Cardiomyopathies: An Overview

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1. Introduction

Cardiomyopathies are a heterogeneous group of pathologies characterized by structural and functional alterations of the heart [1]. The recently proposed MOGE(S) nosology system embodies all of these characteristics, and describes the morphofunctional phenotype (M), organ(s) involvement (O), genetic inheritance pattern (G), etiological annotation (E), including genetic defect or underlying disease/substrate, and the functional status (S) of the disease using both the American College of Cardiology/American Heart Association stage and New York Heart Association functional class. The proposed nomenclature is supported by a web-assisted application and assists in the description of cardiomyopathy in symptomatic or asymptomatic patients and family members in the context of genetic testing [2]. Dilated cardiomyopathy is one of the main causes of heart failure [3][4]. Hypertrophic cardiomyopathy (HCM) is the most common inherited cardiomyopathy due to mutations in numerous genes. Restrictive cardiomyopathy (RCM) is a heart-muscle disease characterized by stiffness of the ventricular walls leading to diastolic dysfunction, raised end-diastolic pressure, and dilated atria [1]. Arrhythmogenic cardiomyopathy (ARCV) is a pathology characterized by the substitution of the myocardium by fibrofatty tissue, which determines the development of arrhythmias, reduced systolic function, and sudden cardiac death, especially in young patients [1]. Takotsubo cardiomyopathy, also known as stress-induced cardiomyopathy or broken-heart syndrome, is defined as an abrupt onset of left ventricular dysfunction in response to severe emotional or physiologic stress [1]. The purpose of this narrative review is to focus on the most important cardiomyopathies, their epidemiology, their genetic aspects, diagnosis, and their management.

2. Hypertrophic Cardiomyopathy (HCM)

It is the most common inherited cardiomyopathy due to mutations in numerous genes, encoding sarcomere proteins and is transmitted with an autosomal dominant pattern with variable penetrance. HCM is characterized by cardiac hypertrophy, particularly of the left ventricle (LV) (wall thickness ≥ 15 mm), in the absence of overload conditions (e.g., hypertension, valvular disease, etc.), which could justify this thickening [5][6]. In particular, in an adult, HCM is defined by a wall thickness >15 mm in one or more MV myocardial segments, as measured by an imaging technique, and is not explained solely by loading conditions. As in adults, in children, the diagnosis of HCM requires wall LV thickness more than two standard deviations greater than the predicted mean [5]. In the literature, it was first described in 1868 by Vulpian et al., who defined it as idiopathic hypertrophic subaortic stenosis [7]. This and the subsequent descriptions by Broke and Teare, in the 1950s, devoted much attention to the obstruction of the outflow tract of the left ventricle (LVOTO). These data in fact are present in about 70–75% of patients with HCM and this constitutes hypertrophic obstructive cardiomyopathy [8][9][10]. Clinically, HCM can remain asymptomatic or paucisymptomatic for a long time. Some of the symptoms include exertional dyspnea, chest pain, syncope, and palpitations. These symptoms can be associated with ventricular and supraventricular arrhythmias. In some cases, fortunately rare, the first clinical manifestation is sudden cardiac death (SCD). The prevalence of HCM reported is equal to 1:500 (0.2%) [11][12][13]. The prevalence of HCM has been underestimated for years because the echocardiogram has a lower sensitivity than magnetic resonance imaging (MRI) [14][15]. Some author defines, considering some correction factors, the estimated prevalence as at least 1:200 (0.5%) [16]. Women are older at diagnosis than men, have greater symptom severity (NYHA class), and are more likely to have left ventricular outflow tract [17][18].

3. Sudden Cardiac Death (SCD)

It has been reported that HCM is the most important cause of sudden death on the athletic field in the United States [19]. In preventive strategies for SCD, competitive sport and strenuous exercise should be discouraged in these patients. Implantable cardioverter defibrillators (ICDs) are recommended for secondary prevention for patients with a history of cardiac arrest due to VT or ventricular fibrillation (VF) or spontaneous sustained VT causing syncope or hemodynamic compromise (38). In primary prophylaxis, the decision to implant an ICD is done case by case. It is usually implanted when at least one of the following major risk markers [10] is present:

- Family history of HCM-related sudden death;
- Massive LVH (≥30 mm);
- Unexplained syncope;
- End stage HF (ejection fraction <50%);
- Multiple, repetitive NSVT;
- Extensive LGE;
- LV apical aneurysm.

If the level of risk remains uncertain, to help make the decision potential risk mediators are considered:

- Marked LV outflow obstruction at rest;
- Hypotensive response to exercise;
- Age ≥ 60 years (reduced risk);
- Alcohol septal ablation.

