Chapter

Cardiomyopathy: Recent Findings

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Abstract

In 1957, Wallace Brigden published an article on the Lancet, such as uncommon myocardial diseases: the non-coronary cardiomyopathy. In this article, he mentioned that "the term cardiomyopathy is used here to indicate isolated noncoronary myocardial disease." Then "cardiomyopathy" has become a commonly used term in the cardiovascular field, and has been defined and classified by many researchers and academic societies. The basic concept of cardiomyopathy is a group of diseases with mechanical and/or electrophysiological dysfunction of the ventricles, and cardiomyopathy is distinguished with normal ischemic heart disease, valvular disease, and hypertensive heart disease. It can often cause heart failure and cardiac death. In this chapter, we describe the classification, details, and treatment of cardiomyopathy, and iPS cell from pathological myocardium.

Keywords: cardiomyopathy, classification, dilated cardiomyopathy, differentiation of dilated cardiomyopathy, hypertrophic cardiomyopathy, treatment of cardiomyopathy, human- induced pluripotent stem cell

1. Introduction

Goodwin et al. stated that, "the term cardiomyopathy has come into use to describe disorders of the heart, not primarily due to rheumatic, hypertensive, coronary-artery, thyroid, or congenital disease" [1]. They mentioned that the definition of cardiomyopathy is not completely satisfactory, but cardiomyopathy is a subacute or chronic disorder of the myocardium of unknown or unclear etiology, often with associated endocardium and sometimes with pericardial involvement. However, atherosclerosis does not cause cardiomyopathy. They described that the classification of cardiomyopathy consists of congestive heart failure including dilated, constrictive, restrictive, obstructive, and hypertrophic cardiomyopathy. Inheriting the concept of cardiomyopathy proposed by Goodwin et al., in 1980, the World Health Organization (WHO)/International Society and Federation of Cardiology (ISFC) task force defined "cardiomyopathies are heart muscle diseases of unknown cause" and classified into dilated cardiomyopathy, hypertrophic cardiomyopathy, restrictive cardiomyopathy and unclassifiable cardiomyopathy [2]. In 1982, arrhythmogenic right ventricular dysplasia (formerly known as ARVC, currently known as arrhythmogenic cardiomyopathy), which is an inherited form of heart disease characterized pathologically by fibrofatty myocardial replacement and clinically by prominent ventricular arrhythmias and impairment of ventricular

systolic function, was reported [3]. Since arrhythmogenic right ventricular dysplasia means a genetically determined heart muscle disorder, the term dysplasia was replaced by cardiomyopathy. In 1995, the WHO/ISFC task force newly defined cardiomyopathies as "diseases of the myocardium associated with cardiac dysfunction." classified into dilated cardiomyopathy, hypertrophic cardiomyopathy, restrictive cardiomyopathy and arrhythmogenic right ventricular cardiomyopathy, unclassified cardiomyopathy [4]. And then, they used the term specific cardiomyopathy for heart muscle disease that is clearly associated with specific cardiac or systemic disorders.

In 2006, the American Heart Association (AHA) proposed a definition and classification of cardiomyopathy as following: "Cardiomyopathies are a heterogeneous group of diseases of the myocardium associated with mechanical and/or electric dysfunction that usually (but not invariably) exhibit inappropriate ventricular hypertrophy or dilatation and are due to a variety of causes that frequently are genetic. Cardiomyopathies either are confined to the heart or are part of generalized systemic disorders" [5]. AHA cardiomyopathy classification roughly divided into primary cardiomyopathy which has main lesion in the heart, and secondary cardiomyopathy which is a systemic heart lesion. Primary cardiomyopathy is classified into three categories: hereditary, mixed (hereditary and acquired), and acquired (**Figure 1**). Genetic cardiomyopathy includes HCM, ARVC, LVNC, glucose accumulation disease, cardiac conduction disorders, mitochondrial cardiomyopathy, and ion channel disease such as LQTS, Brugada, SQTS, CPVT, IVF (**Table 1**). The ion channelopathy are primary electrical diseases without gross or histopathological abnormalities in which the functional and structural myocardial abnormalities responsible for arrhythmogenesis are at the molecular level in the cell membrane itself. Therefore, the basic pathological abnormality in these diseases is not identifiable by either conventional noninvasive imaging or myocardial biopsy during life or even by autopsy examination of tissue. This is a new concept of cardiomyopathy adopted in the AHA classification. Mixed cardiomyopathy includes DCM, restrictive (non-hypertrophied and non-dilated), and acquired cardiomyopathy includes myocarditis, stress-provoked (tako-tsubo), peripartum, tachycardia-induced,

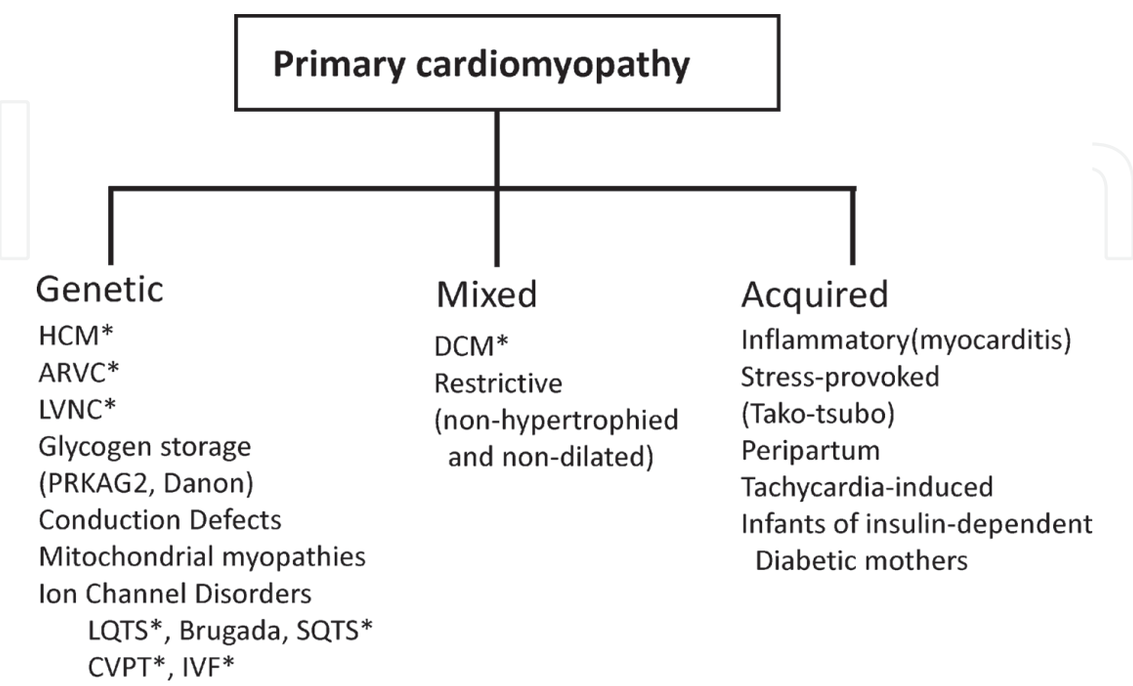

Figure 1.
Definition and classification of cardiomyopathy proposed by AHA in 2006. Modified citation from Ref. [5]. See* ***Table 1****. © 2006 American Heart Association, Inc.*

ARVC: Arrhythmogenic Right Ventricular Cardiomyopathy
CPVT: Catecholaminergic Polymorphic Ventricular Tachycardia
DCM: Dilated Cardiomyopathy
HCM: Hypertrophic Cardiomyopathy
IVF: Idiopathic Ventricular Fibrillation
LVNC: Left Ventricular Noncompaction Cardiomyopathy
LQTS: Long QT Syndrome
RCM: Restrictive Cardiomyopathy
SQTS: Short-QT Syndrome

Table 1.
List of abbreviations

infants of insulin-dependent diabetic mothers. **Tables 2** and **3** display secondary cardiomyopathy that is almost equivalent to the previous specific cardiomyopathy of the WHO/ISFC task force. This looks like a classification from a genetic, biomolecular point of view.

