European cohort, TTs were reported to be responsible for 1.7% of admissions for acute coronary syndrome and to have an incidence of

0.3% for all coronary angiographies [8]. Another study investigating the prevalence of TTS in the United States examined more than 33 million hospitalizations and found an incidence of 6837 (0.02%) patients with a diagnosis of TTs [9]. The majority of the patients were aged from 65 to 79 (43.2%) and women (90.4%). Women older than 55 years of age were at nearly fivefold increased risk of developing TTS than women <55 years old [10]. The real prevalence of TTs is assumed to be underestimated owing to lack of widespread access to coronary angiography and detailed postmortem examination of patients with fatal arrhythmias and sudden cardiac death. The International Takotsubo Registry (InterTAK Registry) has been the largest study cohort of patients with TTS which included 1750 cases from 26 centers in Europe and United States [11]. Although full results have not been published yet and contemporary information about the prevalence of TTS was not available, it was interesting to find that 15.3% of patients with TTS had evidence of concomitant coronary artery disease (CAD) in contrast with the common belief that exclusion of CAD is necessary to establish TTS diagnosis.

3. Triggering factors

In contrast with the common belief of close relationship with emotional triggers (broken-heart syndrome), InterTAK registry demonstrated that physical triggers were more common than emotional triggers (36 vs. 27.7%) while the remainder had no obvious triggering factor. Furthermore, physical triggers were found to be an independent predictor for in-hospital complications [3].

The most common emotional triggers include death of a first-degree relative, severe fear or anger episodes, anxiety disorders, financial or legal matters and less frequently (less than 10%) joyful events such as birthday parties or weddings. Physical triggers are events mostly associated with catecolamine surge including cases of stroke, subarachnoid hemorrhage, surgery, malignancy, drug abuse, psychiatric illness, and so on.

History of a neurologic or psychiatric disorder was detected in more than half of the patients with TTS in the InterTAK registry [3]. The same registry also revealed age and the presence of emotional triggers as protective from in-hospital complications. One-third of patients with sub-arachnoid hemorrhage has TTS [12].

4. Pathophysiology

The relationship between triggering factors and TTS naturally caused accusation of catecolamine excess in the pathogenesis of TTS [13]. Although catecolamine excess hypothesis in TTS was supported by several times higher concentrations of plasma catecholamines including epinephrine, norepinephrine and dopamin in the acute phase of TTS when compared with levels in STEMI and also increased local myocardial release of catecholamine, benefit of b-blockers were derived from trials including patients with heart failure rather than patients with TTS [14].

Another evidence favoring the authors suggesting use of 'Takotsubo syndrome' instead of cardiomyopathy definition is the common existence of endothelial dysfunction in patients with TTS. Myocardial ischemia caused by vasospasm which is triggered by stress and increased catecolamines in coronary vasculature with endothelial dysfunction represents a reasonable cascade of pathophysiology underlying TTS. However, further studies are needed to elicit the role of endothelial dysfunction in TTS as just one of the contributing factors or an essential component. Epicardial coronary spasm was demonstrated in only 20% of patients with TTS in two different studies and confirmed by acetylcholine testing in another study [7, 15]. Spontaneous coronary artery dissection and coronary microvascular dysfunction were the other postulated mechanisms responsible for TTS. Reversible coronary microvascular dysfunction was demonstrated by transient improvement in perfusion defects after infusion of intracoronary adenosine and complete recovery 1 month later [15]. In the postmenopausal period, reduced levels of estrogen end up with increased sympathetic tonus and endothelial dysfunction. When combined with age and the common prevalence of classical risk factors for cardiovascular disease in the typical postmenopausal woman patient profile of TTS, additive effect of increased catecholamines (direct toxicity via circulation or nerve terminals), reduced estrogen levels and endothelial dysfunctions should be considered.

The pattern of LV dysfunction in TTS (apical ballooning) was subject to a great number of studies. Increased expression of β_2-adrenoreceptors in apical segments than basal segments of left ventricle was shown in animal studies whereas norepinephrine β_1-adrenoreceptors had reverse distribution. This finding was supported by a rat model treated with high-dose epinephrine bolus (to mimic catecolamine storm) culminating in apical myocardial depression and basal hypercontractile response. Lack of the same response with equivalent bolus of norepinephrine suggested an epinephrine-specific response [5]. Another hypothesis proposes similarities between preconditioning/ischemic stunning and TTS pathogenesis through

Catecholamine excess (toxicity)
Epicardial coronary spasm
Myocardial ischemia
Endothelial dysfunction (±reduced estrogen levels)
Coronary microvascular dysfunction
Obstruction of left ventricular outflow tract
Spotaneous coronary artery dissection
Transient metabolic disorder on the cellular level
Sudden increase in ventricular afterload
Aborted myocardial infarction with spontaneous recanalization
Myocardial bridging and myocardial edema

Table 1. Mechanisms proposed for the pathophysiology of Takotsubo syndrome.

shutting down contractile apparatus in certain segments of LV and maintenance of vital functions [5]. Actually, this mechanism might be favored for mechanisms responsible for recovery process and was supported by a study demonstrating same cell survival signaling pathways of ischemic preconditioned tissue in biopsies obtained from patients with TTS [16]. The authors from the same study also suggested that transient LV outflow tract obstruction (stimulated by isoprenaline—strong adrenergic stimulus) occurs when LV contracts too forcefully and leads to a pressure gradient between the apex and the aorta thus raising wall tension in regions located more apical than the obstruction [5]. Recent studies employed with nuclear medicine techniques suggested that a transient metabolic disorder on the cellular level is responsible for apical ballooning rather than an impairment in myocardial contractile structure which may be associated with interruption of glucose metabolism via coronary microcirculation. A list of proposed mechanisms involved in the pathophysiology of TTS is shown in **Table 1**.

5. Patient evaluation

5.1. History

The most common symptom in patients presenting with TTS is chest pain (75%) as seen in acute coronary syndromes. The nature of the pain is not specific, thus not helpful in differential diagnosis. The following chief symptom is dyspnea (47%). When the high rate (87%) of patients having reduced LV ejection fraction (EF) in the setting of TTS is taken into account, less than half of the patients (47%) presenting with dyspnea may seem relatively low. Nevertheless, this discrepancy is supported by the fact that patients with TTS frequently have a benign course despite losing >50% functional left ventricular myocardium while a patient with ACS faces death in loss of a similar sized portion of LV myocardium [5, 17]. Nonetheless, it should be noted that in-hospital death rates are similar between patients with TTS and ACS. Syncope, cardiac arrest, cardiogenic shock and ventricular arrhythmias are much less common symptoms but should be kept in mind. These symptoms are more likely to occur with less common clinical subtypes other than apical ballooning. Reverse (inverted) TTS was shown to present at a younger age and with fatal ventricular arrhythmias [18].

5.2. Laboratory

Troponin levels are elevated in the vast majority of patients with TTS; however, the severity of elevation is not helpful for discriminating between acute coronary syndromes. Nonetheless, InterTAK registry significant differences in increased troponin levels between patients with TTS and ACS (1.8 vs. 6, $p < 0.001$). A first troponin measurement of more than 10 times of the upper limit of normal level was deemed as a poor prognostic factor. On the other hand, brain natriuretic levels were almost six times higher in patients with TTS than patients with ACS. When compared with ACS, troponin levels in TTS are lower. Acute ventricular insult in left ventricle triggers stretching and release of neuroendocrine peptides such as

brain-natriuretic peptide (BNP). Levels of NT-proBNP were more than twofold higher in patients with TTS than patients with STEMI (4702 vs. 2138 pg/ml, respectively) in a recent study [19].

Several reports investigating the use of other biomarkers in TTS detected elevations in serum catecolamine, neuropeptide, serotonin, carbonhydrate-antigen 125 levels but none of them is preferred in daily practice. Further research is required for established utilization of those biomarkers.

5.3. Electrocardiography

TTS can present with various changes on electrocardiography. Although the most common presentation includes ST-segment elevation and/or T-wave inversion, several new electrocardiographic alterations including QT-prolongation, attenuation of QRS complexes, new bundle-branch blocks or ventricular arrhythmias have been defined [20]. It should be noted that the timing of medical contact is important for detection of ECG changes since it is a pathological process. QT prolongation is one of the distinct features from STEMI; however, differential diagnosis should not be based on ECG basis in particular ST-elevation in TTS. Typical extension of left ventricle dysfunction beyond the vascular territory of a single epicardial coronary artery is one of the key features of TTS.

5.4. Echocardiography

Transthoracic echocardiography is the primary choice of noninvasive imaging method due to its widespread and practical utility for patients with suspected TTS.

TTS with apical involvement is the most common type (82%) followed with mid-ventricular, basal and focal type in decreasing frequency. Typical findings suggesting TTS include regional wall motion abnormality (mostly apical akinesia and basal hyperkinesia) extending beyond the territory of a certain epicardial coronary artery. End-diastolic diameter measured from the mid-ventricular plane is increased and measurement of EF is usually under 45%. Sudden insult in LV systolic function often leads to mitral regurgitation. Imbalance of wall pressure between akinetic and hyperkinetic segments within the cavity might develop left ventricle outflow tract obstruction (pressure gradient, acceleration of blood flow) in some patients.

Follow-up of patients with TTC by serial echocardiographic examinations demonstrated noticeable recovery in systolic left ventricular function. Naturally, a LVEF <45% is a predictor of a worse prognosis [6, 20].

5.5. Cardiac magnetic resonance imaging

When the clinical presentation of TTS in the acute phase is considered, cardiac magnetic resonance imaging (cMRI) is not suitable for initial evaluation. After documentation of normal or near-normal coronary arteries with coronary angiography, cMRI is the preferred imaging method for its complementary data about three-dimensional LV and RV

anatomy,documentation of regional wall motion abnormality thus TTS subtypes (apical, mid-ventricular, inverted or focal). Diffuse myocardial edema is typically present in both myocarditis and TTS; however, lack of late gadolinium enhancement in TTS is helpful for differential diagnosis from both acute coronary syndrome an acute myocarditis. Though not standard, common practice for timing of cMRI is within 7 days after the index event and 2–6 months later for assessment of improvement in systolic functions [19].

5.6. Coronary angiography

Presentation of patients with chest pain and frequently ST-elevation leads the patients undergo coronary angiography even though TTS is not the diagnosis in the first place. Detection of normal or near-normal coronary arteries should suggest TTS and the operator should perform left ventriculography for the typical appearance of left ventricular apical ballooning.

Similarly, a great portion of patients with TTS (93%) had increased LV end-diastolic pressure (>11 mm) on angiography in the InterTAK registry.

Mayo Clinical criteria included normal or near-normal coronary angiography for establishment of TTS diagnosis; however, InterTAK registry documented by coronary angiography that coronary artery disease was present in 15% of patients with TTS. Coronary angiography remains to be the major method for distinguishing TTS from ACS in spite of increasing non-invasive modalities.

