Sex differences in heart failure

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Chapter 2

Sex differences in cardiomyopathies.

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Abstract

Cardiomyopathies are a heterogeneous group of heart muscle diseases with a variety of specific phenotypes. According to the contemporary European Society of Cardiology classification, they are classified into hypertrophic (HCM), dilated (DCM), arrhythmogenic right ventricular (ARVC), restrictive (RCM), and unclassified cardiomyopathies. Each class is aetiologically further categorized into inherited (familial) and non-inherited (non-familial) forms. There is substantial evidence that biological sex is a strong modulator of the clinical manifestation of these cardiomyopathies, and sex-specific characteristics are detectable in all classes. For the clinician, it is important to know the sex-specific aspects of clinical disease expression and the potential modes of inheritance or the hereditary influences underlying the development of cardiomyopathies, since these may aid in diagnosing such diseases in both sexes.

Introduction

The importance of sex differences is gaining increasing attention in cardiovascular medicine.[1] Various studies have demonstrated marked differences between males and females in ischaemic heart disease, in terms of risk factors, aetiology, disease manifestation, diagnostic modalities, the use and effectiveness of various therapies, and prognoses.[2–4] Likewise, several studies have revealed sex differences in heart failure[5] and cardiac arrhythmias.[6] This has led to worldwide research and educational initiatives on the specific characteristics of cardiovascular disease in women.[7–9] In 2008, the Working Group of the European Society of Cardiology published a position statement on the classification of cardiomyopathies.[10] 'Cardiomyopathy' was defined as a myocardial disorder in which the heart muscle is structurally and functionally abnormal, in the absence of coronary disease, hypertension, and valvular and congenital disease sufficient to cause the observed myocardial abnormality. The disease entity was classified into five distinct morphological and functional phenotypes, as they present to the attending physician. Accordingly, the cardiomyopathies are currently referred to as hypertrophic, dilated, arrhythmogenic right ventricular, restrictive, or 'unclassified'. Each phenotype can be subclassified into inherited (familial) and non-inherited (non-familial) forms. Importantly, in this classification, hypertrophic cardiomyopathy (HCM) merely refers to the phenotype of a hypertrophied left ventricle, routinely diagnosed by increased wall thickness on an echocardiogram. Likewise, dilated cardiomyopathies merely refer to a phenotype characterized by dilatation and reduced systolic function of the left ventricle, and the same principle applies to the remaining three main cardiomyopathy types. Overall, this classification provides a valuable framework for use in daily clinical practice when first confronted with a patient who may be suffering from a cardiomyopathy. However, this phenotype-focused approach leaves the specific underlying aetiology to be determined in any kind of cardiomyopathy. An increasing body of data indicates that sex plays an important role in various forms of cardiomyopathy, in terms of its prevalence, severity, and prognosis. Here we present an overview of the literature on sex

differences in cardiomyopathies. For practical purposes, our overview does not cover very rare forms of cardiomyopathies and is confined to those occurring in adult patients. Where a potential or more definite biological explanation for a sex difference in cardiomyopathy is available, it will be summarized.

Hypertrophic cardiomyopathy

Familial hypertrophic cardiomyopathy

This subgroup of cardiomyopathies comprises 'true' HCM but also other inherited cardiomyopathies with LV hypertrophy: glycogen storage diseases, lysosomal storage diseases, familial transthyretine-related amyloidosis, carnitine deficiency, syndromal disorders, and mitochondrial cardiomyopathies.[10] For the latter two groups there are no known sex differences so far.

Hypertrophic cardiomyopathy

Hypertrophic cardiomyopathy is the most common inherited cardiac disorder, with an estimated prevalence of 1:500.[11] It is characterized by LV hypertrophy, which usually affects the interventricular septum (occasionally causing LV outflow obstruction) but may also affect other parts of the left ventricle.[12] At the histological level, the key findings are myocardial disarray and fibrosis. In the vast majority of cases, HCM is due to a mutation in a gene encoding a component of the cardiac sarcomere.[13] Commonly involved genes are those encoding β-myosin heavy chain (MYH7), myosin-binding protein C (MYBPC3), and cardiac troponin T (TNNT2 and TNNI3), and these are detectable in ~75% of HCM patients.[14,15] However, the relative frequencies of the genes or specific mutations involved may differ across populations and the relationship between genotype and phenotype varies.[14] The mode of inheritance is autosomal dominant, which implies that equal numbers of males and females are carriers of the underlying disease-causing mutation.[11] However, there are