On the other hand, in 2008 European Society of Cardiology (ESC) defined a cardiomyopathy as, "a myocardial disorder in which the heart muscle is structurally and functionally abnormal, in the absence of coronary artery disease, hypertension, valvular disease and congenital heart disease sufficient to cause the observed myocardial abnormality" [6]. Cardiomyopathies are grouped into specific

Infiltrative (Accumulation of abnormal substances between myocytes (ie, extracellular))
Amyloidosis (primary, familial autosomal dominant†, senile, secondary forms)
Gaucher disease (Genetic (familial) origin)
Hurler's disease (Genetic (familial) origin)
Hunter's disease (Genetic (familial) origin)
Storage (Accumulation of abnormal substances within myocytes (ie, intracellular))
Hemochromatosis
Fabry's disease (Genetic (familial) origin)
Glycogen storage disease (type II, Pompe) (Genetic (familial) origin)
Niemann-Pick disease (Genetic (familial) origin)
Toxicity
Drugs, heavy metals, chemical agents
Endomyocardial
Endomyocardial fibrosis
Hypereosinophilic syndrome (Löeffler's endocarditis)
Inflammatory (granulomatous)
Sarcoidosis
Endocrine
Diabetes mellitus
Hyperthyroidism
Hypothyroidism

Hyperparathyroidism
Pheochromocytoma
Acromegaly
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Table 2.
Secondary Cardiomyopathies.

Cardiofacial
Noonan syndrome (Genetic (familial) origin)
Lentiginosis (Genetic (familial) origin)
Neuromuscular/neurological
Friedreich's ataxia (Genetic (familial) origin)
Duchenne-Becker muscular dystrophy (Genetic (familial) origin)
Emery-Dreifuss muscular dystrophy (Genetic (familial) origin)
Myotonic dystrophy (Genetic (familial) origin)
Neurofibromatosis (Genetic (familial) origin)
Tuberous sclerosis (Genetic (familial) origin)
Nutritional deficiencies
Beriberi (thiamine), pallagra, scurvy, selenium, carnitine, kwashiorkor
Autoimmune/collagen
Systemic lupus erythematosis
Dermatomyositis
Rheumatoid arthritis
Scleroderma
Polyarteritis nodosa
Electrolyte imbalance
Consequence of cancer therapy
Anthracyclines: doxorubicin (adriamycin), daunorubicin
Cyclophosphamide
Radiation
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Table 3.
Secondary Cardiomyopathies continued.

morphological and functional phenotypes. Each phenotype is then sub-classified into familial and non-familial forms (**Figure 2**). This classification is an extension of the WHO/ISFC classification, with genetic and non-genetic classifications based on morphological and functional abnormalities. In 2018, Japanese Circulation Society (JCS) has revised the cardiomyopathy clinical practice guidelines [7]. JCS defined a cardiomyopathy as so-called primary cardiomyopathy, is divided into four types: hypertrophic cardiomyopathy, dilated cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy, and restrictive cardiomyopathy (**Figure 3**). Some of the

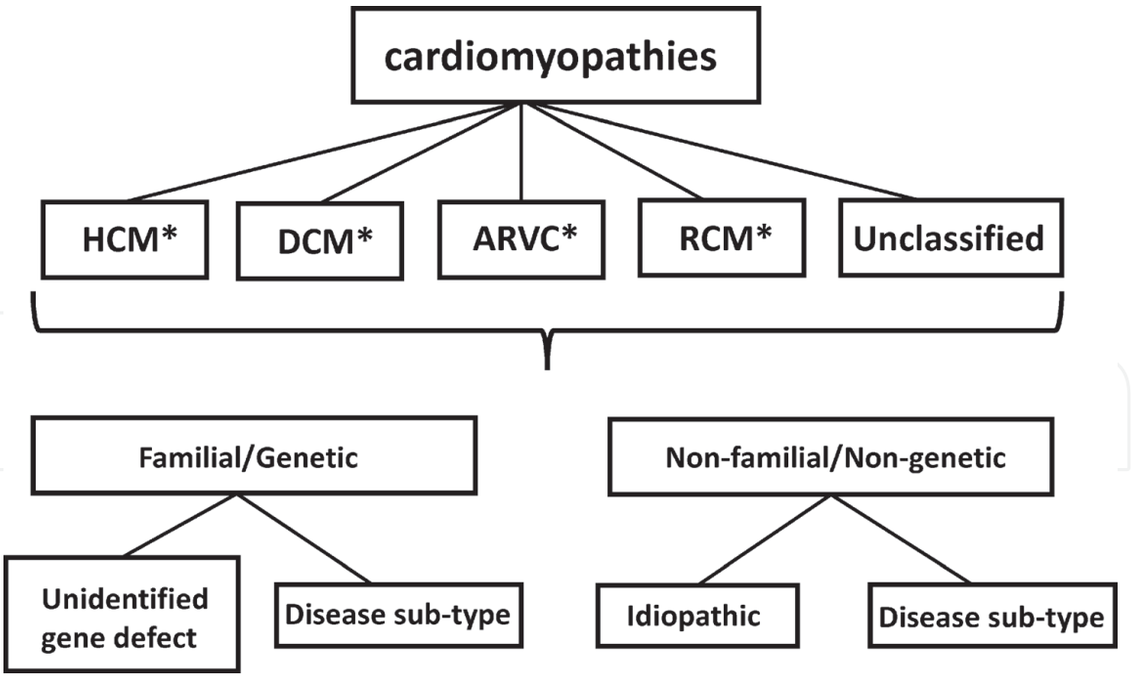

Figure 2.
*Definition and classification of cardiomyopathy proposed by ESCA in 2008. Modified citation from Ref. [6]. * See* ***Table 1****.*

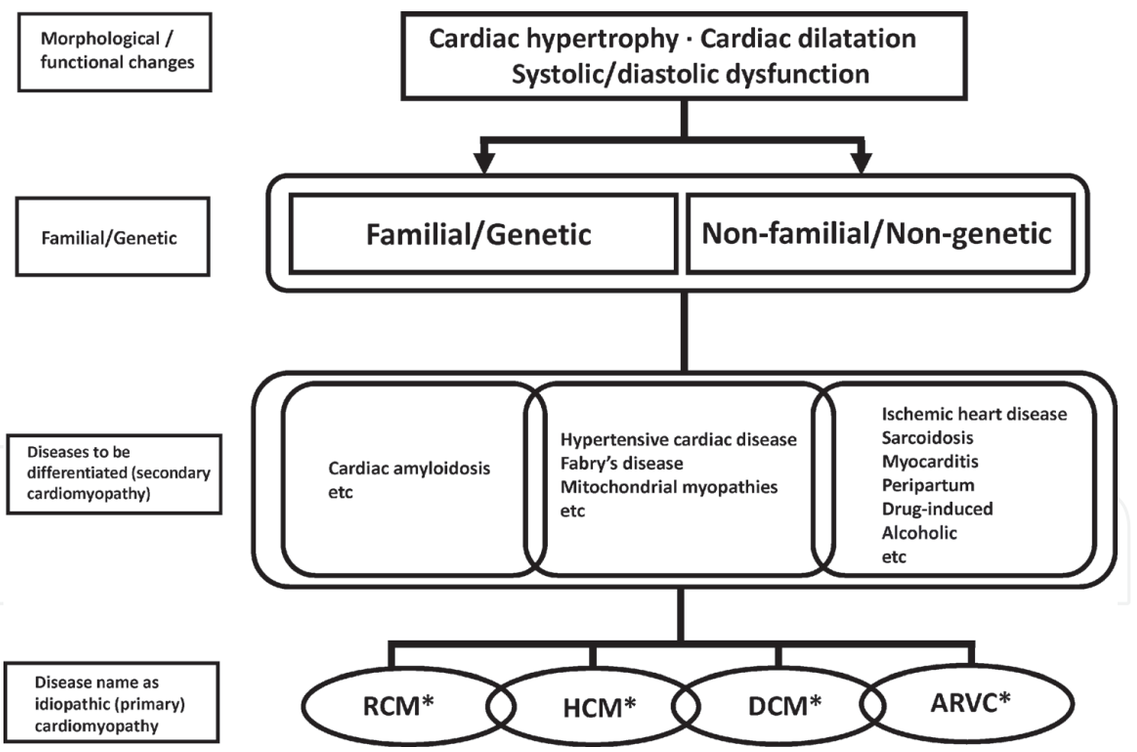

Figure 3.
*Revised definition and classification of cardiomyopathy proposed by JSC in 2018. Modified citation from Ref. [7]. * See* ***Table 1****.*