5.7. Diagnosis

Although a definition accepted worldwide does not exist, the most common one used for a long time in daily practice and research area included The Mayo Clinic diagnostic criteria which were modified in 2008; (1) transient hypokinesis, akinesis, or dyskinesis of the left ventricular mid-segments with or without apical involvement; the regional wall motion abnormalities extend beyond a single epicardial vascular distribution; a stressful trigger is often, but not always present; (2) the absence of obstructive coronary disease or angiographic evidence of acute plaque rupture; (3) new electrocardiographic abnormalities (either ST-segment elevation and/or T-wave inversion) or modest elevation in cardiac troponins; (4) the absence of pheocromocytoma or myocarditis. In 2016, a position statement on TTS published by European Heart Failure Association (EHFA) taskforce updated diagnostic criteria as shown in **Table 2** [6].

Addition of 'reversible' expression for ECG abnormalities and QTc prolongation, replacement of mild with significant for elevation of serum natriuretic peptides, removal of exclusion of pheochromocytoma and addition of recovery of ventricular function in 3–6 months are the first noticeable changes in the EHFA criteria.

Unlike the post-menopausal women profile of classical type, reverse type was shown to be significantly associated with younger age and mental or physical stress rather than catecolamine excess [11, 18]. Of note, death was more common in men than women with TTS [11].

(1) Transient regional wall motion abnormalities of LV (or RV) myocardium which are frequently but not always preceded by stressful trigger (emotional or physical)
(2) The regional wall motion abnormality usually (exceptions reported) extends beyond a single epicardial vascular distribution and often results in circumferential dysfunction of the ventricular segment involved
(3) New and reversible ECG abnormalities (ST segment elevation, ST depression, LBBB, T wave inversion and/or QTc prolongation in acute phase)
(4) Significant elevation of serum natriuretic peptide (BNP or NT-proBNP) during acute phase.
(5) Positive but relatively small elevation of cardiac troponin measured with a conventional assay (troponinnegative cases have been reported)
(6) Absence of culprit atherosclerotic disease including plaque rupture, thrombus formation and coronary dissection or other pathological conditions to explain the pattern of temporary LV Dysfunction,for example, hypertrophic cardiomyopathy, viral myocarditis, and so on
(7) Recovery of ventricular function on cardiac imaging on follow-up (3–6 months).

Table 2. European heart failure association (EHFA) taskforce updated diagnostic criteria.

6. Natural history

Although TTC is assumed to have a benign course in general, InterTAK registry reported the rate of death as 5.6% per patient-year. Patients with TTC may develop recurrence even after years [11]. Furthermore, the rate of serious in-hospital complications (21%) similar to that in ACS should make us question the commonly recognized benign course of the study. The rate of major adverse cardiac and cerebrovascular events including death, stroke/TIA in the first month of admission was 7.1%. Major complications include acute heart failure and cardiogenic shock, LV outflow tract obstruction, severe mitral regurgitation, fatal ventricular arrhythmias, thrombus in the akinetic segments of the ventricle. Predictors of poor prognosis include LV EF < 35%, RV involvement, QTc > 500 ms, BNP > 600 pg/ml, age < 75 years, cardiogenic shock and ventricular arrhythmias. Nevertheless, the prognosis is good for more than 90% of the patients as they regain normal systolic function in 3–6 months after the acute episode [19, 21].

6.1. Treatment

There are no randomized controlled trials to evaluate the efficacy of a certain treatment but retrospective analysis of outcomes reveals improved survival at 1 year with the use of angiotensin-converting-enzyme inhibitors or angiontensin-receptor blockers. Current approach includes a combination of evidence-based acute coronary syndrome and heart failure treatments [6]. Interestingly, in spite of either the ascribed role of catecolamine excess in the pathophysiology of TTC and the left ventricular systolic dysfunction, beta-blocker use was not associated with improved mortality at 1 year. However, retrospective and observational nature of the analysis should always be kept in mind, and further studies with prospective design are needed to obtain more accurate and reliable results. Symptoms of heart failure

must be closely monitored and treated and also the physician should be alert for ventricular arrhythmias during the acute phase. The risk tends to incline in time but is always present until complete recovery of LV systolic function [6].

Treatment of the patients should be categorized in two titles under acute phase and follow-up period. The risk is the highest in the acute phase so the patients should be monitored in coronary care unit with the capabilities of urgent coronary angiography, temporary and permanent pacemaker implantation, ventricular arrhythmia management and advanced heart failure therapy including LV assist devices and extra-corporeal membrane oxygenation (ECMO). In patients with cardiogenic shock, sympathomimetic agents should be avoided. Levosimendan might be a useful option in cardiogenic shock despite limited evidence [22]. Standard heart failure therapy should be implemented in patients with signs of congestion. In a series of 93 patients with TTS, incidence of ventricular fibrillation or Torsades de Pointes (TdP) was 8.6% [23]. Prolongation of QTc > 500 ms is commonly seen in patients with low heart rates, so temporary pacemaker may be life-saving for TdP episodes. Hypomagnesemia and hypokalemia should be checked and corrected as well [19]. ICD therapy should be reserved for patients without recovery of LV systolic function or recurrent ventricular arrhythmias. Notably, wearable defibrillators might be a good option during the acute phase.

During the follow-up period, more than 90% of the patients regain normal LV systolic function in 4–8 weeks. InterTAK registry found recurrence rate as 1.8% per year [3]. In order to prevent recurrences, beta-blockers were the most studied group with ACE inhibitors. In a recent meta-analysis by Brunetti et al. none of the therapies including beta-blockers, ACE inhibitors, angiotensin-receptor blockers, aspirin and statins were found effective in the prevention of recurrence of TTS [24]. Another recent regression meta-analysis found ACEI useful for prevention of recurrence [25]. Randomized controlled trials are awaited for more accurate and definitive results.

7. Future directions

Associated conditions helped better understanding of the mechanisms underlying TTS; however, mechanisms playing role in the recovery process remain largely elusive. It is obvious that randomized-controlled studies are needed to have a more clear aspect for standard therapy. The role of estrogen and progesterone in the pathophysiology of TTS should be addressed by basic scientists and clinicians. Optimal timing and treatment of patients suffering ventricular arrhythmias with ICD (subcutaneous/wearable defibrillator) is not clear and well-studied. The pathogenesis and treatment of TTS are still speculative and the risks of complications in the acute phase are underestimated. Given the variety of associated conditions and increased number of case reports, international data collection by registries like InterTAK registry should be employed and shared for a better understanding and optimal treatment.

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Chapter 6

Isolated Form of Left Ventricular Non-compaction Cardiomyopathy (LVNC) as a Rare Cause of Heart Failure

Skopoulis Sotiris

Additional information is available at the end of the chapter

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Abstract

Non-compaction cardiomyopathy (LVNC) is a rare, hereditary disease manifested by heart failure, thromboembolic complications and arrhythmias, which can even result in a sudden cardiac arrest. This disease is often misdiagnosed as dilated or ischemic cardiomyopathy, apical hypertrophic cardiomyopathy, or other myocardial infiltrative processes, including tumours. Due to its potentially severe complications and outcomes it should be always considered as a part of differential diagnosis.

Keywords: non-compaction cardiomyopathy, heart failure, trabecularisation, echocardiography, cardiomyopathy

1. Introduction

Non-compaction cardiomyopathy (LVNC) is a rare, hereditary disease. It is believed that develops due to a defect during embryogenesis of endocardium and myocardium. In 1996 LVNC was categorised as non-classified cardiomyopathy according to the WHO classification of cardiomyopathy.

A typical image of LVNC is thickening of the apical wall in the left ventricle due to increased trabecularisation and occurrence of deep inter-trabecular recesses communicating with the left ventricle. Dilation and/or systolic dysfunction of the left ventricle (LV) is usually present [1].

The disease may manifest as an isolated myocardial disorder (an isolated form of LVNC) or in relation with congenital heart defects, such as pulmonary atresia, defects in the atrial

and ventricular septum, obstructions of the outflow tract of the left or right ventricle or Ebstein's anomaly.

2. Prevalence

The actual LVNC prevalence value is difficult to determine, because the frequency of its occurrence significantly differs in relation to the studied population.

Based on 14-year reviewing of results of echocardiographic examinations of patients, one of the available studies described 34 patients with LVNC in total, which represented prevalence of 0.014%. A different clinical study diagnosed in the course of 4.5 years 57 patients with LVNC with use of echocardiographic criteria and prevalence reached 0.14% [2, 3].

The normal value of prevalence according to other studies ranges between 0.05 and 0.24% [3, 4].

In children with LVNC it represents the third most frequent cardiomyopathy and approximately 9% of all cardiomyopathies [5].

The age of clinical manifestation of the disease symptoms is very variable—at least two cases were described in the bibliography where the diagnosis was already established in utero [6]. The oldest patient with LVNC was aged 94 when diagnosed [7, 8].

3. Genetics

It is not easy to explain the genetic base for the phenotype expression of LVNC, because cases of both hereditary and also sporadic forms of this disease have been described. It seems that their occurrence in childhood is related to a pronounced genetic base, which cannot be said with certainty, as concerns its occurrence in adulthood. The genes associated with the occurrence of LVNC include tafazzin, beta-dystrobrevin (DTNA), Cypher/ZASP (LDB3), lamin A/C (LMNA), SCN5A, MYH7, and MYBPC3 [9–12].

Although it is obvious that further extensive investigation is needed to describe the genetic base of this disease in detail, we may already conclude with certainty that a certain genetic heterogeneity is needed.

The percentage of cases of hereditary forms of LVNC in three large groups of patients reached 18, 25, and 33% [8, 13, 14].

Heredity of this disease is usually autosomal and dominant with incomplete penetration. LVNC with a defective gene for G4.5 that causes gonosomal hereditary Barth syndrome (dilation cardiomyopathy or LVNC in men with symptoms from childhood accompanied with neutropenia, lactic acidosis and abnormalities in lipid metabolism is an exception [15, 16].

Even though routine genetic testing of patients has not been currently recommended, according to the procedures advised by HFSA (Heart Failure Society of America) detail investigation

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of the history of at least three family generations and cardiological examination of the patient's direct relatives with established LVNC is clearly recommended with regard to its prevailing occurrence in the family [17].

The benefits of screening genetic testing of all direct relatives of the patient with LVNC must also be considered in the future.

