Chapter 1

Introductory Chapter: Last Crossroad

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Cardiomyopathy (CMP) is the heart muscle disease causing cardiac myocyte injury and myocardial dysfunction, which impair structural and/or functional ventricular filling or ejection of blood in the absence of structural or vascular heart disease. Most CMPs are complex and heterogeneous familial diseases, and the inheritance is autosomal dominant in majority of cases. The classification of these cardiac diseases has been based on morphofunctional phenotypes, but it has been changed according to molecular genetics in recent years. As we know, the traditional classification proposed by the World Health Organization (WHO) is easy to differentiate between various CMPs in a couple structural and functional phenotypes (**Table 1**), which helps us to define common treatment strategies [1]. New classification-orientated genomic and molecular science helps us to understand the complexity and heterogeneity of these diseases (**Table 2**), which may occur primary or secondary [2]. The American Heart Association (AHA) Scientific Statement proposes the definition: "Cardiomyopathies are a heterogeneous group of diseases of the myocardium associated with mechanical and/or electrical 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 (primary) or are part of generalized systemic disorders (secondary), often leading to cardiovascular death or progressive heart failure-related disability." The last classification system (MOGES) proposed by the World Heart Federation (WHF) includes all characteristics: morphofunctional phenotype (M), organ(s) involvement (O), genetic inheritance (G), etiology (E), and functional status (S) (**Table 3**) [3].

From the clinical perspective, the most important objective is diagnosis of the mechanism of the heart failure and delivery of the appropriate effective treatment. Heart failure incidence increases with age and rises from 20% in the seventh decade to more than 80% in octogenarians [4]. Advancing age or cardiac aging is another risk factor for heart failure, and it is a heterogeneous process characterized by genomic DNA damage, telomere shortening, and epigenetic modifications, which can affect protein homeostasis, mitochondrial function, and regenerative potential of stem cells adversely [5]. The hemodynamic changes are dependent

on the nature of cardiomyopathies, which cause myocardial dysfunction due to mechanical or arrhythmogenic pathophysiologic mechanisms.

1.	Dilated
2.	Hypertrophic
3.	Restrictive
4.	Arrhythmogenic
5.	Unclassified (mitochondrial diseases, fibroelastosis)
6.	Specific
	a. Ischemic
	b. Valvular
	c. Hypertensive
	d. Inflammatory
	e. Metabolic
	f. General systemic disease
	g. Muscular dystrophies
	h. Neuromuscular disorders
	i. Sensitivity and toxic reactions
	j. Peripartum

Table 1. World Health Organization (WHO) classification for cardiomyopathies.

A.	**Primary (predominantly involving the heart)**
	a. Genetic
	1) Hypertrophic cardiohyopathy
	2) Arrhythmogenic right ventricular dysplasia
	3) Glycogen storage (PRKAG2, Danon)
	4) Conduction defects
	5) Mitochondrial myopathies
	6) Ion channel disorders (LQTS, SQTS, CVPT, Brugada, Asian SUNDS)

b. Acquired

1) Inflammatory (myocarditis)

2) Stress-provoked (Tako-Tsubo)

3) Peri- or postpartum

4) Tachycardia-induced

5) Infants of insulin-dependent diabetic mothers

c. Mixt

1) Dilated cardiomyopathy

2) Restrictive (non-hypertrophied and non-dilated)

2. Secondary

a. Infiltrative (amyloidosis; Gaucher disease; Hurler's disease; Hunter's disease)

b. Storage (hemochromatosis; Fabry's disease; Glycogen storage disease = type II Pompe; Niemann-Pick disease)

c. Toxicity (drugs, heavy metals, chemical agents)

d. Endomyocardial (endomyocardial fibrosis; hypereosinophilic syndrome = Löeffler's endocarditis)

e. Inflammatory = granulomatous (Sarcoidosis)

f. Endocrine (diabetes mellitus; hyperthyroidism; hypothyroidism; hyperparathyroidism; pheochromocytoma; acromegaly)

g. Cardiofacial (Noonan syndrome; Lentiginosis)

h. Neuromuscular/neurological (Friedreich's ataxia; Duchenne-Becker muscular dystrophy; Emery-Dreifuss muscular dystrophy; myotonic dystrophy; neurofibromatosis; Tuberous sclerosis)

i. Nutritional deficiencies (Beriberi, pallagra, scurvy, selenium, carnitine, kwashiorkor)

j. Autoimmune/collagen (systemic lupus erythematosis; dermatomyositis; Rheumatoid arthritis; scleroderma; polyarteritis nodosa)

k. Electrolyte imbalance

l. Consequence of cancer therapy (anthracyclines: doxorubicin (adriamycin), daunorubicin; cyclophosphamide; radiation)

Table 2. American Heart Association (AHA) Classification for Cardiomyopathies.