four basic pathologies of primary cardiomyopathy overlap and are often difficult to distinguish from each other. Diagnosis of these four primary cardiomyopathies should be confirmed after distinguishing secondary cardiomyopathy as much as possible. Cardiomyopathy that cannot be classified into four basic pathological conditions at present is called unclassifiable cardiomyopathy. The classification of JCS may be close to that of ESC.

M Morphofunctional Phenotype	O Organ/System Involvement	G Genetic	E Etiological Annotation	S Stage; ACC/AHA Stage, NYHA Functional Class
(D) Dilated (H) Hypertrophic (R) Restrictive (A) ARVC (NC) LVNC Overlapping (H+R), (D+A), (NC+H), (H+D), (D+NC) or more complex combinations such as (H+R+NC) (E) Early, with type in parentheses (NS) Nonspecific phenotype (NA) Information not available (0) Unaffected	(H) Heart (M) Muscle, skeletal (N) Nervous (C) Cutaneous (E) Eye (A) Auditory (K) Kidney (G) Gastrointestinal (S) Skeletal (0) Absence of organ/system involvement, e.g., in family members who are healthy mutation carriers; the mutation is specified in E and inheritance in G	(N) Family history negative (U) Family history unknown (AD) Autosomal dominant (AR) Autosomal recessive (XLR) X-linked recessive (XLD) X-linked dominant (XL) X-linked (M) Matrilineal (DN) De novo (0) Family history not investigated	(G) Genetic etiology-add gene and mutation; (NC) Individual noncarrier plus the gene that tested negative (OC) Obligate carrier (ONC) Obligate noncarrier (DN) De novo (C) Complex genetics when >1 mutation (provide additional gene and mutation) (Neg) Genetic test negative for the known familial mutation (NA) Genetic test not yet available (N) Genetic defect not identified (0) No genetic test, any reason (no blood sample, no informed consent, etc.) Genetic amyloidosis (A-TTR) or hemochromatosis (HFE) Nongenetic etiologies: (M) Myocarditis (V) Viral infection (add the virus identified in affected heart) (AI) Autoimmune/immune-mediated; suspected (AI-S), proven (AI-P); (A) Amyloidosis (add type of amyloidosis: A-K; A-L, A-SAA) (I) Infectious, nonviral (add the infectious agent) (T) Toxicity (add toxic cause/drug) (Eo) Hypereosinophilic heart disease	ACC/AHA stage represented as letter (A, B, C, D) To be followed by NYHA Functional class represented in Roman numerals (I, II, III, IV) Modified citation from Reference 8
M_D, M_H, M_R, M_A, M_{NC}, M_O, M_{H+R}, M_{D+A}	O_H, O_M, O_K, O_C	G_N, G_U, G_{AD}, G_{AR}, G_{XLR}, G_{XLD}, G_{XD}, G_M, G_{DN}	$E_{G\text{-}MYH7[R403E]}$, $E_{G\text{-}HFE[Cys282Tyr+/+]}$, $E_{V\text{-}HCMV}$, $E_{G\text{-}A\text{-}TTR[V30M]}$, $E_{M\text{-}sarcoidosis}$	$S_{A\text{-}I}$, $S_{A\text{-}II}$

Figure 4.
The MOGE(S) nomenclature of cardiomyopathy. Modified citation from Ref. [8].

In 2013, Arbustini et al proposed the MOGE (S) classification of cardiomyopathy approved by the World Heart Federation [8] (**Figure 4**). This is a classification system similar to the TMM system, which is a system for staging cancers in oncology. This is a classification that integrates cardiomyopathy by morphology and function (M:Morpho-functional phenotype), affected organs (O:Organ/system involvement), gene mutation (G:Genetic inheritance pattern), cause and pathology E: Etiology), and severity (S: Stage) and obtains information necessary for treatment in an easy-to-understand manner. In this way, there are many cardiomyopathy classifications in the world, but it is difficult to say that they are sufficiently unified, including the usage of terms.

2. Dilated cardiomyopathy (DCM)

DCM is a group of diseases characterized by myocardial contractile dysfunction and dilatation of the left ventricular lumen and has a poor prognosis and progressive disease with symptoms of chronic heart failure and repeated acute deterioration. It also causes sudden death due to fatal arrhythmias. The initial report on the prevalence of DCM was published in 1989. This study was analyzed using data from Mayo Clinic and identified 45 new cases of DCM in Olmsted County, Minnesota between 1975 and 1984. The incidence of DCM doubled from 3.9 per 100,000 person-years to 7.9 per 100,000 person-years during the first 5 years. The prevalence of DCM in people younger than 55 years was 17.9 per 100,000, and more than one-third of them were in New York Heart Association functional III or IV at diagnosis [9].

The etiology of DCM has been unknown for a long time, but it has been divided into familial and non-familial categories. In particular, most cases of adult-onset DCM are considered to be caused by both familial and non-familial factors.

Advances in molecular genetic analysis have revealed causative mutations of DCM in more than 60 genes and truncating mutations in the titin (TTN) gene were shown to be present 25% of familial or severe transplant DCM cases [10]. In another report, truncation of the TTN gene was found in about 13% of non-familial DCM cases, but also 2% of the general population [11]. Recently, a polygenic risk score has been developed to predict the cumulative effect of multiple susceptibility genes identified by genome-wide association studies using mathematical models, and it has become clear that genetic variation can be affected by exogenous or environmental factors [12]. In addition, the clinical impact differed by genetic mutation, DCM patients with truncating mutations in TTN having a milder disease phenotype at baseline and a higher incidence of reverse remodeling compared with patients with a pathogenic lamin A/C (LMNA) mutation [13], which is one of the DCM with poor prognosis due to the risk of sudden death [14]. Recently, other mutations such as carriers of a specific phospholamban (PLN) mutation or truncating filamin C (FLNC) mutations have been reported as a risk of sudden death in DCM patients [15, 16]. The causes of non-familial DCM are still unknown. The etiology is considered to be inflammation and necrosis of cardiomyocytes caused by infectious factors such as viruses and bacteria and non-infectious factors such as autoimmunity, drugs and stress. In fact, it has been reported that viral genomes have been detected in the tissues of patients diagnosed with DCM [17].

3. Differentiation of DCM

As mentioned above, DCM is defined as a group of diseases characterized by diffuse contractility disorder and dilatation of the left ventricle. Therefore, it is necessary to exclude specific heart muscle diseases for definitive diagnosis. Specific heart muscle indicates ischemic cardiomyopathy, valvular heart disease, and hypertensive heart disease, inflammatory heart disease, metabolic heart disease, myocardial disease associated with neuromuscular disease or myocardial disease with clear association with systemic disease [4].