4. Embryology, histology

In the course of embryogenesis before development of coronary veins myocardium is made of a free network of intertwined trabeculae and deep recesses. Coronary vessels develop between the 5th and 8th week of intrauterine life and gradual connection of myocardial trabeculae occurs under regular conditions until the compact myocardial layer starts to prevail over the spongeous layer [9]. This process runs quite fast between the 10th and 12th week of the embryonic development and proceeds from the left ventricular base towards the apex and from epicardium to endocardium, while the left ventricular myocardium is more compact then the right ventricular myocardium, which stays more trabecularised also in adulthood.

It is currently anticipated that LVNC occurs due to a disordered myocardium compaction in the course of embryogenesis that is most frequently caused due to mutation of sarcomere proteins, which leads in excessive myocardial trabecularisation that is usually localised on the apex of left ventricle and apical segments of the lateral and inferior wall [10, 11].

Anatomic criteria for determination of the LVNC diagnosis according to Burke et al. include: (1) absence of normally formed papillary muscles in the left ventricle, (2) the proportion of the overall thickness of the left ventricular wall and the layer of compact myocardium exceeds two [18].

The histochemical image is usually dominated with endocardial thickening, endocardial fibrosis to endocardial fibroelastosis, deep intertrabecular recesses and focuses of interstitial fibrosis or even microinfarctions.

5. Clinical manifestation and treatment of the disease

The onset of clinical manifestation of the symptoms in patients with an isolated form of LVNC is variable; many patients remain asymptomatic for years, while some individuals show development of the symptoms since early childhood [19].

In asymptomatic patients, the diagnosis is established during a preventive echocardiographic examination or as consequence of targeted screening due to a positive family history.

The main clinical manifestation of LVNC is left-sided heart failure that most frequently manifests with dyspnoea, stenocardia, palpitation or syncope. Other manifestations of the disease include ventricular arrhythmias and subsequent sudden cardiac death. Thromboembolic complications are frequent.

Men are affected more frequently than women [8].

Standard cardiac failure treatment procedures are applied in the case of left ventricular heart insufficiency, mainly beta-blockers, ACE inhibitors and diuretics. Aldosterone inhibitors, digoxin and vasodilators can also be used in the therapy.

Upon occurrence of ventricular arrhythmia, specifically non-sustained ventricular tachycardia, without significant LV dysfunction, treatment with beta-blockers or amiodarone is indicated. ICD implantation should be considered in patients with obvious sustained ventricular tachycardia, inexplicable syncope or in patients with left ventricular EF under 35% persisting despite adequate therapy, as a primary prevention of sudden cardiac death.

Benefit of resynchronisation therapy has been described in a group of patients with LVNC [20].

Stollberger et al. describe improvement of the systolic function in the left ventricle in the course regular control echocardiography (reduced creation of trabecularisation and improvement in the myocardial compaction) in a number of patients with LVNC after bi-ventricular pacing (follow up programme for the period of 4–68 months) [21].

In the case of patients with end stage heart failure despite adequate pharmacotherapy, the use of mechanical heart support or enlisting in a transplantation programme must be considered. Patients with dilation and significant left ventricular dysfunction are advised to use permanent anticoagulation treatment as a prevention of embolic complications [1, 8].

6. Diagnostics

The currently used diagnostic standard comprises a proper obtainment of family history for the last three generations, an echocardiographic examination and magnetic resonance of the heart.

In most of the patients ***ECG*** is manifested with non-specific changes of repolarization, bundle branch blocks and various degrees of AV blocks [1].

However, the basic diagnostic method for LVNC is ***echocardiography***. A typical echocardiographic examination of LVNC describes a "layered" picture of myocardium made of a thin outer compact layer and a strong trabecularised non-compact endocardial layer with frequent deep intertrabecular recesses that are usually localised in the apical area under the level of papillary muscles and adjacent segments of the lateral and inferior walls [22–24].

In 2001, Jenni et al. proposed criteria based on an end systolic ratio of non-compacted to compacted layers above two. Segments involved are mid ventricular (especially inferior and lateral ones) and apical [25, 26].

A number of authors believe that the current diagnostic criteria have an excessively high sensitiveness, which may cause overestimation of the LVNC prevalence [19].

Finsterer and Stollberger [27] proposed fusion of diagnostic criteria according to Jenni and Stollberger with subsequent classification in the following categories:

1. LVNC diagnosis is possible;

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2. LVNC diagnosis is probable;

3. LVNC diagnosis is definitive.

according to the number of shown characteristics.

In 2008 Belanger et al. proposed a new scheme classifying LVNC as a non-probable, moderate, rather significant and serious disease on the basis of the numerical value of the NC/C Index (ratio of the non-compact layer to the compact layer) of 0, 1, 2 and more than 2. Another criterion should include the size of the area suffering from non-compaction [28].

3D echocardiography or magnetic resonance of the heart (CMR) are methods that may be used if the patient is not easily examinable upon a regular echocardiographic examination, mainly due to inability to visualise the apex of the heart. The criterion to determine the LVNC diagnosis comprises the ratio of non-compact myocardial layer (NC/C Index or NC/C Ratio) exceeding 2.3 during diastole, which distinguishes pathological non-compaction with sensitivity values of 86%, specificity of 99%, positive prediction of 75% and negative prediction of 75% [29].

Computer tomography (CT and CT angiography) is used less frequently in LVNC diagnostics; it enables displaying of coronary vessels and also the associated congenital anomalies (e.g. stenosis or pulmonary atresia).

Contrast left-sided ventriculography shows typical deep recessions and spongeous appearance of the cavity [16].

7. Prognosis

Prognosis for the patients with LVNC differs; almost 60% of the patients described in one of the multicentral studies either died or underwent a heart transplantation within 6 years from establishment of the diagnose [4].

Mortality in the subsequent series of adult patients with LVNC reached 35% during 44 months of monitoring and half of them died suddenly [13].

8. Case report

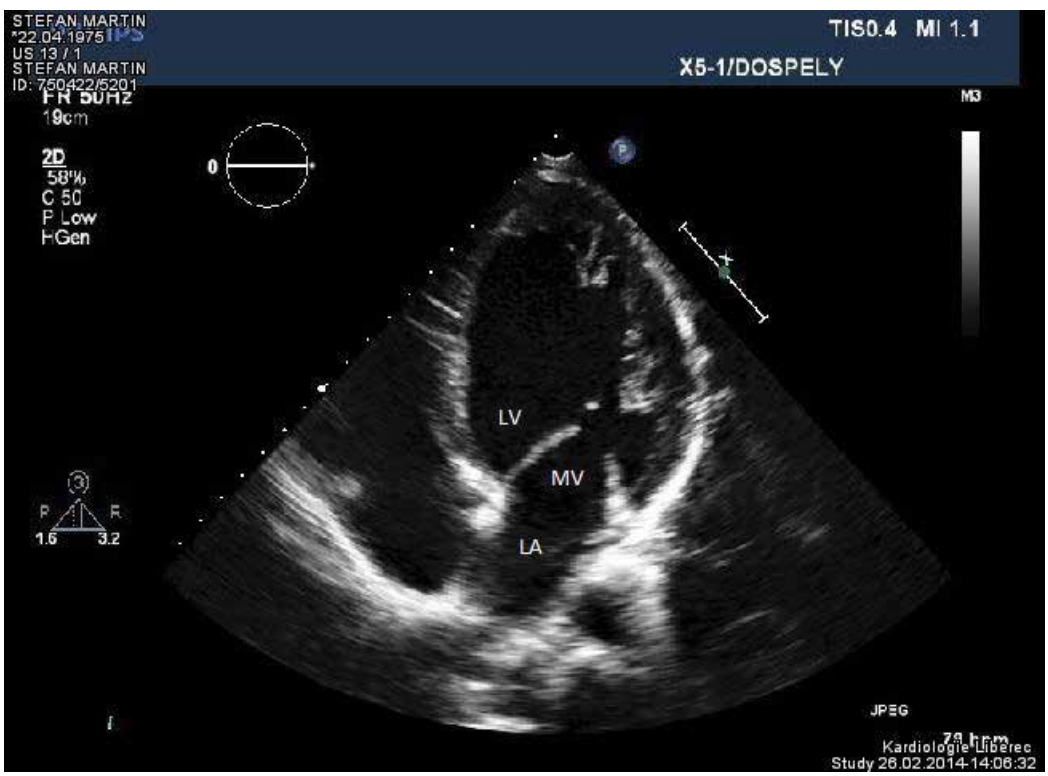
Case of a patient aged 39 that has not been treated so far and was examined at an acute cardiological outpatient office of the district hospital for exertional dyspnoea lasting for already 2 months, functionally according to NYHA (New York Heart Association) classified in grade 3 and oedemas on lower limbs lasting for 3 years. Physical examination showed blood pressure (170/110 mmHg), hepatomegaly and bilateral perimalleolar oedemas. ECG at the admission also described a mild sinus tachycardia, P pulmonale in leads II, III, and aVF, descendent depression of ST sections with a negative T wave in leads II, III, and aVF. Laboratory examination revealed only a slight elevation of cardiac markers without dynamic change corresponding to an acute coronary syndrome, an elevation of natriuretic peptide type B, and a slight elevation of liver enzymes. In the course of hospitalisation was performed transthoracic

echocardiography examination (**Pictures 1** and **2**) and transesophageal echocardiographic examination (**Picture 3**). Both showed severe systolic dysfunction of the remodelled LV with EF of 20%, global hypokinesis, trabecularisation of the left ventricle, a mobile thrombus in LV and severe systolic dysfunction of dilated RV.

Coronary angiography only showed non-significant atherosclerosis of the coronary vessels.

Magnetic heart resonance was carried out electively and confirmed echocardiographic examination findings. The examination confirmed severe systolic LV dysfunction with EF of 16%, significant global LV hypokinesia, visible LV trabecularisation, a fluttering thrombus between trabeculae in the central LV segment, dilation of the left atrium and right-sided chambers (**Picture 4**).

Heart failure therapy was immediately initiated. Anticoagulation therapy was added. It led to a prompt improvement of the clinical condition. Despite the adequate therapy an improvement of the systolic function of the left ventricle was not observed. The patient was referred as a candidate of ICD implantation for primary prevention of sudden cardiac death and was also enlisted as a candidate for heart transplantation.



Picture 1. 2D echocardiography: apical four-cavity projection. Significant trabecularisation of spherically remodelled left ventricle in different projections.