Notation	M Morpho-functional phenotype		O Organ/system involvement		G Genetic inheritance		E Etiology		S Stage	
Characteristics	Cardiomyopathy diagnosis (DCMP, HCMP, RCMP, ARVC/D, LVNC)		Clinical history and evaluation *- organ involvement* *- multidisiplinary evaluation*		Genetic counseling with pedigree *- familial (inheritance)* *-nonfamilial (sporadic)* clinical family screening *-affected and asymptomatic* *-with ECG and/or ECHO abnormalities* *-healthy family members*		Genetic testing in the proband: -positive -negative		Functional status (ACC/AHA; NYHA)	
Subscript	D	Dilated	H	Heart	N	Family history negative	G	Genetic cause	A-D	ACC/AHA stages
	H	Hypertrophic		*LV=left ventricle*	U	Family history unknown	OC	Obligate carrier	NA	Not applicable
	R	Restrictive		*RV=right ventricle*	AD	Autosomal dominant	ONC	Obligate non-carrier	NU	Not used
	R EMF	Endomyocardial fibrosis		*RLV=biventricular*	AR	Autosomal recessive	DN	De novo	I-IV	NYHA classes
		LV=left ventricle	M	Muscle	XLD	X-linked dominant	Neg	Genetic test negative for the known familial mutation		
		RV=right ventricle	N	Nervous	XLR	X-linked recessive	N	Genetic defect not identified		
		RLV=biventricular	C	Cutaneous	XL	X-linked	O	No genetic test, any reason		
	A	Arrhythmogenic right ventricular cardiomyopathy	E	Eye, ocular	M	Matrilineal	G-A-TTR	Genetic amyloidosis		
		M=major	A	Auditory	O	Family history not investigated	G-HFE	Hemochromatosis		
		m=minor	K	Kidney	S	Phenotpically sporadic				
		c=category	G	Gastrointestinal			*non-genetic etiologies:*			
		LV=left ventricle	Li	Liver			M	Myocarditis		
		RV=right ventricle	Lu	Lung			V	Viral infection (add the virus)		
		RLV=biventricular	S	Skeletal			AI	Autoimmune/immune-mediated (suspected AI-S; proven AI-P)		
	NC	Left ventricular noncompaction	O	Abscence of organ involvement			A	Amyloidosis (add type: A-K, A-L, A-SAA)		
	E	Early					I	Infectious, non-viral		
	NS	Nonspecific phenotype					T	Toxicity (add cause/drug)		
	NA	Information non available					Eo	Hypereosinophilic heart disease		
	O	Unaffected					O	Other		

Table 3. World Heart Federation (WHF) MOGE(S) classification for cardiomyopathies.

Cardiac contraction is a specific motion of myocardium that results in an adequate ejection (>60%) with lower dynamic change and energy consumption (15% fiber shortening) [6]. Subendocardially located cardiomyocytes create right-handed helix (smaller-radius) and subepicardially located cardiomyocytes left-handed helix (larger-radius), and this helixodical structure of the myocardium generates a torsional motion pattern caused by rotation in a clockwise direction at basal level and counter clockwise rotation at the apical level. In hypertrophic CMP, basal rotation increases and if the septum has sigmoid curvature apical rotation is more certain, and both mechanisms increase outflow tract obstruction level, decrease untwisting velocity, and cause subendocardial ischemia. In dilated CMP, the abnormal shape of the left ventricle changes fiber orientation and increasing dilatation is associated with more decreased twist.

The diagnosis of CMPs is assessed echocardiographically, but cardiovascular magnetic resonance (MR) is also powerful tool in diagnosis. Both are complementary imaging modalities. Echocardiography is superior in assessment of diastolic function and dynamic outflow tract obstruction. Cardiac MR has several advantages such as three-dimensional visualization, demonstration of relationships between the heart and thoracic structures, quantification of cardiac volumes and function, excellent resolution, tissue characterization (scar or infiltration), safely repetition [7].