3.1 Ischemic cardiomyopathy

Ischemic cardiomyopathy is caused by ischemia due to coronary atherosclerosis and it is characterized by left ventricular dilatation and contractile dysfunction, similar to DCM. Ischemic cardiomyopathy is the most common cause of heart failure in clinical cases and should be excluded initially. In addition to a history of ischemic heart disease, coronary angiography or coronary computed tomography is necessary to be differentiated. If contrast medium is not available, scintigraphy can be used as a substitute. In rare cases, left ventricular dysfunction such as DCM may occur due to multiple vessel coronary artery spasm, even in the absence of coronary artery stenosis. If this is suspected on symptoms, an acetylcholine provocation test should be considered [18].

3.2 Hypertensive cardiomyopathy

Hypertensive cardiomyopathy is similar to DCM, which presents with systolic dysfunction as a result of histological abnormalities such as left ventricular hypertrophy and myocardial cell hypertrophy, interstitial proliferation and perivascular fibrosis due to persistent hypertensive conditions. It is a pathological condition and is characterized by efferent hypertrophy with left ventricular enlargement. In addition to the histological and functional disorders of the heart, other organ disorders

due to sustained hypertension such as blood vessels and kidneys often contribute to the onset of heart failure.

3.3 Amyloidosis Cardiomyopathy

Amyloidosis indicates a general team of diseases characterized by the extracellular deposition of misfolded amyloid fibrils in organs. Clinically, it is roughly divided into systemic amyloidosis in which multiple organs and peripheral nerves are damaged, and focal amyloidosis in which amyloid deposits occur locally in an organ or organs. Cardiac amyloidosis is one of the common infiltrative or restrictive cardiomyopathies associated with an unfavorable prognosis. The pathophysiology of amyloidosis is the misfolding of abnormal protein that is amyloid fibrils resulting in its accumulation to extracellular on the affected tissues. Although there are multiple causes of the misfolding, one of them is a gene mutation that encodes a different amino-acid leading to the conformational change of protein [19].

Clinical outcome depends on the extent of tissue involvement and on the type of amyloid fibril deposits. The major subtypes of systemic amyloidosis classified based on the underlying etiologies are as follows: primary (AL) amyloidosis, Secondary (AA) amyloidosis (or reactive amyloidosis), familial transthyretin-associated amyloidosis (ATTR or hereditary amyloidosis), dialysis-related amyloidosis, and senile systemic amyloidosis. AL amyloidosis has an incidence of 1 case per 100,000 person-years in western countries. ATTR is a less common systemic type of amyloidosis with unknown incidence

Cardiac manifestations predominantly include symptoms of right heart failure. Infiltration of amyloid fibrils results in stiffening and thickening of ventricles causing decreased compliance and increased pressure altering the mechanics of ventricular function manifesting as diastolic dysfunction. Furthermore, cytotoxic effects of amyloid fibrils result in apoptotic and fibrotic changes of the heart. Finally, these changes lead to heart failure. Amyloid deposits to cardiac conduction system result in heart block or arrhythmias [20]. Syncope due to heart block or arrhythmia may be a marker of prognosis [20]. Atrial fibrillation (AF) is the most common arrhythmia described in approximately 10%-20% of patients who have cardiac amyloidosis [21].

It is possible that patients of cardiac amyloidosis are completely asymptomatic or may present with various signs and symptoms. Therefore, a diagnostic approach is important in cases of suspected cardiac amyloidosis. Pseudoinfarction, which is low voltage in limb leads and poor R wave progression in ECG, is one of the most common electrocardiographic characteristics in cardiac amyloidosis. This finding has been demonstrated in up to half of patients with AL [22]. Furthermore, amyloid deposits also result in various arrhythmias, such as various heart blocks, AF, and complex ventricular tachycardia [23].

The echocardiography is recommended in all patients with suspected amyloidosis, and findings include bilateral dilatation and thickening of ventricular wall and valves, decreased diastolic filling, and classic granular sparkling appearance. The wall thickness is attributed to infiltrative amyloid deposition instead of myocyte hypertrophy [24]. Decreased left ventricular ejection fraction is of grim prognostic significance [25]. Cardiovascular magnetic resonance imaging (CMR) is an important diagnostic and prognostic tool in the assessment of severity of cardiac amyloidosis. Injury to the myocardium secondary to deposition of amyloid fibrils in the interstitium denotes a reservoir for gadolinium accumulation leading to characteristic late gadolinium enhancement (LGE) [26]. This technique has a sensitivity of close to 80% and impressive specificity of 94% [27]. Strain analysis based on CMR can be accomplished with the recent advances, a technique known as Displacement Encoding with Stimulated Echoes with high sensitivity and specificity close to echo

[28]. It is a highly precise modality and hold promises in generation of strain time curves with "tissue tracking" techniques. Use of radiotracers has been used to diagnose amyloidosis. Most commonly, 99mTc-DPD (technetium-3,3-diphosphono-1,2-propanodicarboxylic acid) and 99mTc-PYP is used. As 99mTc-PYP preferentially binds to ATTR relative to AL fibrils, this technique also serves as an on invasive way to distinguish the aforementioned amyloidosis subtypes [29]. Biopsy with histopathology remains the gold standard showing deposition of amorphous deposits of amyloid fibrils.

Treatment can be divided into HF therapy, specific therapy for each amyloidosis. Chemotherapy is based on the concept of reducing the number of amyloid fibrils and retarding the disease process. In AL, chemotherapy and autologous hematopoietic stem cell transplant is the main stay of treatment. Chemotherapy in AL is aimed at reducing free light chains. Bortezomib is a proteasome inhibitor that induces rapid hematological response either alone or in combination with dexamethasone [30]. As mutant amyloid ATTR is produced in liver, orthotropic liver transplantation is the established treatment since 1990. Transthyretin (TTR) tetramer stabilizers (tafamidis and diflunisal) work by binding to TTR and by stabilizing its normal tetrameric structure preventing amyloid fibril formation [31]. Drugs such as tafamidis and diflunisal, could have role in the treatment of senile systemic amyloidosis (SSA) which is amyloidosis that mainly affects the heart of the elderly.

3.4 Sarcoidosis

Sarcoidosis is a systemic inflammatory disease characterized by the formation of granulomas in affected organs, especially the lungs. Diagnosis is challenging for clinicians because various organs can be affected. The exact prevalence of cardiac lesions in sarcoidosis is unknown due to ethnic differences, but the incidence of sarcoidosis has been reported to 11-24 cases per 100,000 per a year in Scandinavian countries and 1 case per 100,000 per a year [32, 33]. The incidence is higher in women (45-60%) and the average age of diagnosis is younger in men (30-50 years) compared to women (50-60 years) [34]. The etiology of sarcoidosis is unknown, however, it has been reported that not only genetic factors but also living environment and lifestyle are contributing factors [35]. The inflammatory response in sarcoidosis is thought to involve autoimmunity, possibly including autoantigens, although there are no specific diagnostic markers or biomarkers for activity.

Cardiac sarcoidosis is present 2-7% of patients with sarcoidosis, and cardiac sarcoidosis can occur without pulmonary or systemic involvement [36]. In the early stages of the disease, ventricular wall thickening coinciding with regions of granulomatous inflammation and interstitial edema is observed, and as inflammation gradually fades and fibrosis of the lesions progresses, the base of the ventricular septum often shows characteristic wall thinning. Regional hypokinesia of the left and right ventricles and ventricular aneurysm are observed and if the lesion is extensive, DCM-like pathology may be observed [37].

The detection rate of myocardial biopsies is low, and currently gadolinium-enhanced cardiac magnetic resonance imaging is the optimal test for determining the presence and extent of cardiac lesions. 18F-FDG-PET is useful for evaluating the degree of granulomatous inflammation and activity of cardiac lesions [38].

3.5 Drug-induced cardiomyopathy

Drug-induced cardiomyopathy is commonly seen in clinical situations as a serious side effect of anticancer drugs and antiretroviral therapy. In particular, patients with

a history of cancer treatment need to be asked about what kind of anticancer drug treatment they have received and whether they have received radiation therapy.