4. Arrhythmogenic Cardiomyopathy (ARCV)

Arrhythmogenic cardiomyopathy (ARCV) is an arrhythmogenic disorder of the myocardium not secondary to ischemic, hypertensive, or valvular heart disease. ARCV incorporates a broad spectrum of genetic, systemic, infectious, and inflammatory disorders. This designation includes, but is not limited to, arrhythmogenic right/left ventricular cardiomyopathy, cardiac amyloidosis, sarcoidosis, Chagas disease, and left ventricular noncompaction. The ARCV phenotype overlaps with other cardiomyopathies, particularly dilated cardiomyopathy with arrhythmia presentation that may be associated with ventricular dilatation and/or impaired systolic function [20]. In 1968 in France, there was the first demonstration of an infiltration of fibrofatty tissue in the right ventricle [21]. Initially it was called arrhythmogenic right ventricular dysplasia; then it became arrhythmogenic right ventricular cardiomyopathy. The term “arrhythmogenic cardiomyopathy” is used to describe a family of diseases that features structural myocardial abnormalities (identified by macro and microscopic pathological examination besides cardiac imaging) and ventricular arrhythmia [22]. The manifestations were more present in the right ventricle, but over time it was understood that the left ventricle could also be involved equally to the right or it could be predominant[23][24][25]. The prevalence of arrhythmogenic cardiomyopathy ranges from 1:1000 to 1:5000. This variability is linked to the fact that sudden cardiac death is often the presentation and arrhythmogenic cardiomyopathy is not recognized as a cause in 30% of cases [26][27]. A characteristic element is the high prevalence in Northeast Italy [28]. There, cardiomyopathy has the highest prevalence in cases of sudden cardiac death. In fact, European and American studies indicate that, in the post mortem evaluations of subjects with sudden cardiac death, arrhythmogenic cardiomyopathy was present in 20–31% [28].

4.1. Causes

Arrhythmogenic cardiomyopathy is a disease with a genetic basis, and it is characterized by the progressive replacement of the myocardium with fibrofatty tissue that progressively starts from the epicardium to become transmural, with the development of multiple aneurysms. The localization typically is in the dysplasia triangle, which includes apex, influx tract, and outflow tract of the right ventricle, but often also involves the left ventricle (up to 76% of cases) [29][30]. Another interesting element is the finding of a viral genome in autopsies, suggesting an infectious cause. Most likely viruses are

not the cause and myocardial degeneration could encourage a viral infection [31]. From the genetic point of view, the most important mutations related to arrhythmogenic cardiomyopathy are those of the desmosome genes.

The most involved genes are:

- JUP,
- DSP,
- PKP2,
- DSG2,
- DSC2.

The JUP mutation causes Naxos disease, which is a disease typical of the Greek island in which patients have palmoplantar keratoderma, woolly hair, and arrhythmogenic cardiomyopathy with a recessive pattern. The mutations of the DSP gene have been found in South America in a recessive disorder characterized by keratoderma, wooly hair, and arrhythmogenic cardiomyopathy, but with a prevalence of the left ventricle.

Other genes involved are those linked to the nuclear envelope:

- LMNA and TMEM43 genes.

Then there are mutations of the composite area. The area composita is a mixed type of junctional structure composed of both desmosomal and adherens junctional proteins.

However, there are genes in common with other cardiomyopathies (such as DES, PLN, TGFB3, TTN, SCN5A) [30].

5. Restrictive Cardiomyopathy (RCM)

Restrictive cardiomyopathy (RCM) is a heart-muscle disease characterized by stiffness of the ventricular walls leading to diastolic dysfunction, raised end-diastolic pressure, and dilated atria. The ventricles are not dilated and there is physiological wall thickness. Therefore, systolic function is usually preserved. Impairment of the ventricular structure and its systolic function may be present only in the advanced stages of secondary RCM [32]. RCM is not a single disease but can be the result of multiple inherited or acquired predispositions. As in other cardiomyopathies, also in RCM there are genetic mutations in the genes encoding the sarcomere proteins that have been associated. Epidemiology of this disease in not so well represented in literature, but RCM is the least common of the cardiomyopathies. An idiopathic pattern in which no identifiable cause is found is a really rare disease. It can affect people at any age. Children have the worst prognosis and girls seem to be more affected [33]. It can be acquired or inherited. In the latter case, for each cause some peculiar gene mutations have been identified.

5.1. Causes

RCM is classified in:

- Infiltrative:

  (a)Amyloidosis (acquired/inherited);

  (b)Genes: TTR gene variants (V122I; I68L; L111M; T60A; S23N; P24S; W41L; V30M; V20I), APOA1;

  (c)Sarcoidosis (acquired);

  (d)Primary hyperoxaluria (inherited).