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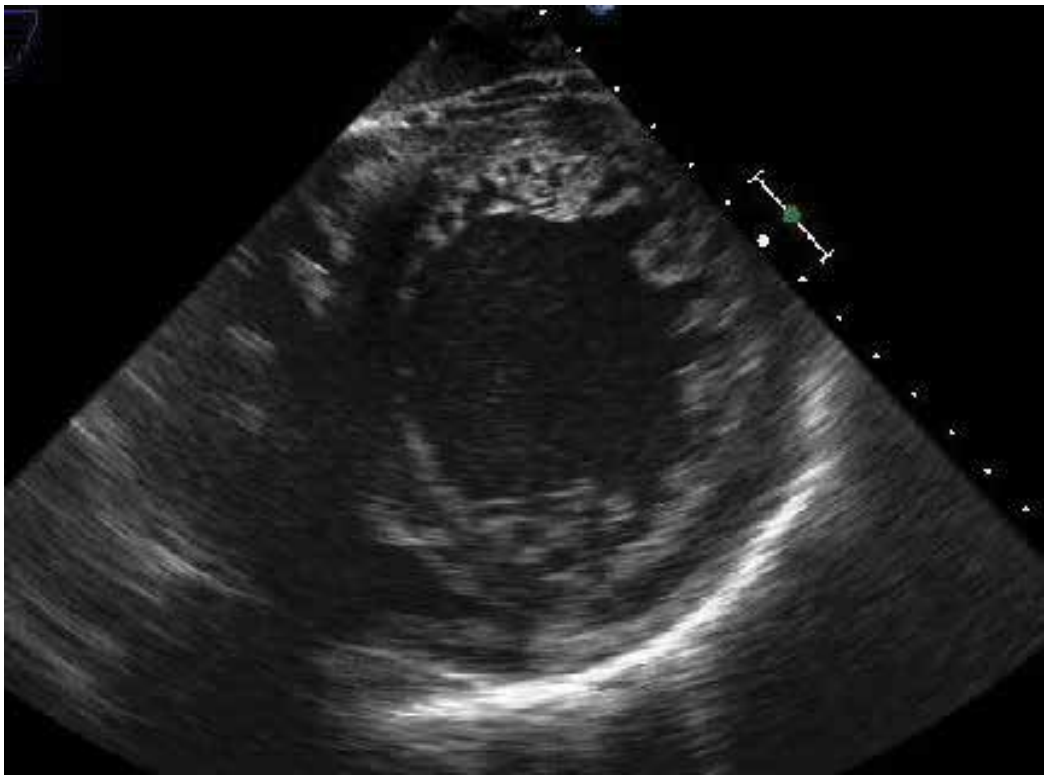
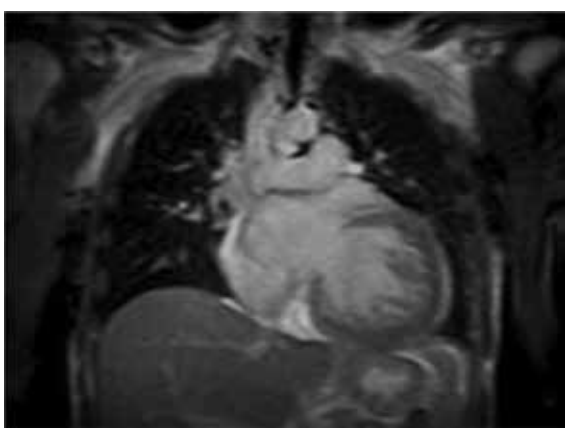
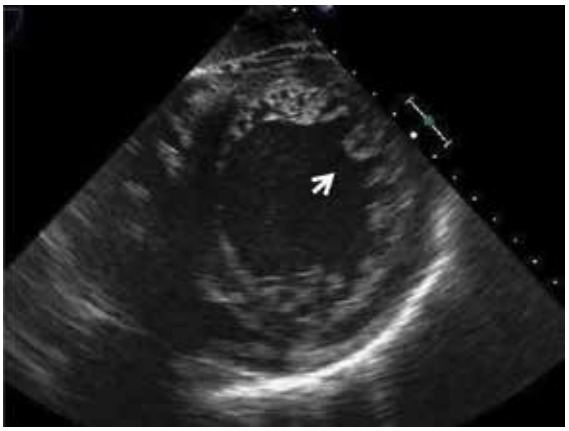


Picture 2. 2D echocardiography from parasternal short axis. Significant trabecularisation of spherically remodelled left ventricle in different projections.



Picture 3. Transesophageal echocardiography with a typical finding of trabecularised dysfunctional LV and dilation of the left atrium.



Picture 4. MRI scan. CMR scan supporting the standard echocardiographic examination findings.

9. Conclusion

Occurrence of LVNC is rare, nevertheless due to its potentially severe complications and outcomes it should be always considered as a part of differential diagnosis.

The goal for the future is to collect as much data as possible concerning the clinical course of the disease, its genetic background, diagnostics, and treatment. This strategy may positively influence interpretation of genotype-phenotype correlation, the epidemiology of the disease and clinical management.

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Chapter 7

Ischemic Cardiomyopathy: Contemporary Clinical Management

Burhan Sheikh Alkar, Gustav Mattsson and Peter Magnusson

Additional information is available at the end of the chapter

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Abstract

Ischemic cardiomyopathy, disease of the heart muscle due to coronary artery disease, is the most common cardiomyopathy. It is often difficult to discern the etiology of heart failure, and often there are multiple underlying causes. Ischemic cardiomyopathy most often presents with a dilated morphology with wall motion defects and a history of previous myocardial infarction or confirmed coronary artery disease. Mechanisms of myocardial depression in ischemia are necrosis of myocardial cells resulting in irreversible loss of function or reversible damage, either short term through myocardial stunning or long term through hibernation. In ischemic cardiomyopathy, echocardiography may be extended with stress testing or other imaging modalities such as myocardial scintigraphy and cardiac magnetic resonance tomography. Coronary angiography is often considered a gold standard; however, other modalities such as positron emission tomography can be needed to detect small vessel disease. Cardiac revascularization, through percutaneous coronary intervention and coronary artery bypass grafting, both in acute coronary syndrome and in stable coronary artery disease, relieves symptoms and improves prognosis. Therapy should aspire to treat ischemia, arrhythmias in addition to heart failure management, which includes device therapy with cardiac resynchronization therapy, implantable cardioverter defibrillators, and mechanical support as bridging or destination therapy in end-stage disease.

Keywords: cardiomyopathy, coronary artery disease, heart failure, ischemic, myocardial infarction

1. Introduction

Disease of the heart muscle, cardiomyopathy, appears in various disease manifestations, which are often either poorly defined or difficult to distinguish in clinical practice. Despite

these shortcomings, it is important to determine the underlying etiology of cardiomyopathy, both for evidenced-based clinical practice and for research purposes. This chapter offers a definition of ischemic cardiomyopathy, the most common form of heart failure, as well as describes its epidemiology, pathophysiology, diagnosis, evaluation, and treatment. It aims to facilitate for clinicians who treat patients with ischemic cardiomyopathy, researchers, and other professionals with an interest in the field and also patients and their relatives.

1.1. Definition

The term ischemic cardiomyopathy describes a state of left ventricular systolic dysfunction due to coronary artery disease [1]. However, both European and American guidelines refer to the concept of cardiomyopathy as a primary heart muscle disease rather than the acquired forms of heart disease [2, 3]. Clinically, and for definitions in numerous scientific studies, patients with heart failure attributed to ischemic etiology are labeled as having ischemic cardiomyopathy. Thus, a heart failure patient with a history of myocardial infarction and evidence of coronary artery disease from imaging tools or functional tests is said to have an ischemic etiology. In practice, the etiology in an individual patient is not always clearly discernable. Patients with heart failure and no coronary artery disease may have angina/wall motion abnormalities [4]. On the other hand, severe coronary artery disease does not necessarily imply symptoms, myocardial infarction, or heart failure [1]. Even with information from an invasive coronary angiography when evaluating heart failure, the etiology is not always unambiguous. In science, the same overlap between an ischemic cause and other contributing causes frequently occur; heart failure may be complicated by hypertension, diabetes mellitus, valvular disease, and other factors that may interplay [5]. Nevertheless, it is important to interpret subgroup analyses with this in mind as it may explain inconsistency between studies. It has been proposed that patients with single-vessel disease should be classified as having nonischemic cardiomyopathy [1]. Typically, patients with ischemic cardiomyopathy include those with reduced ejection fraction with a cutoff at 35–40%, although this is also somewhat arbitrary [1, 6]. The boundaries between ischemic, nonischemic, and mixed dilated cardiomyopathy are worth taking into account depending on the context [7].

1.2. Epidemiology

Ischemic cardiomyopathy is common, and it is increasing worldwide based on risk factors for coronary artery disease becoming more prevalent. According to the World Health Organization (WHO), ischemic heart disease is considered the most common cause of death worldwide, and cardiovascular heart disease, which is predominantly coronary artery disease, claims a global death toll of 17.7 million every year, comprising 31% of all deaths [8]. More than three quarters of cardiovascular deaths come from low- and middle-income countries [9]. Furthermore, coronary artery disease is considered the most common cause of heart failure which affects 1–2% of the general population and 10% of people aged 70 years or more [10]. The risk of having heart failure diagnosed during the remaining lifetime at an age of 55 years is higher for men (33%) than women (28%) [11]. Etiological causes of heart failure are diverse, but the ischemic component is considered to be the largest contributor. Ischemic

heart disease includes myocardial scar, stunning/hibernating myocardium, epicardial coronary artery disease, abnormal coronary microcirculation, and endothelial dysfunction [6]. The incidence of ischemic cardiomyopathy is likely to increase globally over the coming decades.

1.3. Pathophysiology

The pathophysiology consists of two major mechanisms: reversible and irreversible damage of the myocardium that results in reduced myocardial function and cardiac output, with progression into a dilated phase. This myocardial damage is typically caused mainly by atherosclerosis of coronary arteries that result in reduced perfusion of cardiac muscle tissue, which clinically presents as acute coronary syndromes: ST-segment elevation myocardial infarction (STEMI), non-ST-segment elevation myocardial infarction (NSTEMI), and unstable angina pectoris. Both STEMI and NSTEMI are characterized by the presence of necrosis of the myocardium and elevated cardiac biomarkers, whereas unstable angina is characterized by myocardial ischemia without necrosis of myocardial cells; however, all forms of myocardial ischemia can cause impaired myocardial function and ischemic cardiomyopathy. Prompt revascularization restores parts of viable myocardium, whereas other parts undergo necrosis and are thus irreversibly damaged. The transient myocardial depression during acute coronary syndrome is referred as stunning. Long-lasting but potentially reversible ischemic depression is described as hibernating myocardium. Hibernation and stunning are interchangeable when it occurs from repetitive temporary ischemic triggers [12]. This is important to recognize as triggers may be managed, and successful revascularization in conjunction with an optimal pharmaceutical approach may improve ejection fraction. From this perspective ischemic cardiomyopathy is a dynamic disease. It does not necessarily lead to deterioration and clinical improvement is possible. Occlusion of a coronary artery causes a localized myocardial injury in areas of reduced perfusion, whereas global coronary artery disease may lead to diffuse myocardial injury. Both global and localized myocardial impairments constitute components of ischemic cardiomyopathy.