The most commonly identified chemotherapeutic drugs with cardiotoxicity are anthracyclines and these drugs are still used in clinical practice [39]. It has been reported that cutoff value for anthracycline administration to affect cardiovascular risk is 250 mg/m^2 or higher, but even lower doses can cause cardiac dysfunction [40, 41]. With the improvement of chemotherapy outcomes, the number of long-term survivors of childhood cancer has increased and delayed drug-induced cardiomyopathy often develops in adulthood after anthracycline treatment in childhood [42].

Trastuzumab (Herceptin) is a humanized IgG kappa monoclonal antibody that targets the extracellular domain of human epidermal growth factor receptor 2 (HER2) [43]. The HER2 has been found to be amplified 2 to 20 times or more in 30% of breast cancer patients, and gene amplification has been reported to be a significant predictor of both survival and time to recurrence [44]. Trastuzumab-induced cardiomyopathy usually presents as an asymptomatic decrease in left ventricular ejection fraction and can lead to complications such as heart failure, but the cardiotoxicity is transient and reversible, in addition it isn't dose-dependent as with anthracyclines [45, 46].

To evaluate such drug-induced cardiomyopathy, American Society of Echocardiography has defined that cancer therapeutics-related cardiac dysfunction as decrease in left ventricular ejection fraction (LVEF) or greater to less than 53%. In addition, LVEF is reevaluated after 2 to 3 weeks and is considered reversible if the decline is within 5% of baseline, and irreversible if the improvement in EF is less than 10% and remains below 5% of baseline. In particular, it is recommended that the LVEF and global strain be evaluated in combination [47]. Even in facilities that do not have echocardiography, troponin I has been reported to be elevated indicating the possibility of cardiotoxicity and measurement of troponin I is also recommended [48].

3.6 Myocarditis

Myocarditis is an inflammatory disease in which inflammation spreads to cardiomyocytes. Most of them are viral infections, and adenovirus, enterovirus including the coxsackievirus B, parvovirus, cytomegalovirus and HIV are the most frequent as causative virus of myocarditis [49]. Bacteria that causes non-viral myocarditis include corynebacterium infection, streptococcal infection, tuberculosis, Whipple's disease, and Lyme carditis. The definitive diagnosis of myocarditis is based on myocardial biopsy and histological diagnosis. A typical finding of myocardial biopsy of myocarditis is infiltration of inflammatory cells such as neutrophils and mononuclear cells between myocardial fibers, and a necrotic lesion such as rupture/melting of adjacent cardiomyocytes. The interstitium becomes edematous and capillary angiogenesis occurs. The prevalence of cardiomyopathy during whole heart failure varies by age and region, but ranges from approximately 0.5% to 4.0% [50]. Although about half of myocarditis patients are cured, sudden death due to myocarditis is not uncommon.

3.7 Alcoholic cardiomyopathy

It is one of addictive cardiomyopathy caused by long-term and heavy drinking. In general, it is estimated that the onset occurs when 80 to 90 g/day of pure ethanol

equivalent is ingested daily for 5 years or more. Initially, diastolic dysfunction and left ventricular hypertrophy occur, and then the left ventricle is dilated as it progresses of pathologic state. Treatment is complete abstinence first.

3.8 Left ventricular noncompaction cardiomyopathy

Left ventricular noncompaction cardiomyopathy (LVNC) is a structural abnormality of the left ventricular myocardium of unknown cause. Since LVNC is associated with genetic disease, particularly neuromuscular disorders (NMDs) and chromosomal defects in the majority of patients, in the AHA cardiomyopathy classification, LVNC is classified as one of the genetic primary cardiomyopathies [5]. Mortality of patients with LVNC ranges from 5% to 47% [51]. LVNC is characterized by a two-layered structure usually of the apical and lateral left ventricular myocardium, distal to the papillary muscles. The two-layered structure consists of an excessive spongy endocardial layer (noncompacted layer: NC) and a compacted epicardial layer (compacted layer: C), which is usually thinner than the endocardial layer and NC/C ratio is 2 or more by echocardiography. In LVNC, many genetic abnormalities have been reported such as TAZ, DTNA and LDB3 gene mutation, and many genetic abnormalities of sarcomere protein have also been reported [51]. LVNC is usually asymptomatic, but can be complicated by heart failure, thromboembolism, or ventricular arrhythmias, including sudden cardiac death. LVNC is diagnosed primarily by echocardiography, and is frequently associated with myocardial fibrosis, as shown by the presence of late gadolinium enhancement (LGE) on CMR [51, 52].

3.9 Beriberi heart

Vitamin B1 (thiamine) is a coenzyme essential for glucose metabolism. It is thought that thiamine supplementation is insufficient due to high-calorie infusion and unbalanced diet during the growth period, and then deficiency occurs [53]. If this deficiency lasts for more than 3 months, beriberi occurs.

3.10 Mitochondrial cardiomyopathy

Mitochondrial disease is a multi-organ disease characterized by oxidative phosphorylation disorders caused by mitochondrial dysfunction due to mutations in the nucleus and mitochondrial DNA. Therefore, mitochondrial cardiomyopathy is often recognized as a symptom of mitochondrial disease. The prevalence of inherited mitochondrial disease has been estimated to be greater than 1 in 5,000 births [54]. A common pathology of mitochondrial cardiomyopathy is a decrease in mitochondrial ATP production capacity per one cardiomyocyte [55]. Since the myocardium is an organ that continuously consumes energy through aerobic metabolism, ATP deficiency is directly linked to a decrease in myocardial contractility. Many nuclear and mitochondrial DNA mutations associated with mitochondrial cardiomyopathy have been reported. Typical mitochondrial diseases MELAS (mitochondrial myopathy，encephalopathy，lactic acidosis and stroke-like episodes), MERRF (myoclonus epilepsy associated with ragged-red fibers), CPEO (chronic progressive external ophthalmoplegia), and KSS (Kearns-Sayre syndrome) also develop mitochondrial cardiomyopathy. The typical cardiac manifestations of mitochondrial cardiomyopathy are diverse such as hypertrophic and dilated cardiomyopathy, arrhythmias, left

ventricular myocardial noncompaction, and heart failure, and may worsen rapidly due to infection or sudden death due to lethal arrhythmia [55].

3.11 Anderson-Fabry disease

Anderson-Fabry disease (AFD) is an X-linked hereditary glycolipid metabolism disorders due to deficient activity of the enzyme alpha-galactosidase A (α-Gal A) located on the X-chromosome (Xq22.1) resulting in progressive lysosomal deposition of globotriaosylceramide (GL-3) in cells throughout the body [56]. AFD is one of sex-linked recessive inheritance diseases. This indicates that all hemizygous men are affected, whereas their daughters are obligate heterozygous carriers. However, AFD is a disease that is more likely to onset the disease in heterozygotes (female). In female, it is thought that one of the two X chromosomes is inactivated. In a female who is heterozygotes, when the rate of inactivation of the X chromosome with the mutant allele is high, it is close to normal. On the other hand, when the rate of inactivation of the X chromosome with normal allele is high, symptoms of AFD will appear. Females with AFD tend to develop and diagnose symptoms later than males. In classic of AFD, glycosphingolipid accumulates in organs throughout the body especially in the skin, kidneys, nerves, eyes, and heart, on the other hand, a cardiac variant phenotype or a renal variant phenotype lack systemic findings and present with organ-specific symptoms [56, 57]. Since the heart is involved in up to 70% of patients who have AFD, the diagnostic procurer of AFD include the cardiac diagnosis strategy such as baseline ECG, echocardiography and CMR with or without symptoms. The typical cardiac manifestations of AFD often mimic hypertrophic cardiomyopathy [58]. That is, it is recognized as a disease that causes cardiac hypertrophy and is classified as one of secondary cardiomyopathy. So clinically, the distinction between sarcometic HCM and AFD is extremely important. CMR is an excellent way to non-invasively diagnose cardiac involvement in AFD. Non-contrast T1 mapping of CMR significantly displays lower value in AFD, compared to healthy volunteers and patients with other confounding diseases [59].