phenotypic differences between the sexes. The largest study to date, by Olivotto et al.[16] was in 969 consecutive patients with HCM; they showed a higher prevalence in males than females (3:2). Interestingly, males were more often diagnosed fortuitously by routine medical examination than females (41% vs. 23%), in whom the diagnosis was mainly established after onset or worsening of cardiac symptoms or occurrence of cardiovascular events. In addition, the average age at diagnosis was significantly lower in males than in females (38 ± 18 years vs. 47 ± 23 years). However, at presentation, females were more symptomatic than males (NYHA class 1.8 ± 0.8 vs. 1.4 ± 0.6) and more frequently showed LV outflow obstruction (37% vs. 23%). Moreover, female sex was independently associated with the risk of symptom progression to NYHA class III/IV or even death from heart failure or stroke. Essentially similar findings were reported in other studies,[17–19] although females were under-represented, generally presenting at an older age, with more symptoms than males, and showing a more severe disease course. In order to delineate possible underlying mechanisms, Schulz-Menger et al.[20] performed a magnetic resonance imaging (MRI) study, using the LV remodelling index (LV mass/LV end-diastolic volume). This index was comparable in males and females with LV outflow obstruction, but, in patients without obstruction, females had a lower remodelling index compared with males. Although the clinical implications of these findings are currently uncertain, it shows that sex is associated with differences in LV remodelling in HCM.

Danon's disease

Danon's disease is a rare glycogen storage disorder[21] caused by a deficiency of lysosome-associated membrane protein 2 (LAMP2). This is due to mutations in LAMP2, the gene encoding LAMP2, located on chromosome Xq24. A number of missense mutations, small deletions or insertions, and splice site mutations have been reported. The precise function of LAMP2 is unknown, but it is involved in lysosomal enzyme targeting, autophagy, and lysosomal biogenesis, and deficiency leads to storage of glycogen in various tissues. Danon's disease is characterized by

mental retardation, skeletal myopathy, and cardiomyopathy.[22,23] Because it is an X-linked disorder, males are primarily affected, but female (heterozygous) mutation carriers may also exhibit the phenotype.[21] Cardiomyopathy usually develops before 20 years of age in males and in adulthood in females.[21] The cardiomyopathy can be severe, with massive LV hypertrophy, and may be associated with pre-excitation (Wolff–Parkinson–White syndrome), which is a discriminating feature from HCM. The echocardiographic features are different between the sexes, with males predominantly showing an HCM phenotype, whereas females show an equal prevalence of HCM and dilated cardiomyopathy (DCM).[24,25] The diagnosis is made by muscle biopsy, which shows intracytoplasmic vacuoles containing autophagic material and glycogen. These vacuoles can also be found in myocardial tissue. Detection of a mutation in LAMP2 confirms the diagnosis. However, the diagnosis is usually established in teenage years in males, whereas females are diagnosed ~15 years later.[26]

Fabry's disease

Fabry's disease is a rare disease, caused by storage of glycosphingolipids in various organs and tissues due to a deficiency of the lysosomal enzyme α-galactosidase A (α-Gal A).[27] The underlying disorder is a mutation in GLA, the gene encoding α-Gal A, located on chromosome Xq22. More than 100 mutations have been reported, including missense, nonsense, or splice site mutations, and insertions/duplications and deletions. The phenotype of this multisystem disease is usually dominated by renal failure, neurological features (neuropathy), and skin abnormalities (angiokeratoma, anhydrosis). In addition, the heart is often affected; LV hypertrophy may develop due to myocardial deposition of glycosphingolipids, which is indistinguishable on a standard echocardiogram from HCM, including septal hypertrophy and LV outflow tract obstruction. The hypertrophy can be massive, with an LV wall thickness up to 30 mm. Short PR intervals are often seen on ECGs (without pre-excitation). Fabry's disease is an X-linked disease, affecting predominantly males, with females being carriers. Indeed, the clinical picture is far more pronounced

in males, although females may show the phenotype,[28] mostly characterized by neurological and cardiac symptoms.[29] In males with a suggestive phenotype, the diagnosis is made by demonstrating low α-Gal A activity in leucocytes or plasma. In females, demonstration of a mutation in GLA is required to confirm the diagnosis. Females usually show less progression of hypertrophy than males,[30] and it was recently suggested in an MRI study that replacement fibrosis may be a valid screening tool in females as opposed to males in the early stages of Fabry's disease.[31]

Familial transthyretine-related amyloidosis

Familial transthyretine-related amyloidosis (ATTR) is a form of amyloidosis caused by mutated transthyretine (or pre-albumin), leading to deposition of amyloid in various tissues and organs.[32] The underlying disorder is a autosomal dominant mutation of TTR, the gene encoding transthyretine. More than 100 mutations in TTR have been reported, but there are several mutational hot spots, with some populations having a high prevalence of certain mutations. For instance, in Portugal, Sweden, and Japan, the prevalence of ATTR is relatively high, mainly due to a common mutation in TTR leading to substitution of methionine to valine at position 30. The phenotype of ATTR is dominated by neurological alterations (neuropathy), but cardiomyopathy is also a common finding. However, several studies have shown that sex differences are present in both the occurrence of cardiomyopathy and the degree of the hypertrophy. Males with ATTR more often exhibit cardiomyopathy than females and have higher degrees of hypertrophy.[33] It is noteworthy that post-menopausal females with ATTR have more hypertrophy than pre-menopausal females, whereas an analogous age-related association is not present in males, implicating the influence of sex hormones. Indeed, in a mouse model, 5α-dihydrotestosterone was a strong inducer of transthyretine synthesis.[33,34]