1.3.1. Coronary artery disease

Coronary artery disease is a consequence of atherosclerosis, which is attributed to many risk factors. Increasing age and male sex independently imply higher risk. The majority of risk factors are modifiable. In the international study INTERHEART, several risk factors for myocardial infarction were identified [13]. In this study, moderate amount of alcohol was beneficial, especially in women, but these results should be interpreted with caution:

- ApoB/ApoA1 ratio
- Smoking
- Diabetes mellitus
- Physical inactivity
- Psychosocial risk factors
- Abdominal obesity

- Hypertension
- Diet (less fruit/vegetables)

There is a strong age-related increase of atherosclerosis and myocardial infarction. Approximately 4% of the population, aged 75–84 years, suffers from symptomatic coronary disease [14]. There is a strong link between angina and risk of coronary artery disease mortality on a group level [14, 15]. Hypertension has been demonstrated to be causally linked to coronary artery disease [16]. Hypercholesterolemia is a major pathway to manifest coronary disease, and clinical events have been shown in this group in several studies over decades [16–19]. Diabetic patients have an approximately threefold risk of myocardial infarction based on increased risk of coronary artery disease [20]. Smoking is a risk factor because of its vascular damaging effects [21]. Obesity and lifestyle factors, such as physical inactivity, also constitute risk factors [22]. Family history is complex but is an independent risk factor for coronary artery disease [23]. These factors, often in combination, may lead to multivessel disease; ischemic cardiomyopathy patients have more proximal locations of stenoses, greater lumen loss lesions and thus more extensive ischemic burden, and severe clinical manifestation with reduced working capacity [24].

2. Symptoms and signs

Ischemic cardiomyopathy patients present with the same general symptoms that are common in heart failure regardless of etiology. Typical symptoms of ischemic cardiomyopathy are breathlessness, orthopnea, exercise intolerance, fatigue, ankle swelling, less typically nocturnal cough, wheezing, bloated feeling, loss of appetite, confusion, palpitations, dizziness, and syncope. Symptoms are often accompanied by signs such as elevated jugular venous pressure, hepatojugular reflux, third heart sound (gallop rhythm), and laterally apical chamber impulse. There may also be less specific signs: weight gain due to fluid retention but also weight loss and cachexia in advanced heart failure, hepatomegaly, ascites, cold extremities, oliguria, and crepitations at pulmonary auscultation [6]. The first presentation might be as acute coronary syndrome, arrhythmias (atrial/ventricular tachycardia or bradycardia), or thromboembolic complications of left ventricular thrombus/atrial fibrillation after myocardial infarction such as stroke or systemic thromboembolism. Psychiatric symptoms such as depression and anxiety are common as a consequence of the mentioned symptoms and signs [25].

2.1. NYHA functional classification

The New York Heart Association (NYHA) Functional Classification is frequently used to classify heart failure into four categories according to the severity of symptoms [26]:

- NYHA Class I: asymptomatic.

  No limitation in physical activity despite the presence of heart disease. This can be suspected only if there is a history of heart disease, which is confirmed by investigations, for example, echocardiography.

- NYHA Class II: mild.

  Slight limitation in physical activity, more strenuous activity, causes shortness of breath, for example, walking on steep inclines or several flights of steps. Patients in this group can continue to have an almost normal lifestyle and employment.

- NYHA Class III: moderate.

  More marked limitation of activity that interferes with work. Walking on flat ground produces symptoms.

- NYHA Class IV: severe.

  Unable to carry out any physical activity without symptoms, patients are breathless at rest and mostly housebound [26].

3. Diagnosis

History taking and physical examination remain important, but laboratory tests and cardiac imaging are today a key part of diagnosis and management of ischemic cardiomyopathy.

3.1. History

Assessment of risk factors for atherosclerosis and cardiovascular disease is an important part of the history and can support clinicians by enabling the classification of patients into three categories, low-, intermediate-, and high-risk groups, and thus aid in the selection of appropriate testing and treatment to minimize risk. According to American guidelines for assessment of cardiovascular risk, global risk scores (such as the Framingham Risk Score) that use multiple traditional cardiovascular risk factors should be obtained for risk assessment in asymptomatic adults without a clinical history of cardiovascular disease. These scores are useful for combining individual risk factor measurements into a single quantitative estimate of risk that can be used to target preventive interventions [27, 28]. Framingham Risk Score is an algorithm used in assessment of 10-year cardiovascular risk and is based on data that was obtained from the Framingham Heart Study, which is a study on the residents of the city of Framingham, Massachusetts, that began in 1948 [27, 28]. The predictors used in the Framingham Heart study are age, sex, diabetes mellitus, smoking, treated and untreated systolic blood pressure, total cholesterol, high-density lipoprotein (HDL) cholesterol, and body mass index (BMI) replacing lipids in a simplified model [30]. Moreover, familial history of coronary artery disease should be investigated to assess the risk of ischemic heart disease in asymptomatic individuals [27, 28]. This assessment of risk factors and classification of risk groups determine the next step of investigations and treatment; for example, low risk patients do not need further investigations for risk evaluation. On the other hand, intensive preventive interventions are already indicated in high-risk patients, and thus further testing or risk assessment would not give additional benefit [27]. Other manifestations of atherosclerosis such as stroke, carotid artery disease, and intermittent claudication are signs of increased risk for ischemic heart disease because atherosclerosis is generalized and can affect any part of the vasculature [29]. History taking should also include questions about symptoms that indicate the presence of ischemic heart disease, such as

retrosternal chest pain or discomfort that indicates angina, and this is often described as squeezing, burning pain or as a pressure, tightness, fullness, or a heavy weight in the middle of the chest that extends to the neck, left arm, jaw, and back. These symptoms can be accompanied by sweating, nausea, and vomiting [30]. Angina itself can be stable or unstable angina, and unstable angina comes in many different forms according to the American Heart Association [31]:

- Rest angina within 1 week of presentation.
- New-onset angina of the Canadian Cardiovascular Society (CCS) classification grade III or IV within 2 months of presentation.
- Angina increasing in CCS grade to at least grade III or IV.
- Variant angina.
- Non-Q-wave myocardial infarction.
- Post-myocardial infarction angina (>24 hours).

Canadian Cardiovascular Society (CCS) grading of angina pectoris is a practical way to define severity of angina by the level of physical activity needed for symptoms to arise (**Table 1**) [30].

3.2. Physical examination

Physical examination is of value in the assessment of a patient with suspected ischemic cardiomyopathy and grants important information. Heart murmurs and sounds might indicate valvular disease or other hemodynamic defects. Swelling of the ankles, an enlarged liver, crepitations on lung auscultation, and tachycardia can be signs of congestive heart failure [32]. Signs of atherosclerosis risk factors can predict the presence of coronary artery disease, for example, abdominal obesity and xanthelasma that is often associated with hyperlipidemia.

Blood pressure might be elevated, which is a risk factor for atherosclerosis and myocardial infarction, or it might be low, which could indicate hemodynamic compromise because of decreased cardiac output in severe heart failure. According to the American College of Cardiology guidelines from 2017, blood pressure is classified as normal, elevated, stage 1, or stage 2 hypertension (**Table 2**) [31].

Grade	Activity evoking angina	Limits to normal activity
I	Prolonged exertion	None
II	Walking >2 blocks	Slight
III	Walking ≤2 blocks	Marked
IV	Minimal or rest	Severe

Table 1. Canadian Cardiovascular Society grading of angina pectoris.

Classification	Blood pressure
Normal	<120/<80 mmHg
Elevated	120–129/<80 mmHg
Hypertension stage 1	130–139 or 80–89 mmHg
Hypertension stage 2	≥140 or ≥90 mmHg

Table 2. Blood pressure classification according to ACC guidelines 2017.

3.3. Resting electrocardiography

A 12-lead electrocardiography (ECG) is simple, easily accessible, cheap, and noninvasive as well as an important tool in the management of ischemic cardiomyopathy. It is recommended that a 12-lead ECG is performed in patients with hypertension or diabetes mellitus even if no symptoms are present. Additionally, in patients without these risk factors and without symptoms, it may still be of value [27].

Myocardial ischemia may present with different changes on ECG, and these changes may appear temporarily during acute myocardial ischemia (e.g., ST-segment elevations) or remain permanently such as pathological Q-waves after a transmural infarction:

- ST-segment morphology changes [33]. ST-segment elevation occurs in acute STEMI, whereas ST-segment depression occurs in NSTEMI or unstable angina.
- T-wave morphology changes. The T-wave becomes upright and tall, *coronary T-waves*, in the first few minutes of myocardial infarction (STEMI) or may be become inverted/negative in NSTEMI and unstable angina.
- Pathological Q-waves which are negative and deep appear on ECG in transmural myocardial infarction and remain as a sign of permanent damage [33].
- Tachyarrhythmias such as ventricular tachycardia and ventricular fibrillation or bradyarrhythmia such as atrioventricular block degrees I–III.
- New left bundle branch block and less commonly right bundle branch block.

ECG abnormities may provide clues for the diagnosis of ischemic cardiomyopathy but have low specificity [34]. ECG signs can guide therapy. If atrial fibrillation is present, lifelong oral anticoagulation is warranted since all patients with ischemic cardiomyopathy and atrial fibrillation are at risk of thromboembolism. Symptomatic sinus node dysfunction or high-degree atrioventricular block can necessitate permanent pacemaker, except for intermittently during the acute phase of STEMI/NSTEMI because bradyarrhythmia is often transient following myocardial infarction. In ischemic cardiomyopathy patients with bundle branch block, typically left, cardiac resynchronization therapy (CRT) can be an option to improve symptoms of heart failure and survival. A completely normal ECG makes ischemic cardiomyopathy unlikely.

3.4. Laboratory tests

Laboratory tests can reveal and quantify many risk factors for ischemic cardiomyopathy, such as diabetes mellitus, hypercholesterolemia, renal failure, and C-reactive protein (CRP) [35].

3.4.1. Creatine kinase-MB

Creatine kinase-MB (CK-MB) is a myocardial enzyme that is elevated in blood in cardiac muscle damage and ischemia, but it is not a specific marker for myocardial ischemia and can be elevated in other conditions, for example, renal failure, rhabdomyolysis, heart failure, and hypothyroidism [36, 37].