3.12 Peripartum cardiomyopathy

Peripartum cardiomyopathy is a dilated cardiomyopathy-like state in women who have no history of heart disease during pregnancy or childbirth. In some cases, severe heart failure associated with postpartum cardiomyopathy is developed. Although the detailed mechanisms of postpartum cardiomyopathy are still unknown, the causes are thought to be hemodynamic changes due to pregnancy, preeclampsia, viral infections, allergies, nutritional disorders, etc. In Japan, the prevalence of peripartum cardiomyopathy has been estimated 1 in 10,000 to 20,000 births [60]. This is a lower rate than that of the United States [61]. However, the prevalence rate is increasing year by year due to the aging of pregnant women, improvement of reproductive technology, and improvement of cardiomyopathy diagnosis rate.

3.13 Cardiomyopathy in muscular dystrophy

Muscle dystrophy is heterogeneous group of disorders characterized by genetic and progressive degeneration of skeletal muscle and muscle weakness [62]. In Japan the overall incidence of this disease is estimated as 2 to 3 out of 100,000. Duchenne muscular dystrophy (DMD), Becker muscular dystrophy (BMD) are X-linked

recessive (Xp21), Emery- Dreifuss Muscular Dystrophy (EDMD) is X-linked recessive (Xq28 in EDMD1, Xq26 in EDMD 6), Autosomal dominant (EDMD2; LMNA gene at 1q21), autosomal recessive (EDMD3, also involving the LMNA gene at 1q21), Limb Girdle Muscular Dystrophy (LGMD) is usually autosomal recessive (LGMD2C. 2D, 2E & 2F: sarcoglycanopathies; LGMD2I: mutation of fukutin-related protein gene; 19q), Rarely autosomal dominant (LGDM1; 1B due to mutation of the LMNA gene encoding lamin A/C), and Myotonic Dystrophy (DM) is autosomal dominant: type 1 (DM1, Steinert's disease): unstable expansion of CTG the myotonic dystrophy protein kinase gene (DMPK) on chromosome 19q13.3, type 2 (DM2): CCTG tetranucleotide repeat expansion in intron 1 of the zinc finger protein 9 gene (ZNF9) on chromosome 3q21.3 [63]. Almost all DMD patients develop cardiomyopathy early on, on the other hand, symptom progression in BMD patients is slow but may present with severe heart failure [64, 65]. Cardiomyopathy in EDMD patients develops in the same way as that of DMD patients [66]. LGMD patients develop sinus node dysfunction, atrioventricular node dysfunction, ventricular arrhythmias as cardiomyopathy manifestations [67]. Common cardiomyopathy manifestations in DM1 and DM2 patients are atrioventricular and intraventricular conduction defects. Infra-hisian block is likely an important cause of sudden death in these patients [68, 69].

4. Hypertrophic cardiomyopathy (HCM)

Hypertrophic cardiomyopathy (HCM) is the common primary cardiomyopathy, with a prevalence of 1:500 persons [64]. It is defined as left ventricular hypertrophy without chamber dilation and is caused by gene mutations that encode 8 sarcomere proteins: beta-myosin heavy chain (MYH7), cardiac myosin-binding protein C (MYPBC3), cardiac troponin T (TNNT2), cardiac troponin I (TNNI3), cardiac actin (ACTC), alpha-tropomyosin (TPM1), essential myosin light chain (MYL3) and regulatory myosin light chain (MYL2) [70]. Mutations in MYH7 and MYPBC3 often occur and account for approximately 50% of HCM cases, while mutations in TNNT2, TNNI3, ACTC, TPM1, MYL3 and MYL2 collectively account for less than 20% of HCM cases [71]. Septal thickening predominates and may cause left ventricular outflow tract obstruction or mitral valve dysfunction [65]. Phenotypic expression is variable. Many patients with HCM are asymptomatic and are diagnosed during family screening, by incidentally after an abnormal result on electrocardiography. Presenting signs and symptoms most characteristic of HCM include atypical chest pain and sudden cardiac death (SCD). Patients who are diagnosed with HCM may have a family history of unexplained sudden cardiac death. ECG often show left ventricular hypertrophy and Q waves, and echocardiography often show hypertrophy of the left ventricle coupled with reduction in ventricular chamber volume [66].

The natural history of HCM is quite variable. Signs and symptoms range from none, to atrial fibrillation, heart failure, embolic stroke and SCD. In heart failure in HCM, since decreased left ventricular diastolic function due to cardiac hypertrophy is the basic pathology of HCM, three categories of HCM patients emerged [67]: (1) patients with obstruction at all times, (2) patients without obstruction in the basal state in whom obstruction could be provoked, (3) patients without obstruction in whom obstruction could not be provoked. The severity of the outflow gradient is related to prognosis, and diastolic failure is a common dysfunction of HCM patients [68]. Ventricular fibrillation is one of cause of SCD in HCM. All patients with HCM should undergo risk stratification for SCD and be evaluated for placement of an

implantable cardioverter-defibrillator [69]. Additionally, these devices are recommended for secondary prevention of SCD when there is any personal history of ventricular fibrillation or sustained ventricular tachycardia [64]. Although the main goals of therapy in HCM patients are to decrease exertional dyspnea and chest pain and prevent SCD, about 25% of HCM patients achieve normal longevity. Particular the MYPBC3 variant carries a good prognosis.

5. Arrthymogenic cardiomyopathy (ACM)

As mentioned in history of classification in cardiomyopathy, ARVC was one of cardiomyopathies characterized by right ventricular enlargement, decreased right ventricular wall contractility, and right ventricular tachycardia due to myocardial cell shedding and fibrofatty replacement in right ventricle. However, although the original article defines as disease phenotype characterized by predominant involvement of right ventricular dysfunction, recent reports show increased left dominant and biventricular forms. Therefore, the recent recognition of the term of ARVC has been replaced by arrthymogenic cardiomyopathy (ACM) [72].

ACM is an inherited heart disease characterized pathologically by fibrofatty myocardial replacement and clinically by prominent ventricular arrhythmias and impairment of ventricular function including both ventricles. The classical ARVC phenotype in ACM shows the right ventricle with fibrofatty infiltration, regional dilatation and aneurysm formation at the right ventricular inflow tract, outflow tract and the right ventricular apex which are called as triangle of dysplasia. Phenotype of left ventricular dominant type of ACM is characterized by the early left ventricular (LV) involvement with arrhythmias prior to gross structural alterations, on the other hand global RV function of this type is preserved. Biventricular ACM is characterized by early involvement of both ventricles with disease progression characterized by systolic impairment and biventricular dilation, with clinical features of global congestive heart failure, and ventricular arrhythmias originating from either ventricle at an early stage. Frequency of occurrence of ACM has been estimated at 1:1000 to 5,000, and it often occurs in the 30s, and the Sudden Cardiac Death in the Young |Ten Points to Remember disease declared by American College of Cardiology includes ACM as ARVC [73–75]. In ACM, there are gene abnormalities of the desmosome proteins which works in adhesion between cardiomyocytes, and gene abnormalities in the ryanodine receptor (RyR2) gene, which is a Ca^{2+} handling protein. The desmosomal complex is formed the trans-membrane proteins (cadherins), desmocollin-2 (DSC2), desmoglein-2 (DSG2), desmoplakin (DSP), the linker armadillo proteins plakoglobin (JUP) and plakophi-lin-2 (PKP2). JUP and PKP2 are mediators between the cadherins and DSP. Mutations in PKP2, DSP, and DSG2 are identified in up to 80% of confirmed pathogenic mutations. PKP2 accounts for 36–92% of mutations identified in desmosomal genes [72].