1. Irreversible cardiomyhopaties

Dilated CMP is the most common (>60%) final pathway during clinical nature of CMPs, which has more than 50% idiopathic etiology. Furthermore, some infiltrative CMP diseases may progress, as a consequence of remodeling, from one state (non-dilated) to another (dilated) during their natural clinical course. Mechanical impairment of filling or ejecting of ventricles causes significant cardiac decompensation with a clinic presentation from asymptomatic left ventricular dysfunction to severe heart failure symptoms. Annual mortality ratio changes between 10 and 50%, whereas between 1/4 and 1/3 of patients with new-onset dilated CMP presents cardiac recovery. Reverse remodeling may develop spontaneously or occur after medical or device treatment. Most patients have normal coronary circulation, and a definition for ischemic CMP needs a >70% stenosis in a major epicardial coronary artery. The main pathophysiologic mechanism is progressive systolic dysfunction dependent on four-chamber dilatation of the heart with normal left ventricular wall thickness. The annular enlargement causes significant valvular insufficiency, which makes the clinical status worse. Pulmonary hypertension with increased pulmonary vascular resistance develops gradually and diagnosis can result from cardiac catheterization. The diagnosis and management of patients with CMP are evaluated with noninvasive (echocardiography, MR imaging, multidetector computed tomography) or invasive cardiac tests (cardiac catheterization, endomyocardial biopsy). Large-scale treatment options give clinicians a wide range of follow-up of their patients. Asymptomatic patients can be followed medically, but mild-moderate symptomatic patients must be treated pharmacologically (diuretics, neurohormonal antagonists, anti-pulmonary hypertensives). Severe symptomatic conditions require invasive treatment options in a sequence: anti-

arrhythmogenic devices, anti-regurgitant devices, anti-failure mechanic devices, and heart transplantation. Assessment of exercise capacity guides this treatment sequence, and 6-min walk test is the simplest valuable tool for switching to invasive treatments. The best test to gradate exercise capacity and to determine the cardiac-cause is the cardiopulmonary exercise testing, which is the most important test to determine whether to put patients on to waiting list.

Hypertrophic CMP is the most common cardiomyopathy with genetic transmission and characterized by a thickened, hypertrophied left ventricle without dilatation. Hypertrophic CMP is caused by a variety of mutations encoding contractile proteins of the cardiac sarcomere. Hypertrophy is usually diffuse and involves both septum and left ventricular free wall (≥15 mm; +family history 13–14 mm; in children ≥ +2 standard deviation). Diastolic dysfunction develops due to the presence of a small left ventricular cavity; contrarily, systolic function can be preserved at the beginning of the pathology. Longstanding left ventricular outflow tract obstruction due to ventricular thickness with or without systolic anterior motion of mitral valve is the main predictor of heart failure or sudden death. Myocardial ischemia occurs due to microvascular dysfunction, which results in left ventricular scarring and remodeling. Reduced ventricular compliance causes diastolic dysfunction, which is diagnosed by exertional dyspnea. The greatest risk for adverse outcome is arrhythmogenic complication without heart failure symptoms. Atrial fibrillation is the most common (20%) rhythm disorder and cannot be tolerated well and results in embolic stroke or progressive heart failure. The lethal arrhythmia is ventricular fibrillation and has several signs: family history, unexplained syncope, hypotensive blood pressure response to exercise, abnormal ventricular tachycardia, massive left ventricular hypertrophy. The first stage treatment is the implantation of a cardioverter-defibrillator. Dual chamber pacing has limited effect. Septal myectomy or alcohol septal ablation is an alternative invasive treatment option, but heart transplantation is the final and only option for curative therapy.

Restrictive CMP appears increasing in stiffness of the ventricular walls and consequently developing diastolic failure. At the beginning, the systolic function is normal, but it decreases during the progress of the disease. The most common specific etiology is amyloidosis. The pathologic changes of impairment of diastolic filling are myocardial fibrosis, infiltration or scarring of the endomyocardial surface. The first symptom is exercise intolerance, but with advancing disease, volume balance shifts to the generalized edema due to diastolic dysfunction and to the filling reduction in ventricles due to diuresis. In the late period of the restrictive CMP, ventricular dilatation can be added to the pathology and prognosis deteriorates rapidly. Treatment options are limited: anti-arrhythmogenic devices, biventricular pacing, and heart transplantation. Left ventricular assist devices (LVAD) cannot be used in this group of diseases.