3.4.2. Troponins

Cardiac troponins are proteins that regulate the contraction of striated muscles and include three subunits (troponin C, troponin T, and troponin I) [38]. Cardiac troponin T and troponin I are cardiac regulatory proteins that control the calcium-mediated interaction between actin and myosin [39]. Cardiac troponin C is also identified in skeletal muscles, and thus it is not specific for myocardial damage [37]. The elevation of serum levels of cardiac troponins (T, I) is used in the diagnosis of acute myocardial infarction as a biochemical marker [39, 40]. They are superior compared to CK-MB as biomarkers for detection of the myocardial damage that is associated with myocardial infarction, and moreover, while levels are affected by renal function, they still have a reliable predictive value in patients with acute coronary syndrome regardless of renal function [41]. The raised cardiac troponin in serum may not be detectable for up to 4 hours after myocardial infarction; therefore, repeated tests should be performed again, for example, after 3 and 9 hours, if troponins were not raised on admission in patients with suspected acute coronary syndrome [39, 42]. Troponin I has a high specificity for myocardial muscle injury. Troponin I has three isoforms: cardiac, skeletal slow twitch, and skeletal fast twitch [36, 37]. It does not increase in skeletal muscle diseases, after normal physical exercise or in hypothyroidism [36]. It is not detected in healthy individuals without acute coronary syndrome or another disease with damage to myocytes such as myocarditis [36, 43]. Raised cardiac troponins have an important diagnostic and prognostic value in acute coronary syndrome, caused by atherosclerosis and occlusion of coronary arteries (primary myocardial ischemia), but it can be detected in secondary myocardial ischemia associated with many other conditions such as cardiac arrhythmias, large pulmonary embolization, heart failure of other etiologies such as idiopathic dilated cardiomyopathy and hypertrophic cardiomyopathy, or after therapeutic procedures, for example, coronary intervention (angioplasty), vasospastic angina, electrophysiological ablations, or electrical cardioversions [38, 39]. Furthermore, raised cardiac troponins can be caused by nonischemic myocardial damage in conditions such as perimyocarditis, cardiac trauma, septicemia, and chemotherapy [39]. In addition, cardiac troponins are raised in patients with renal failure without acute coronary syndrome, and the exact mechanism of this increase of cardiac troponin levels is still unclear, although raised cardiac troponin I in individuals with renal failure is controversial [36, 37, 39]. It appears that elevated troponin in renal failure is not associated with myocardial infarction rather with chronic myocardial damage and depends upon the assay

technology [42]. However, cardiac troponins remain of predictive value in individuals with chest pain and suspected acute coronary syndrome despite renal failure [39]. Cardiovascular death is common in end-stage renal disease, and both increased cardiac troponin I and T predict a two- to fivefold increase in mortality in these patients [41].

3.4.3. B-type natriuretic peptide

B-Type natriuretic peptide (BNP) and its N-terminal fragment (NT-proBNP) are secreted by ventricular cardiomyocytes as a result of stress and tension in the muscle fibers of the ventricular wall and by myocardial ischemia. They have a strong prognostic and diagnostic value in patients with heart failure. Both BNP and NT-proBNP are significantly elevated in individuals with systolic or diastolic myocardial dysfunction. High levels are predictive of worse prognosis and higher risk of cardiovascular death and readmission to hospital. Furthermore, BNP and NT-proBNP levels indicate the severity of heart failure [44]. Until recently, the clinical application of BNP and NT-proBNP measurement in patients with coronary artery disease has been unclear, but many recent studies have found that both BNP and NT-proBNP levels increase in myocardial ischemia and acute coronary syndromes. This has led to the suggestion that these biomarkers can be secreted by cardiomyocytes as a direct result of myocardial ischemia regardless of ventricular wall stress [44, 45]. In support of this, it has been found that transient myocardial ischemia that occurs due to coronary interventions (stent inflation) can lead to elevation of BNP levels [46]. However, the diagnostic and prognostic value of these biomarkers in coronary artery disease remains unclear, and further investigations are needed.

3.5. Cardiac imaging

Cardiac imaging is an essential tool in understanding heart failure and guiding treatment. Historically, X-ray played a role to show pulmonary congestion and may add other clues to a dyspnea investigation. Instead, today echocardiography is the cornerstone in management of heart failure. It provides information about the morphology of all four chambers, function of wall motion and valves, ejection fraction, pulmonary artery pressure, and pericardial effusion, and is available, noninvasive, and cheap. Other imaging methods are used in the evaluation and provide incremental value, some are an essential part of clinical practice, and others are mainly used in research, but this may change in the future.

3.5.1. Transthoracic echocardiogram

Transthoracic echocardiography includes two- and three-dimensional techniques, pulsed and continuous Doppler, color Doppler, tissue Doppler imaging and contrast, and strain measurements. Assessment of ejection fraction is important as it guides therapeutic choices with regard to pharmaceutical agents and device therapy and provides information about prognosis. Therefore the method used to determine ejection fraction is crucial. According to ESC guidelines, Simpson's rule is the preferred choice. It should be obtained from the apical four-chamber view and two-chamber view but requires accurate tracing of the endocardium. Echocardiography is the most common diagnostic investigation for coronary artery disease after ECG and chest X-ray [47] and can provide detailed information about left ventricular

function, cardiac output, left ventricular ejection fraction, wall motion abnormalities in ischemic cardiomyopathy, and possible complications of acute coronary syndromes such as myocardial aneurysm [48], mitral regurgitation secondary to papillary muscle dysfunction or rupture [47, 49], intracardiac thrombus [50], ventricular free wall rupture, and pseudoaneurysm formation after myocardial infarction [47]. Transthoracic echocardiography is an important tool in the assessment of patients with acute chest pain, both for diagnosis of acute coronary syndromes and for exclusion of other causes of acute chest pain such as aortic dissection and pericardial effusion.

Echocardiogram findings in ischemic cardiomyopathy include:

- Decreased left ventricular ejection fraction, which is one of the most important predictors of mortality [51, 52].
- Left ventricular diastolic dysfunction [53]. The evaluation of left ventricular dysfunction and filling pressures is of great benefit to distinguish ischemic cardiomyopathy from other syndromes that cause dyspnea such as pulmonary diseases [54].
- Regional or diffuse wall motion abnormalities [53, 55].
- Mitral and tricuspid regurgitations [53].
- Detection of both localization and size of myocardial infarction [47].

According to 2013 ESC guidelines on the management of stable coronary artery disease, resting echocardiography should be performed in all patients with the first presentation of coronary artery disease:

- Exclusion of alternate causes of angina.
- Identification of regional wall motion abnormalities suggestive of coronary artery disease.
- Measurement of left ventricular ejection fraction for risk stratification and quantification of heart failure severity.
- Evaluation of diastolic function [54].

3.5.2. Stress echocardiography

The principle of stress echocardiography is the combination of physical (treadmill or bicycle), pharmacological (dobutamine, dipyridamole, or adenosine), or electrical stress (external pacing) with two-dimensional echocardiography [56]. The goal of this technique is the provocation of myocardial ischemia that can be detected with a two-dimensional echocardiogram. It is a noninvasive and easy test for both the patient and the physician and has accuracy in diagnosis of coronary artery disease comparable to that of radionuclide stress perfusion imaging or cardiac magnetic resonance, but it is ultimately less expensive [57].

The response of the myocardium depending on regional wall function during stress echocardiography can be classified into four patterns: normal, ischemic, necrotic, and viable [57].

- Normal response: normokinetic wall function at rest and normo- or hyperkinetic at stress.
- Ischemic response: normokinetic regional wall function at rest and hypokinesia, akinesia, or dyskinesia at stress. Stress exacerbates wall dysfunction.
- Necrotic response: an area with wall dysfunction at rest stays immobile at stress.
- Viability response: an area with dysfunction at rest responds either with recovery and improvement at stress or with improvement at an early phase of stress and thereafter impairment (biphasic response); this indicates viability despite ischemia.

A common indication for stress echocardiography is the diagnosis of coronary artery disease in the group of patients in whom exercise ECG is contraindicated, unfeasible, or not diagnostic [57, 58]. It can also be used in the assessment of viability in ischemic cardiomyopathy before revascularization. In addition, stress echocardiography can be used in the assessment of a patient with established coronary artery disease after revascularization, but also to evaluate the preoperative risk in patients with coronary artery disease and too reveal the region of ischemia in the myocardium.

3.5.3. Coronary computed tomographic angiography

Computed tomography of the coronary arteries is an accurate noninvasive diagnostic test for coronary artery disease [59]. In addition, it provides information on cardiac valves and chambers [60]. The main practical application of computed tomography angiography has been in the outpatient setting in patients with suspected coronary artery disease, but many studies now examine its application in the setting of low-risk chest pain patients in the emergency department [60]. The advantage of computed tomography angiography is its negative predictive value, while the method is lacking in positive predictive value (i.e., it is good at ruling out, but less good at confirming coronary artery disease) [60]. It should be considered in patients with lower risk of coronary artery disease as an alternative to stress testing or when results have been inconclusive [55].

3.5.4. Nuclear imaging modalities

Myocardial scintigraphy, positron emission tomography (PET), and single photon emission computed tomography (SPECT) all utilize radioactive isotopes for imaging. Scintigraphy forms two-dimensional images, while images from PET and SPECT form images in three dimensions. Scintigraphy and SPECT utilize gamma cameras to detect gamma radiation, while PET simultaneously detects two gamma rays emitted at a 180° angle to each other. Cardiac nuclear imaging at rest gives information about areas damaged by myocardial infarction and myocardial viability by mapping metabolism and perfusion. Exercise or pharmacological (usually dobutamine) stress testing provides information on the presence of angina and low perfusion in coronary arteries resulting in ischemia. Importantly, measurement of perfusion by scintigraphy is relative (not absolute) to the area with the highest perfusion. Because of this relative expression of quantification, three-vessel coronary disease with equally reduced perfusion in the whole heart might appear to be well perfused. In cases where this relative perfusion will be misleading, PET should be performed instead. The SHIFT trial viability substudy

indicated that viability or absence thereof did not identify patients with more benefit from coronary artery bypass grafting [61]. However, decision-making about revascularization based on viability using imaging could be considered in special cases. Sympathetic innervation imaging with specific tracers can be used in heart failure for risk stratification, although this is seldom used in clinical practice [62]. Stress testing is valuable in the evaluation of manifest or suspected coronary artery disease; however, it is mainly those who are unable to perform exercise testing (treadmill or bicycle) or those with defects on resting ECG that make exercise ECG difficult to interpret (pacemaker rhythm/bundle branch block) that are in need of radionuclide imaging. Scintigraphy should also be considered in patients with high pretest probability of coronary artery disease as an alternative to exercise ECG. All nuclear imaging modalities expose the patient to a small, but not negligible, amount of ionizing radiation. PET and SPECT are further limited by comparatively high cost and limited accessibility (especially of PET tracers because of short half-life time) and are not routinely used. PET can be used to measure regional myocardial blood flow, by comparing this at maximal hyperemia, and at resting flow, an estimation can be made of noninvasive fractional flow reserve. This otherwise requires an invasive coronary angiography to measure (decline in arterial pressure over a stenosis) [63].