6. Restricted cardiomyopathy (RCM)

RCM is characterized by limited filling of one or both ventricles, reduced diastolic volume, and normal or near-normal contractility and wall thickness [76]. Ventricular wall thickness and contractility are almost normal, but diastolic volume decreases due to decreased myocardial compliance, resulting in heart failure. Endocardial fibrotic thickening and myocardial fibrosis may also be present.

7. Treatment of cardiomyopathy

7.1 Medical treatment of cardiomyopathy

Treatment of symptomatic heart failure associated with various cardiomyopathy should follow current guideline for the management of heart failure from American College of Cardiology/American Heart Association or guidelines for the diagnosis and treatment of acute and chronic heart failure from European Society of Cardiology [77, 78]. Beta blocker, angiotensin-converting enzyme inhibitor (ACEi), angiotensin receptor blocker (ARB), diuretics, angiotensin receptor-neprilysin inhibitor (ARNI), or sodium/glucose cotransporter 2 (SGLT2) blocker are used as pharmacologic therapy, when cardiomyopathy is associated with systolic dysfunction [79]. Patients with more severe heart failure symptoms should be evaluated for placement of an implantable cardioverter-defibrillator, and may require cardiac transplantation in refractory cases.

7.2 Mavacamten: new treatment for HCM

Mavacamten selectively inhibits cardiac myosin ATPase leading to reducing actin–myosin cross-bridge formation [80]. As a result, it is expected that mavacamten will improve pathophysiology of hypertrophic cardiomyopathy such as left ventricular outflow tract (LOVT) obstruction, decreased left ventricular filling. In preclinical and early clinical studies of mavacamten succeeded reduction of LVOT gradients and improved parameters of left ventricular filling [81, 82]. In the phase 2, PIONEER-HCM study revealed that mavacamten was well tolerated and significantly reduced post-exercise LVOT gradients in obstructive HCM [83]. On the basis of these results, the short-term results of the phase 3 EXPLORER-HCM trial have been published. EXPLORER-HCM was a phase 3, multicentre, randomised, double-blind, placebo-controlled trial [84]. Eligible patients were aged at least 18 years with a diagnosis of obstructive HCM; peak LVOT gradient at least 50 mm Hg at rest, after Valsalva manoeuvre or exercise; left ventricular ejection fraction (LVEF) at least 55%; and NYHA class II–III symptoms. The patients had to be able to safely perform upright cardiopulmonary exercise testing (CPET). Finally, 429 adults were assessed for eligibility, of whom 251 (59%) were enrolled. In the placebo group, post-exercise LVOT gradient had changed from 84mmHg to 73mmHg after 30weeks, meanwhile that of the mavacamten group improved from 86 mmHg to 38 mmHg (difference from the placebo group: -36 mmHg, 95% CI:-43.2 to -28.1 mmHg, $P < 0.0001$). The average increase in pVO2 was also significantly greater in the mavacamten group than in the placebo group (1.4 mL / kg / min, 95% CI: 0.6-2.1 mL/kg/min, $P = 0.0006$). The number of patients whose NYHA classification improved by 1 degree or more was 40 of 128 (31%) in the placebo group and 80 of 123 (65%) in the mavacamten group (difference between groups: 33.8%, 95% CI: 22.2-45.4%, $P < 0.0001$). Treatment with mavacamten improved exercise capacity, LVOT obstruction, NYHA functional class, and health status in patients with obstructive HCM. EXPLORER-HCM trial is ongoing to assess long-term (5 year) efficacy and safety.

7.3 Surgery for dilated and hypertrophic cardiomyopathy

Cardiomyopathy is categorized as a disease of the cardiomyocytes and is complicated with heart failure due to reduced ejection fraction or diastolic dysfunction.

Moreover, mitral valve regurgitation (MR) and ventricular arrhythmia are commonly associated with cardiomyopathy. Surgical treatment for cardiomyopathy is a combination of maneuvers on the ventricle, mitral annulus and leaflets. We herein summarize the current surgical management of dilated and hypertrophic obstructive cardiomyopathy (HOCM).

7.4 Hypertrophic cardiomyopathy

In patients with HOCM, heart failure is caused by left ventricular outflow tract (LVOT) obstruction, mitral valve dysfunction due to systolic anterior motion and diastolic dysfunction. Surgical treatment should relieve such dysfunctions, and the use of a mitral prosthetic valve should be avoided if possible.

7.4.1 Procedures on the left ventricle

Septal hypertrophy is a typical physiological feature of HOCM. Echocardiography during exercise is a reliable diagnostic modality and could provide significant prognostic information [85]. Peteiro and colleagues reported that, as only 13% of patients presented with LVOT obstruction at rest, 27% developed exercise-induced LVOT obstruction [85]. Cui and colleagues proved that septal hypertrophy with a significant LVOT pressure gradient truly generated obstruction of blood flow to the aorta [86]. Different from aortic valve stenosis, increased LVOT gradient caused decreased stroke volume [86]. In addition, the efficacy of septal myectomy was compared with valvular aortic stenosis. After myectomy with a normalized LVOT gradient, the aortic flow pattern returned to normal [86]. Therefore, septal myectomy is the principal surgical maneuver for HOCM. The improvement in stroke volume after myectomy explains the improvement in exercise capacity postoperatively [86]. Furthermore, Parbhudayal and colleagues compared myectomy for HOCM with aortic valve replacement for valvular stenosis and reported reverse remodeling after surgery [87]. They reported that recovery of systolic function was only observed after aortic valve replacement, while patients with HOCM demonstrated systolic functional deterioration, which was a negative impact of septal myectomy on cardiac function and was associated with ongoing pathophysiological conditions [87].

The spectrum of HOCM is of great variety in terms of location and severity of hypertrophy, positional relationship between the septum and anterior mitral leaflet and papillary muscles. For patients with mid-ventricular hypertrophy, broad myectomy concomitant with mitral valve replacement is necessary to relieve dilatation dysfunction.

7.4.2 Procedures on the mitral valve

Both ventricular hypertrophy and structural abnormalities of the mitral valve are frequently found in HOCM. An elongated anterior mitral leaflet is commonly associated with systolic anterior motion and MR. Regarding surgery for MR, analysis of the Society of Thoracic Surgeons database suggested that mitral etiology was not significantly associated with an incremental risk of early mortality [88].

Systolic anterior motion is associated with anomalously elongated anterior mitral leaflet. Balaram and colleagues recommended that the standard maneuver for the mitral leaflet was horizontal plication through the aortic valve when the anterior mitral leaflet was elongated by 30 mm, and the standard technique is plication of the leaflet, usually performed through the aortic valve [89, 90]. The plication can shorten the leaflet length by 2–5 mm [91]. Recently, the edge-to-edge technique was reported

to be useful in HOCM and can be applied through either the aortic valve [92] or the left atrium [93]. Chordal cutting was also reported to be effective for relieving LVOT obstruction through geometric modification [94].

Septal myectomy is the primary maneuver for HOCM. In addition to myectomy, the maneuvers for the leaflet and sub-valvular apparatus are viable surgical options, especially when septal hypertrophy is not severe.

7.5 Idiopathic and ischemic dilated cardiomyopathies

For ischemic cardiomyopathy, MR was commonly found without any prolapse or deformity of the leaflets and chordal elongation or rupture. Such MR is usually functional and associated with apical displacement of the papillary muscles and dilatation of the mitral annulus. The presence of MR causes heart failure during follow-up and significantly worsens patient prognosis. Therefore, it has been widely accepted that surgical management of MR is crucial.

7.5.1 Procedures on the mitral valve

Ischemic or dilated cardiomyopathy causes functional MR. Patients have severe dilatation of the left ventricle, which causes mitral annular dilatation, leaflet tethering and the gap between the leaflets. Consequently, severe MR causes volume overload, fibrosis and adverse remodeling of the ventricle [95, 96].