Arrhythmogenic right ventricular dysplasia is a rare, inherited pathology that is characterized by ventricular arrhythmias, sudden cardiac death, and right ventricular dysfunction due to myocyte loss with fatty or fibro-fatty tissue replacement of the right ventricular myocardium (and less commonly left). The pathophysiologic basis of this disease can be dependent on defective desmosomal proteins (impaired mechanical coupling between individual cells) or intracellular signaling pathways [8]. Several genes and gene loci are associated with this

disease, but cardiac magnetic resonance and signal-averaged electrocardiography are more definitive diagnostic tests than endomyocardial biopsy. Genetic testing is essential for family screening, because more than 60% of patients have a pathogenic mutation. The natural progress of the pathology has four steps: asymptomatic period, arrhythmogenic period, development of the right heart failure, and finally biventricular failure. The prior clinic course is syncope or sudden death (20%) before development of heart failure, which is the late manifestation of the disease. Diagnosis must be evaluated on major and/or minor criteria, where several signs on the electrocardiography are essential for diagnosis: T wave inversion in the right precordial leads (v1–v3), right bundle branch block, Epsilon wave, and terminal activation delay. Because prevention of sudden cardiac death caused by ventricular arrhythmias is the primary goal of management, a cardioverter-defibrillator implantation is the first stage of the therapy. Beta-blocker therapy with exercise restriction should be included in the medical treatment, because exercise is the only triggered predictor for ventricular arrhythmias and sudden death. But, the curative treatment for significant heart failure is the cardiac transplantation.

2. Specific reversible cardiomyopathies

Secondary CMPs affects the myocardium in a multi-organ approach. There are several etiologic diseases that impair the physiologic functions of the heart and cause structural changes, which can result in chronic heart failure and/or arrhythmias [9]. Most of them are reversible, if the appropriate management is implemented.

Ischemic CMP is included in dilated CMP group with the highest frequency (2/3–3/4 of all cases). Hibernating, stunning or severe ischemic myocardium make the clinical status worse temporarily, but diffuse fibrosis or necrotic and scarred myocardium results in irreversible myocardial dysfunction. In the presence of viable tissue, coronary revascularization with or without surgical correction of mechanical complications may remove this adverse remodeling. Transmural myocardial infarction, incomplete coronary revascularization, coronary bypass graft failure or inadequate myocardial protection during open-heart surgery can trigger ischemic CMP. If ischemia cannot be resolved, this pathology causes irreversible remodeling and left ventricular dilatation, therefore medical treatment is poor. Mechanical complications of coronary artery disease such as mitral regurgitation and left ventricular aneurysm can complicate the clinic course and precipitate heart failure, but surgical treatment modalities of heart failure can only extend patient-life. Left ventricular assist device or heart transplantation must be the preferred treatment in patients with end-stage heart failure. In limited cases, left ventricular reconstruction associated coronary revascularization can terminate irreversible remodeling phase and improve left ventricular function.

Myocarditis is defined as inflammation of the myocardium, and it has an acute or chronic process. The pathology is characterized by inflammatory cells, interstitial edema, focal myocyte necrosis, and fibrosis, whereas autoimmune reaction can cause myocardial damage. Etiologic factors are different: infectious agents (viruses), toxins, drugs, cytotoxic chemother-

apy, and hypersensitivity reactions. Viral cause (coxsackie, cytomegalovirus, HIV, etc.) is the most common reason for myocarditis, and three pathophysiological phases show pathologic course: viral, immunologic response, and cardiac remodeling phases. The most important phase is the immunologic response with a dual role. It is activated to eliminate as many virus-infected cells as possible to control the infection. Second role is the control of this response to prevent excessive tissue damage and organ dysfunction against monoclonal antibodies, which attack directly to receptors on viruses and also receptors on cardiomyocytes. This causes in subacute and chronic inflammation, which results in myocyte necrosis, fibrosis, and remodeling. Ventricular remodeling includes chamber dilatation, regional hypertrophy, and regional wall motion abnormalities. Patients with mild cardiac involvement will generally recover without long-term sequel, whereas chronic form has a lower recovery rate (30%) and the majority develops dilated CMP. The first-line therapy is supportive care; a hemodynamic support can be necessary in a small group of patients. Patients with end-stage heart failure must be treated with mechanical support using LVAD or heart transplantation.

Sepsis-induced CMP occurs very common (60%) during sepsis or septic shock with high incidence of death. The myocardium is functionally and structurally injured by inflammatory cytokines and mitochondrial dysfunction [10]. It has a classical triad: affecting both ventricles and causing global ventricular dysfunction (decreasing biventricular ejection fraction), left ventricular dilatation (diastolic dysfunction with elevated left ventricular end-diastolic volume), and recovery in 7–10 days. Chemical mediators (endotoxins, cytokines, histones, and nitric oxide) decrease myofibril response to calcium, downregulate β-adrenergic receptors and induce mitochondrial dysfunction. The therapy should include antibiotics, vasopressor support, and perhaps, plasmapheresis. Inotropic catecholamines support, such as dobutamine and dopamine, is not suggested due to causing of hyperkinesis; on the contrary, β-blockade may be effective by lowering adrenergic stimulation. Levosimendan and/or intra-aortic balloon pumping can improve myocardial function and cardiac output.