3.5.5. Cardiac magnetic resonance tomography

The main advantage of magnetic resonance in the evaluation of ischemic cardiomyopathy is the ability to visualize scar tissue, which is nonviable and the remaining contractile myocardial tissue which is viable. In this context, there are two modalities of cardiac magnetic resonance tomography: the modality first utilizes late gadolinium enhancement in the assessment of nonviable tissue, and the second modality uses low-dose dobutamine stress magnetic resonance in the assessment of viable tissue [64]. The method assesses ventricular volumes, functions in addition to scar tissue, and is free of ionizing radiation; complications are rare and almost exclusively related to stress testing [65–67]. For patients with suspected coronary artery disease, normal cardiac magnetic resonance tomography is a predictor of good prognosis with 1-year cumulative incidence of adverse events at 1.0% (all-cause mortality, aborted sudden cardiac death, myocardial infarction), which is comparable to the population at large [67]. Moreover, magnetic resonance has been shown to both detected ischemic cardiomyopathy that was not previously suspected and conversely to find an alternate diagnosis in previously suspected coronary artery disease [65, 66].

3.5.6. Diagnostic invasive coronary angiography

Invasive coronary angiography is a procedure where a catheter is inserted into the coronary arteries, usually through the radial artery. By using radiocontrast and X-ray images, coronary vasculature can be assessed. Coronary angiography retains the advantage that if a stenosis or culprit lesion requiring intervention is found, it can be treated by balloon angioplasty and the insertion of a stent. Fractional flow reserve is a way of determining the physiological significance of a stenosis and is the ratio of blood pressure measured distally to and proximally to the stenosis; this is usually considered to be significant at 0.8 [68]. The purpose should be to either perform coronary angiography to treat confirmed coronary artery disease (percutaneous coronary

intervention) or to rule out stable coronary artery disease with noninvasive testing: Only if this has failed, a diagnostic coronary angiography should be considered [55]. Patients with severe angina (CCS 3) should perform coronary angiography, as well as patients with a clinical profile or noninvasive testing indicating high risk of cardiovascular death or myocardial infarction [55].

4. Treatment

Broadly speaking, the treatment of ischemic cardiomyopathy could be said to consist of four strategies: the primary and secondary prevention of coronary artery disease, anti-ischemic treatment such as revascularization and antiplatelet therapy, treatment of heart failure with medications or cardiac devices, and the prevention and treatment of arrhythmia and sudden cardiac death that often accompany ischemic cardiomyopathy.

4.1. Prevention of coronary artery disease

Physical activity, weight loss in patients with the metabolic syndrome or obesity, cessation of smoking, and treatment of hypertension, diabetes mellitus, and hypercholesterolemia (especially lowering of LDL) prevent progression of coronary artery disease and thus the development or worsening of ischemic cardiomyopathy [69].

4.1.1. Statins

All individuals with coronary artery disease have high risk of cardiovascular events and should be treated with statins according to the recommendations of the ESC/European Atherosclerosis Society guidelines for the management of dyslipidemia, regardless of low-density lipoprotein cholesterol (LDL-C) levels [70]. The goal of treatment is to reach LDL-C target <1.8 mmol/L and/or >50% reduction if it could not reach the target level [55]. Other medications (e.g., fibrates, resins, nicotinic acid, and ezetimibe) may reduce the LDL cholesterol level without any benefit on clinical outcomes [55].

4.2. Anti-ischemic therapy

Ischemia is by definition the root cause of ischemic cardiomyopathy; thus, targeting this pathophysiological mechanism is of great importance for prevention and treatment. Revascularization should if possible be the first line of therapy in acute coronary syndrome. Antiplatelet therapy inhibits the formation of blood clots in coronary arteries, thereby decreasing risk of myocardial infarction, while other medications increase vasodilation and coronary blood flow or decrease heart rate and myocardial oxygen demand.

4.2.1. Revascularization

In patients with ischemic cardiomyopathy, revascularization should always be considered in addition to optimal pharmacological treatment [71]. Revascularization can be performed

as open heart surgery, coronary bypass grafting, or percutaneous coronary intervention. The choice of method should be discussed with expertise in revascularization preferably including cardiothoracic surgery and anesthesiology in selected cases. In one study, all-cause mortality after 9.8 years was significantly lower in the coronary artery bypass graft group compared with patients in the medical therapy group (59 versus 66% [359 versus 398 patients]; hazard ratio 0.84; 95% confidence interval 0.73–0.97). In the STICH trial, the following variables were associated with improved outcome after coronary artery bypass grafting: 6-minute walk test more than 300 m, three-vessel disease, mitral regurgitation, and ejection fraction less than 27% [72]. Median follow-up was 56 months, and it also significantly improved health-related quality of life (at 4, 12, 24, and 36 months as assessed by the Kansas City Cardiomyopathy Questionnaire) [73]. Most studies show improvement in both survival and ejection fraction after revascularization compared to optimal pharmacological therapy alone [74–76]. It seems like viable myocardium is a predictor of improved survival [75, 76]. Unfortunately, there are no randomized controlled trials comparing percutaneous coronary intervention and coronary artery bypass grafting in ischemic cardiomyopathy. In an observational study, death rates were similar at median follow-up of 2.9 years. Patients who underwent percutaneous coronary intervention had larger risk of myocardial infarction and repeated revascularization but lower risk of stroke [77].

4.2.2. Antiplatelet and anticoagulant therapy

Antiplatelet drugs prevent occlusion by inhibiting platelet adhesion and thus the formation of thrombi in coronary vessels [78]. Acetylsalicylic acid is well studied, it exerts its effect by inhibiting cyclooxygenase (COX-1 and COX-2) enzymes and reduces cardiovascular death by 15% in high-risk patients [79]. Low-dose acetylsalicylic acid therapy is essential in secondary prevention of cardiovascular events in coronary artery disease, and its benefit in this case is clear, but it is not recommended in the primary prevention of myocardial infarction [55, 79]. The $P2Y_{12}$ receptor is a protein, which exists on the surface of platelets and plays an essential role in the aggregation process activated by adenosine diphosphate. In acute coronary syndrome, a $P2Y_{12}$ antagonists such as clopidogrel, prasugrel, or ticagrelor is recommended in addition to acetylsalicylic acid; this treatment should be continued for up to 12 months in the case of revascularization with a stent [80]. A $P2Y_{12}$ inhibitor can also be considered for secondary prevention when acetylsalicylic acid is unsuitable. In cases of primary percutaneous coronary intervention due to STEMI, dual antiplatelet therapy should be complemented with unfractionated heparin. A parenteral glycoprotein IIb/IIIa inhibitor, which inhibits platelet aggregation, may be considered as bailout therapy if thrombi or falling fractional flow reserve is seen during primary percutaneous coronary intervention [80]. In acute coronary syndrome without ST-segment elevation, a low-molecular-weight heparin, such as fondaparinux, should be administered subcutaneously [81].

4.2.3. Beta-blockers

Beta-blockers exert beneficial effects on the myocardium that decrease heart rate, contractility, atrioventricular conduction, and risk of arrhythmia. Beta-blockers reduce the risk for cardiovascular death and myocardial infarction by 30% in post-myocardial infarction patients and

are useful in the management of effort-induced angina [55, 82]. In Europe, the most widely used beta-blockers provide predominantly β_1-blockade, such as bisoprolol, metoprolol, atenolol, and nebivolol. Carvedilol, which is a nonselective β-blocker that targets the α_1-receptor, is also used, especially in advanced heart failure. By decreasing heart rate and contractility, the oxygen demand of the heart muscle decreases, thus also decreasing ischemia and ventricular arrhythmia. However, beta-blockers might worsen prognosis in the context of bradycardia or circulatory shock, because of negative inotropic effects, and should be used with caution in heart failure with decompensation.

4.2.4. Ivabradine

Ivabradine is a blocker of the *funny* channel, I_f, which is found almost exclusively in the sinus node. By selective inhibition of the sinus node, reduction of heart rate and minimization of myocardial oxygen demand can be achieved, without negative inotropic effect that could result in lowered blood pressure [55]. Ivabradine has been shown to improve heart failure outcomes both in ischemic and unspecific etiologies. It is indicated in patients with sinus rhythm above 70 beats per minute [83, 84]. The combination of atenolol with ivabradine 7.5 mg twice daily gave better heart rate control and amelioration of angina symptoms [55].

4.2.5. Vasodilators

Calcium channel blockers play a role in the management of coronary artery disease by its main effect on vessels with vasodilation and lowering of peripheral vascular resistance. Calcium channel blockers are classified into two main groups: the dihydropyridines that include amlodipine, nifedipine, felodipine, lacidipine, and lercanidipine and the non-dihydropyridines that include verapamil and diltiazem. Dihydropyridines have a greater vascular selectivity, whereas non-dihydropyridines have a property of nodal suppression and tendency of heart rate lowering, which is why the combination of beta-blockers and non-dihydropyridines (verapamil and diltiazem) must be avoided because of the risk of bradyarrhythmia or AV block [55]. By reducing heart rate and increasing dilation of coronary vessels, calcium channel blockers, like the beta-blockers, reduce the ischemic burden in coronary artery disease, although due to decreased contractility they should be avoided in heart failure [85]. Nitrates cause vasodilation of both coronary arteries and veins that gives symptomatic relief of angina due to its active component nitric oxide. There are two types of nitrates: short-acting nitrates (sublingual nitroglycerin 0.3–0.6 mg, tablet or spray form, and isosorbide dinitrate 5 mg sublingually) that is used for acute angina. Long-acting nitrates are used for angina prophylaxis: isosorbide dinitrate (oral preparation), mononitrates, and transdermal nitroglycerin patches [55].

4.3. Treatment of heart failure

Treatment of heart failure includes pharmaceutical agents, comorbidities like anemia, implantable cardioverter defibrillators, cardiac resynchronization therapy, and mechanical circulatory support and transplant.

4.3.1. Angiotensin-converting enzyme inhibitors/angiotensin receptor blockers

Renin-angiotensin-aldosterone system (RAAS) inhibition that is achieved by either angiotensin-converting enzyme inhibitors or angiotensin receptor blockers is an essential component of heart failure management. Both European and American guidelines for the management of heart failure recommend inhibition of the renin-angiotensin system for patients with chronic heart failure to reduce mortality and morbidity [86]. ARNi is a combination of an angiotensin receptor blocker and an inhibitor of neprilysin, which is an enzyme that breaks down vasoactive peptides such as natriuretic peptides, adrenomedullin, and bradykinin and as a result brings about vasodilation. The first approved ARNi product was valsartan/sacubitril. ARNi should not be administered together with angiotensin-converting enzyme inhibitor, which has to be withdrawn [86].