- Storage disease:

(a)Fabry disease (inherited). Gene: GLA;

(b)Gaucher disease (inherited). Gene: GBA;

(c)Hereditary hemochromatosis (inherited). Genes: HAMP, HFE, HFE2, HJV, PNPLA3, SLC40A1, TfR2;

(d)Glycogen storage disease (inherited);

(e)Mucopolysaccharidosis type I (Hurler syndrome) (inherited). Gene: IDUA;

(f) Mucopolysaccharidosis type II (Hunter syndrome) (inherited). Gene: IDS;

(g)Niemann–Pick disease (inherited). Genes: NPC1, NPC2, SMPD1.

- Non-infiltrative:

(a)Idiopathic (acquired);

(b)Diabetic cardiomyopathy (acquired);

(c)Scleroderma (acquired);

(d)Myofibrillar myopathies (inherited). Genes: BAG3, CRYAB, DES, DNAJB6, FHL1, FLNC, LDB3, MYOT;

(e)Pseudoxanthoma elasticum (inherited). Gene: ABCC6;

(f) Sarcomeric protein disorders (inherited). Genes: ACTC, β-MHC, TNNT2, TNNI3, TNNC1, DES, MYH, MYL3, CRYAB;

(g)Werner's syndrome (inherited). Gene: WRN.

- Endomyocardial:

(a)Carcinoid heart disease (acquired);

(b)Endomyocardial fibrosis idiopathic (acquired);

(c)Hypereosinophilic syndrome (acquired);

(d)Chronic eosinophilic leukemia (acquired);

(e)Drugs (serotonin, methysergide, ergotamine, mercurial agents, busulfan) (acquired);

(f) Endocardial fibroelastosis (inherited). Genes: BMP5, BMP7, TAZ;

(g)Consequence of cancer/cancer therapy: metastatic cancer, drugs (anthracyclines), radiation (acquired).

6. Takotsubo Cardiomyopathy

Takotsubo cardiomyopathy, also known as stress-induced cardiomyopathy or broken-heart syndrome, is defined as an abrupt onset of left ventricular dysfunction in response to severe emotional or physiologic stress (1). Post-menopausal women are most commonly affected. The exact prevalence has been estimated at 0.02% of hospitalized patients. It has been reported that takotsubo cardiomyopathy accounts for 1–2% of admissions for acute coronary syndrome [34][35][36][37]. It often presents with angina. Typical ischemic changes may be seen with EKG and with elevated cardiac enzymes [34]. On echocardiography, a pattern of apical ballooning of the left ventricle has been reported. Because its presentation closely mirrors that of acute coronary syndrome, takotsubo cardiomyopathy initially should be treated in the same way.

Acute complications, such as shock or heart failure, should be managed appropriately. Stable patients may be treated with diuretics, ACE inhibitors or ARBs, and beta-blockers [34]. Anticoagulants should be provided to patients with loss of wall motion in the left ventricular apex [34]. Symptoms and abnormalities typically reverse within one month, and treatments may be withdrawn accordingly [34][35].

7. Peripartum Cardiomyopathy

Peripartum cardiomyopathy is a cause of heart failure during pregnancy and the peripartum period [38]. The ESC Working Group defined the following characteristics to identify peripartum cardiomyopathy:

- Development of heart failure (HF) toward the end of pregnancy or within five months following delivery.
- Absence of another identifiable cause for the HF.
- Left ventricular (LV) systolic dysfunction with an LV ejection fraction (LVEF) of less than 45 percent. The LV may or may not be dilated [38].

The incidence is highly variable, ranging from 1:968 to 1:4000 live births in the USA, 1:10,149 in Denmark, 1:5719 in Sweden [39][40][41]. The etiology remains quite uncertain; some mechanisms have been considered, such as angiogenic imbalance. In this regard, studies have shown how the lack of the PGC-1α gene, a regulator of pro-angiogenic factors such as VEGF, can lead to the development of peripartum cardiomyopathy [42]. Some studies show how mice knockout in the cardiac tissue-specific signal transduction and activator of transcription 3 (STAT3) develop peripartum cardiomyopathy. Reduction in STAT3 leads to increased cleavage of prolactin into an antiangiogenic and proapoptotic 16kDa isoform by cathepsin D. This alteration in prolactin processing may contribute to the angiogenic imbalance [43]. The 16 kDa prolactin fragment also causes endothelial damage and myocardial dysfunction [36]. Other studies reported that there is an increased presence of TNF alpha and Il-6 in women with peripartum cardiomyopathy, so there may be a correlation between cytokines and peripartum cardiomyopathy [37]. Some authors have proposed a genetic predisposition, evaluating the frequent overlap between peripartum cardiomyopathy and dilated cardiomyopathy on the basis of alteration of some genes such as that of titin [44]. Possible risk factors are [45][46][47][48][49]:

- Age greater than 30 years;
- African descent;
- Pregnancy with multiple fetus;
- Preeclampsia, eclampsia;
- Cocaine abuse;
- Long-term use (>4 weeks) of tocolytics (terbutaline).