During mitral valve repair, annuloplasty is frequently performed for ischemic cardiomyopathy. In the procedure, the artificial full and semi-rigid ring is implanted to reduce the annular diameter. Noack and colleagues reported that even for patients with poor ventricular ejection fraction of <30%, mitral valve repair could be safely performed [97]. Xu and colleagues reported that under-sizing annuloplasty was effective for eliminating MR [98]. Kainuma and colleagues reported favorable remodeling, decreased tethering distance and inter-papillary muscle distance during the follow-up period [99]. Conversely, choosing a downsized artificial ring might cause functional mitral stenosis and recurrence of MR compared with mitral valve replacement [100]. In some cases, ventricular or sub-valvular reconstruction procedures are necessary to achieve successful and durable mitral valve repair.

7.5.2 Procedures on the left ventricle

In ischemic cardiomyopathy, surgical coronary revascularization is beneficial to achieve favorable remodeling after surgery and avoid clinical outcomes [101]. Surgical ventricular reconstruction (SVR) such as the Dor procedure and its modifications contributed to improved long-term clinical outcomes with a reasonable perioperative risk [102]. Moreover, appropriate surgical maneuver of SVR had a significant impact on prognosis after surgery [102]. However, the clinical advantage of SVR concomitant with coronary artery bypass graft was not demonstrated in the STICH (Surgical Treatment for ischemic Heart Failure) trial, which was a randomized study of SVR in ischemic cardiomyopathy [103]. Patient selection for SVR may be an issue in the future.

7.5.3 Summary of surgery for dilated and hypertrophic cardiomyopathy

The clinical and morphological manifestations of cardiomyopathy vary greatly depending on etiology, severity and cardiac function. Especially procedures on

the ventricle are not necessarily beneficial in the long-term follow-up. Surgical treatment for cardiomyopathy should be individualized for patients.

8. iPS cell development from DCM heart

Induced pluripotent stem (iPS) cell development is one of the most promising technologies in regenerative medicine [104]. iPS cell is evoked via the epigenetic silencing of somatic cells by the Yamanaka factors, i.e., the four transcription factors Oct4, Sox2, Klf4, and c-Myc. Advances in iPS cell reprogramming technology could allow aging or damaged cells to be replaced by the patient's own rejuvenated cells; therefore, the clinical application of iPS cell reprogramming technology may be a solution to the problem of age-related degenerative diseases. However, senescent or pathologic tissue has a relatively low reprogramming efficiency compared with juvenile or robust tissue, resulting in incomplete cell reprogramming. Our laboratory developed a new reprogramming method for generating iPS cells using pathologic somatic cells from a recipient heart that states the severe heart failure associated with DCM [105].

For gene transfection of iPS cell differentiation, in addition to the Yamanaka factors, GLIS1 and TET-1 were added. Gli-similar transcription factors (Glis) belong to the group of Krüppel-like zinc-finger transcription factors, and three GLIS genes (GLIS1–3) have been identified [106]. Yoshioka et al. reported that Yamanaka factor RNAs with Glis-1 RNA that were purified from an RNA-replicative vector yielded high-efficiency iPS cell reprogramming from older adult human cells [107]. Tet-1, which is one of DNA demethylase, contributes to the differentiation of the inner cell mass at the blastocyst stage and regulates the maintenance of ES cells by altering the DNA methylation status [108]. Olariu et al. found that TET1 could replace OCT4 in the iPS cell reprogramming Yamanaka

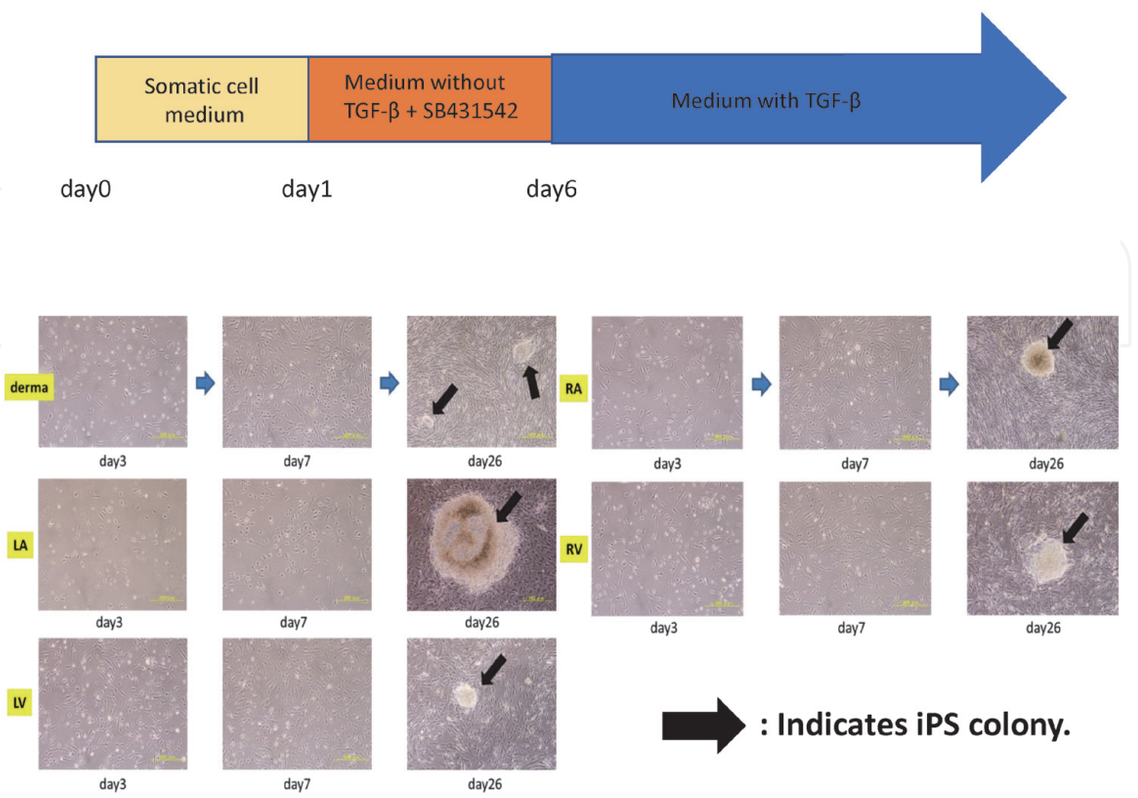

Figure 5.
Gene transfection.

cocktail and that DNA methylation is the key to regulating pluripotency genes [109]. Since Tet-1 may also evoke the induction of Dnmt3b expression upon transition to the epiblast stage, TET-1 was included in the final set of six genes to be transfected in our protocol.

Cardiac fibroblasts obtained from a recipient heart highly expressed α-smooth muscle actin (α-SMA) that is a representative marker of myofibroblast. Myofibroblasts occur at a converging spot of mesenchymal cells, resulting from acute or chronic inflammation caused by stimulation with TGF-β, Ang II, and cytokines [110]. Interestingly, the myofibroblasts from our patient's heart tissue did not differentiate into human iPS cells by previous methods [111]. Therefore, the cell culture medium for iPS cell induction was also prepared in detail. During the first 5 days post-transfection, TGF-β was removed from the cell culture medium for iPS cell induction, and selective TGF-β inhibitor SB431542 was added. Finally, by combining these methods, we developed a highly efficient method for inducing human iPS cells from pathologic somatic cells (**Figure 5**) [105].

9. Summary of cardiomyopathy recent findings

We outlined the recent findings of cardiomyopathy. In addition to the development of the cardiac devices and regenerative medicine, clinical trials of heart failure drugs such as ARNI, SGLT2 inhibitors and cardiac function improving drugs as mavacamten have shown effective results leading to desirable situation for cardiologists to expand their options. Our goal is to improve the QOL of cardiomyopathy patients.

Conflicts of interest

We confirm there are no conflicts of interest.

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