4.3.2. Beta-blockers

Both in coronary artery disease and in heart failure, beta-blockers are a crucial part of therapy. Beta-blockers are useful independent of blood pressure levels in patients with heart failure and improve survival. Bisoprolol was shown to reduce mortality of patients with heart failure in the CIBIS-II trial [87]. The CIBIS-III trial showed non-inferiority for titration of bisoprolol before enalapril as compared to the reverse order [88]. Considering the beneficial and well-documented effect of beta-blockers in coronary artery disease, in ischemic cardiomyopathy, titration of beta-blockers first should be considered in hemodynamically stable patients. Metoprolol is also beneficial in heart failure and was in the MERIT-HF trial shown to improve survival by both preventing worsening of heart failure and decreasing risk of sudden cardiac death [89]. In the US Carvedilol HF trial, decreased risk of death was seen for carvedilol as well [90].

4.3.3. Selective aldosterone receptor antagonists

The selective aldosterone receptor antagonist group includes spironolactone and eplerenone. This class of medication exerts pharmacological effect by blocking the aldosterone receptor; therefore, sodium reabsorption and diuresis are decreased, while potassium retention is increased. Consequently, they cause water loss and lower blood pressure. Spironolactone has been shown to decrease morbidity and mortality in symptomatic heart failure but is associated with antiandrogen side effects such as gynecomastia and disadvantageous mineral corticoid steroid effects [91]. Eplerenone has milder side effects and has shown at least similar beneficial effect on prognosis [92]. In symptomatic heart failure, a selective aldosterone receptor antagonist should be administered in addition to baseline therapy, if tolerated by the patient [6].

4.3.4. Digoxin

Digoxin, first isolated from the digitalis plant, has inotropic properties; it increases contractility and decreases heart rate. It is most commonly used in rate control of atrial fibrillation preferably in addition to beta-blockers. The role of digitalis in the treatment of patients with chronic heart failure is controversial, and its long-term effect on mortality remains unclear. Studies indicate that digoxin decreases the frequency of hospitalization and relives symptoms

of heart failure, but it has no effect on survival or mortality in individuals receiving angiotensin-converting enzyme inhibitors and diuretics [93].

4.3.5. Loop diuretics

By far the most commonly used loop diuretic is furosemide; alternative substances are bumetanide and torsemide. Blockage of sodium-potassium-chloride cotransporters results in increased excretion of sodium, chloride, and potassium and thereby increased diuresis [94]. This decreases the congestion induced by heart failure and therefore it can be useful for symptomatic relief. High doses of loop diuretics have been linked to increased mortality; however, it is the patients with most severe heart failure and congestion that receive the highest doses. For stable patients enteral administration is used, while in cases of worsened heart failure with congestion, intravenous therapy is recommended [94].

4.3.6. Levosimendan

Levosimendan is an inodilator, with both vasodilator and positive inotropic properties. It increases calcium sensitization of troponin C and thus increases cardiac contractility [95]. It can be indicated in acutely decompensated patients with chronic heart failure due to systolic dysfunction of the left ventricle [95, 96]. Levosimendan is well tolerated in general but might have adverse effects such as hypotension, tachycardia, atrial fibrillation, hypokalemia, and headache [95]. Levosimendan has an active metabolite (OR-1896); due to this, effects such as improved hemodynamics and contractility can last for over 1 week. Infusions are administered intermittently. Levosimendan infusions reduce symptoms, hospitalizations, and short-term mortality [95].

4.3.7. Management of anemia

Anemia can mimic symptoms of heart failure such as dyspnea and tiredness. It also worsens prognosis and symptoms in heart failure. In the RED-HF trial darbepoetin alfa, an agent that binds to the erythropoietin receptor and thus stimulates formation of red blood cells did not decrease cardiovascular mortality in anemic heart failure patients; in fact it increased the risk of stroke [97]. Intravenous iron on the other hand has been shown to decrease symptoms and improve quality of life, and enteral iron substitution is associated with gastrointestinal side effects that might be exacerbated in heart failure where gastrointestinal swelling and malabsorption are common [98]. Anemia might worsen ischemia in coronary artery disease, the underlying cause of ischemic cardiomyopathy, and thus extra care is warranted in this group of patients.

4.3.8. Implantable cardioverter defibrillators

Implantable cardioverter defibrillators (ICDs) effectively not only abort ventricular arrhythmias by either antitachycardia pacing or cardioversion but also provide protection against bradycardia. In heart failure, a major cause of death is due to sudden arrhythmic events. Notably, the proportion of sudden cardiac death is higher in patients with NYHA II than NYHA III. Therefore, even patients with mild heart failure symptoms need to be considered for an ICD as primary

prevention. Antiarrhythmic drugs, including amiodarone, might reduce the risk of tachyarrhythmia, but they do not reduce overall mortality and may even increase it. In survivors of cardiac arrest, ICD is recommended as secondary prevention. Patients who have documented ventricular tachycardia with hemodynamic compromise have a secondary prevention indication for ICD for protection from sudden cardiac death [99–102]. Primary prevention indication for ICD should be considered in patients who never experienced a ventricular arrhythmia, with ejection fraction below 35% despite at least 3 months of optimal pharmacological therapy, NYHA functional classes II–III, and at least an estimated survival above 1 year. Two randomized controlled trials showed no benefit in patients who had an ICD the first 40 days after myocardial infarction [103, 104]. If the patient is considered at high risk, during this period a wearable defibrillator is an option [105, 106]. Before offering the patient an ICD, the physician should integrate information about comorbidity and life expectancy; if it is estimated to be less than 1 year including patients with NYHA IV despite pharmacological optimization, ICD is not indicated, but the patient may be reevaluated if improvement occurs. For the group of patients with mild heart failure (NYHA II), an ICD saves one life per year for every 50 patients. Ischemic cardiomyopathy patients have higher risk of sudden death, and the benefit in that group is believed to be higher [107]. In elective replacement of an ischemic cardiomyopathy device, careful judgment is warranted including reevaluation of risk [108–112]. Subcutaneous ICD (S-ICD) is an alternative in selected cases where risk of infection is high or vascular access is difficult and when there is no need of pacing or expected need of antitachycardia pacing. In general 20% of ICD leads fail over a period of 10 years; therefore, S-ICD may be more advantageous in cases of long life expectancy [113, 114].

4.3.9. Cardiac resynchronization therapy

Cardiac resynchronization therapy (CRT), which can be used either with a pacemaker (CRT-P) or with an ICD (CRT-D), reduces morbidity and mortality and improves health-related quality of life in selected patients who fulfill certain criteria [115]. The principle of these devices is to use a pacing system that is biventricular to decrease dyssynchrony and thus heart failure, in patients with heart failure, reduced ejection fraction, and a bundle branch block [116].

According to ESC guidelines from 2013 regarding the indications of CRT in patients with heart failure and sinus rhythm:

- Left bundle branch block with QRS duration >150 ms. CRT is recommended in chronic heart failure patients with left ventricular ejection fraction ≤35% who remain in NYHA functional classes II, III, and ambulatory IV despite adequate medical treatment (recommendation class I, level of evidence A).
- Left bundle branch block with QRS duration 120–150 ms. CRT is recommended in chronic heart failure patients with left ventricular ejection fraction ≤35% who remain in NYHA functional classes II, III, and ambulatory IV despite adequate medical treatment (recommendation class I, level of evidence B).
- Non-left bundle branch block with QRS duration >150 ms. CRT should be considered in chronic heart failure patients with left ventricular ejection fraction ≤35% who remain in

NYHA functional classes II, III, and ambulatory IV despite adequate medical treatment (recommendation class IIa, level of evidence B).

- Non-left bundle branch block with QRS duration 120–150 ms. CRT may be considered in chronic heart failure patients with left ventricular ejection fraction ≤35% who remain in NYHA functional classes II, III, and ambulatory IV despite adequate medical treatment (recommendation class IIb, level of evidence B).
- CRT in patients with chronic heart failure with QRS duration <120 ms is not recommended (recommendation class III, level of evidence B) [117].

In clinical practice it has been revealed that CRT in patients with severe heart failure has positive effects on symptoms and exercise tolerance. Furthermore, it improved quality of life and minimized the need for rehospitalization. However, some patients are nonresponders and receive little or no benefit from CRT. The level of ejection fraction in the trials varies: RAFT and MADIT-CRT used 30% as a cutoff [118, 119]. REVERSE used 40% and BLOCK-HF 50% [118, 120–122]. The QRS width is important in selecting patients. None of the landmark trial selected patients based on sex, QRS morphology, or ischemic vs. nonischemic subgroups. It is not clear if CRT itself reduces the need for ICD or if the improvement of heart failure may expose the patient to a longer period of risk for sudden death. Imaging tests with regard to dyssynchrony are not part of guidelines in selecting patients for CRT [123]. When there is an extensive myocardial scar, the improvement in ejection fraction will be less, and the optimal placement of the left ventricular lead will be more difficult to gain acceptable pacing thresholds without phrenic nerve stimulation.

4.3.10. Mechanical circulatory support and transplant

In patients who do not stabilize with optimal pharmacological therapy, the need for further therapeutic options including mechanical assists should be addressed. In cardiogenic shock, extracorporeal support like Impella™ can be used for temporary bridging. When long-term mechanical assist is indicated, left ventricular assist device can be used for recovery or more often as destination therapy if transplant is not possible. In the meantime, extracorporeal membrane oxygenation (ECMO) may be used to support patients with heart failure (left or biventricular failure) until a decision about a permanent solution is taken. In a randomized trial on high-risk percutaneous coronary intervention in patients with impaired left ventricular function, the 30-day cumulative incidence of major adverse events was not different for patients with intra-aortic balloon pump as compared to left ventricular assist device [124]. Due to lack of heart donors, the left ventricular assist device as a destination therapy has been advocated. The survival rates after 3 years in those receiving the latest continuous flow devices are at least as good as in transplanted patients, but long-term survival is unknown [125].

5. Conclusions

Ischemic cardiomyopathy, which is commonly encountered as an underlying cause of heart failure, warrants qualified management to improve survival. This includes thorough evaluation

and optimal pharmaceutical treatment, device therapy with cardiac resynchronization therapy with/without an implantable cardioverter defibrillator, and mechanical support as bridging or destination therapy in end-stage disease. From a general perspective, it is crucial to reduce risk factors for coronary artery disease to prevent ischemic cardiomyopathy.

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Advances in the understanding of cardiomyopathies and the growth of cardiology have paralleled one another. Over the years, many classification methods have been developed for cardiomyopathies based on aetiology, structural models and the functional approach. The new concepts and events that have occurred in cardiology generally and in cardiomyopathies specifically are sufficient changes to justify this book. Developments in cardiomyopathies have advanced at a rapid rate, largely because of the progress that has been made in instrumental analysis and the integration of clinical cardiology with other fields of basic research. The material in this book encompasses and blends the knowledge recently acquired in genetics, pathology and physiology with the practical matters of diagnosis and treatment.

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