Peripartum CMP is a rare phenotype of dilated CMP, and congestive heart failure can develop in the third trimester of pregnancy or the first 6 months postpartum. The cause is unknown, but this cardiomyopathy develops generally in obese, multiparous women >30 years of age with preeclampsia. The pathologic etiology is increased fetomaternal transfer of cells (fetal microchimerism), which may trigger an exaggerated autoimmune response in the postpartum period [11]. Peripartum CMP can recover completely or almost completely within 6 months in a half of patients, if not, progressive cardiac failure is the prognosis requiring LVAD support or heart transplantation.

Sympathoexcitation-induced CMP is also known as stress or Takotsubo CMP, or apical ballooning syndrome. It is most present in older women like an acute coronary syndrome without any angiographic findings. Increased catecholamines lead to elevation of systemic vascular resistance and systolic blood pressure, and cardiac output. During hypercontraction of the left ventricle, basal segments of the left ventricle contract more strongly than mid and apical segments, and that asynchronism increases stress in the left ventricular apex and produces a balloon-like appearance of the distal left ventricle during systole (regional dys-

function). Restriction of exercise and the use of β-adrenergic blockers return the left ventricular function to normal within a few weeks.

Metabolic CMP can develop secondary to several endocrine diseases, familial storage pathologies, or nutritional deficiencies. Typical phenotype is thyroid dysfunction, where dysthyriodism (hyper- or hypothyroidism) causes a low cardiac output CMP. Thyroid hormones act as receptors and ion channels in the myocardium to improve myocardial function, and they also have a peripheral vasodilatory effect to reduce peripheral vascular resistance. Both pathologies cause heart failure by upregulation or downregulation of the previously mentioned myocardial structures. ß-adrenoreceptor blockers normalize the left ventricular mass index and systolic function after treatment, and also prevent atrial arrhythmias.

Cirrhotic CMP is a chronic cardiac dysfunction without any cardiac disease and develops secondary to end-stage liver failure caused by several factors, especially by toxic effect of alcohol. The pathophysiologic changes include attenuated systolic contractile response to any strain, diastolic dysfunction, electrophysiological abnormalities, and chronotropic incompetence. The typical hemodynamic signs of alcoholic cirrhosis are hyperdynamic circulation with high cardiac output, decreased peripheral resistance and arterial pressure. Depression or desensitization of β-adrenergic receptors impairs chronotropic and inotropic responses of the heart and can be the early sign of cirrhotic CMP [12]. The second mechanism is downregulation of intracellular calcium kinetics. The third mechanism is rising of circulatory vasodilatations such as nitric oxide (peripheral), carbon monoxide (hepatic), and endocannabinoids (splanchnic), which can have adverse effect on the heart. Because CMP worsens with the progression of the underlying liver failure, liver transplantation with withdrawn of alcohol is the first-line therapy to reverse cardiac failure.

Obesity (lipotoxic) CMP has hyperdynamic circulation because of increased adipose tissue metabolism, which may cause left ventricular hypertrophy and dilatation. Obesity is one of the main causes of insulin resistance and hyperglycemia, and glucotoxicity increases pathophysiologic changes. The other reasons can be an imbalance in the adiponectin-leptin ratio, cardiac lipotoxicity or steatosis, and/or non-oxidative pathway induced by excess fatty acids. All these changes cause defective intracellular signaling, chronic inflammation, intracellular dysfunction, and apoptosis [13].

Diabetes mellitus-related CMP occurs due to myocardial microangiopathy or disturbed myocardial metabolism in the absence of coronary artery atherosclerosis. It has two different phenotypes: dilated left ventricular cavity with reduced ejection fraction or restrictive left ventricular cavity with reserved ejection fraction [14]. In restrictive phenotype, the left ventricle is normal sized but stiff with high resting tension due to hypertrophied cardiomyocytes with normal sarcomeres and limited collagen deposition in-between cardiomyocytes. In dilated phenotype, the left ventricle is enlarged due to damaged cardiomyocytes with loss of sarcomeres and severe collagen deposition with fibrosis. Several pathophysiologic mechanisms affect myocardial remodeling and dysfunction: hyperglycaemia, lipotoxicity, insulin resistance, microvascular advanced glycation end-products deposition, microvascular rarefaction, and autoimmunity (especially for dilated phenotype).

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