The most typically observed symptoms are dyspnea, cough, orthopnea, nocturnal dyspnea, peripheral edema, fatigue; these latter symptoms are not very specific during pregnancy. Possible complications can be arrhythmias and the development of thromboembolism [50][51].

The diagnosis is mostly clinical, but EKG, laboratory, and radiological tests may present alterations:

- EKG: in 50%, it presents anomalies such as sinus tachycardia, repolarization anomalies, Q waves [52];
- BNP: BNP is typically high [53];
- Chest X-ray: Enlargement of the cardiac silhouette, redistribution of flow, and pleural effusion may be found [54];
- Echocardiography: Reduction in left ventricular ejection fraction (<45%) and frequent left ventricle dilatation [55].

There are few studies about novel markers, such as plasma concentrations of proangiogenic and antiangiogenic factors, including placenta growth factor, fms-like-tyrosine-kinase 1 receptor, and their ratios, which have been proposed to be used to distinguish patients with peripartum cardiomyopathy, but other studies are needed [56]. The management of peripartum cardiomyopathy therefore follows the guidelines of the management of heart failure: adequate oxygen must be administered, preload optimized, inotropes administered, if necessary, for relief of symptoms. Arrhythmias must be

managed and if necessary, an ICD must be implanted. Anticoagulant therapy [57] must be set up. There are currently experimental protocols under study: bromocriptine, intravenous immune globulin, antisense therapy against micronRNA-146a and apheresis [57][58][59][60]. As for the delivery, the decision must be shared in a team with the presence of the cardiologist, gynecologist, anesthetist, and neonatologist [57]. A hemodynamically stable patient can undergo vaginal delivery with epidural. In a woman with hemodynamic instability, an emergency delivery is necessary. In women with advanced heart failure and use of inotropes, a caesarean delivery should be planned [38]. As regards breastfeeding, there are no reliable data; some authors suggest that women with advanced heart failure should not breastfeed due to the potential role of prolactin, but certainly those who are hemodynamically stable should be encouraged to breastfeed [37][61]. The mortality of peripartum cardiomyopathy is 10% in two years, 6% in five years (11). Complete recovery of left ventricular function is reported in 20–70% of patients, with recovery usually within six months of diagnosis [62][63][64].

8. Cardiotoxicity and Chemotherapy Drugs

Cancer patients undergoing chemotherapy may develop cardiomyopathies. The agents most involved are anthracyclines and trastuzumab. The mechanism by which anthracyclines create myocardial damage may be linked to the development of oxygen free radicals (ROS) which increase oxidative stress and therefore create myocardial damage. More recent studies find the implication of the enzyme topoisomerase II; doxorubicin binds topoisomerase 2 and DNA forming a ternary complex leading to cell death, cardiomyocytes present topoisomerase 2 alpha and beta, and it appears that doxorubicin can bind cardiac topoisomerases, resulting in the death of myocytes [63][64]. Among the most implicated risk factors are[65][66] :

- Old age (<65 years) or young (>4 years);
- Female gender;
- Pre-existing heart disease;
- Hypertension;
- Smoke;
- Hyperlipidemia;
- Obesity;
- Diabetes;
- High cumulative anthracycline exposure.

As for trastuzumab, a monoclonal antibody that targets the human epidermal growth factor receptor 2, the modality with which it determines cardiotoxicity is different from anthracyclines, because it does not cause myocardial damage, but an alteration to the contractility, which therefore makes the latter cardiomyopathy more frequently reversible and less linked to drug accumulation [67][68].

Risk factors for developing trastuzumab cardiomyopathy are[69][70]:

- Over 50 years of age;
- Previous or concomitant use of anthracyclines;
- Obesity;
- Preexisting cardiac dysfunction;
- Hypertension.

The clinical manifestations of anthracycline cardiomyopathy are linked to early symptoms such as EKG abnormalities, arrhythmias, atrioventricular blocks, and pericarditis-myocarditis; vice versa, we can find late signs that are related to the development of heart failure such as dyspnea, asthenia, edema, orthopnea [70][71][72][73][74][75]. Other chemotherapy agents that can cause cardiomyopathies are:

- Paclitaxel: Associated with doxorubicin, it has been shown to cause heart failure in 20% of patients [76][77];
- Cyclophosphamide: Heart failure is found in patients with high dose protocols; negative prognostic factors are lymphoma, preceding mediastinal irradiation, advanced age, cardiac abnormalities [78][79];
- Cisplatin: Cardiotoxicity due to cisplatin can be manifested by supraventricular tachycardia, bradycardia, ST-T wave changes, left bundle branch block, acute ischemic events, myocardial infarction, and ischemic cardiomyopathy. This toxicity may be related to electrolyte abnormalities secondary to cisplatin-induced nephrotoxicity [80][81].

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