Carnitine deficiency

Carnitine deficiency is a rare, autosomal recessive disorder, caused by mutations in SLC22A5, which encodes a sodium-dependent carnitine transporter protein involved in cellular carnitine uptake. Carnitine deficiency leads predominantly to metabolic or cardiac disease manifestations, including cardiomyopathy.[35] Although typically occurring in childhood, the onset of disease may vary and, rarely, the disease may also present in adulthood.[36] The disease is diagnosed preferentially in females, probably because of intensified screening activities in the mothers of infants with the disease.[36,37]

Non-familial hypertrophic cardiomyopathy

This subgroup of cardiomyopathies comprises non-inherited forms of LV hypertrophy, such as those seen in the setting of athletic training (athlete's heart), obesity, and non-familial amyloidosis. No sex differences have been reported regarding the cardiomyopathies associated with obesity and amyloid light-chain (AL) amyloidosis.

Athlete's heart

It is well established that athletic training may lead to cardiac remodelling, both electrophysiologically and structurally. Depending on the training intensity and duration, the size of the cardiac cavities often increases, in particular that of the left ventricle. In addition, LV wall thickness may eventually reach the level of LV hypertrophy. However, this remodelling process mainly affects males; at a comparable training intensity and duration, male athletes, on average, develop a higher degree of LV hypertrophy than females.[38,39] The hypertrophy is occasionally hard to distinguish from pathological hypertrophy caused by HCM. Importantly, in the athlete's heart, the diastolic function usually remains largely intact, yet subtle changes may occur, in particular in male athletes.[40] In

addition, recent evidence also suggests that athletic training may lead to adverse right ventricular remodelling, even towards a right ventricular cardiomyopathy phenotype.[41]

Senile systemic amyloidosis

The non-familial form of transthyretine amyloid deposition (wild-type) is referred to as senile systemic amyloidosis (SSA) and nearly exclusively affects the heart of elderly people.[32] Notably, SSA mainly occurs in males, suggesting a role for the sex hormones. Indeed, Goncalves et al.[42] demonstrated the effects of androgens and oestrogens on the expression of transthyretine in the liver of mice, which translated into a rise of transthyretine protein levels in the peripheral circulation. Importantly, 5α-dihydrotestosterone appeared to be a stronger inducer of transthyretine than 17β-oestradiol. The slow, life-long decrease in testosterone synthesis in males might serve to explain the predominant prevalence of SSA seen in elderly males[42] compared with the lesser incidence seen in females, with their rather steep pre-menopausal decrease in testosterone levels and their post-menopausal oestradiol withdrawal.

Dilated cardiomyopathy

In at least one-third of the patients with idiopathic DCM, familial occurrence can be noted, pointing to inherited disease.[43,44] Familial DCM mainly comprises autosomal dominant forms, caused by mutations in several different genes coding for the cytoskeleton, sarcomeric protein/Z-band, nuclear membrane, and intercalated disc proteins. In addition, there are a few X-linked forms, some of which are associated with muscular dystrophies, and other forms seen in mitochondriopathies and inherited metabolic disorders. Duchenne and Becker muscular dystrophies are the most common forms of myopathies, and they frequently show cardiac involvement.[45,46] Both muscular dystrophies are caused by mutations in DMD, the gene encoding dystrophin, which is a protein in the sarcolemma

linking the cytoplasm and extracellular matrix. Mutations in DMD result in either no functional (Duchenne) or inadequate (Becker) dystrophin production, leading to structural instability of the muscle cell membrane and muscle degeneration. Because of the compensatory function of the second, non-mutated X-chromosome in females, they have a lower chance of disease manifestation, but may also express the disease phenotype,[47] probably due to random X-chromosome inactivation or a gene dosage effect.[48] In general, familial DCM primarily affects males, with a reported male/female ratio of up to 1.5:1,[49] despite the usual mode of inheritance, which is autosomal dominant.[50] Herman et al.[51] reported on various mutations in TTN, the gene encoding the sarcomeric protein titin, in 312 patients with idiopathic DCM, which underlies the DCM phenotype in ~25% of cases. Interestingly, almost all patients developed DCM after the age of 40 years (full penetrance), and adverse DCM events, such as cardiac transplantation, implantation of an LV assist device, and cardiac death, occurred significantly earlier in males than in females carrying the TTN mutations. Likewise, Van Rijsingen et al.[52] observed sex differences in 269 patients with DCM due to mutations in the lamin A/C gene (LMNA). Males significantly more often developed relevant reduction of LVEF, malignant ventricular arrhythmias, and end-stage heart failure compared with females, and mortality was also higher in males. The molecular mechanism for the sex difference was established by Arimura et al.[53] who proved direct involvement of the androgen receptor and its co-activators in a mouse model, demonstrating testosterone effects on gene/protein expression and morphological disease expression.

Non-familial dilated cardiomyopathy

This subgroup comprises a variety of disorders, including cardiomyopathies due to myocarditis, alcohol abuse, peripartum cardiomyopathy, autoimmune diseases, drug toxicity, nutritional deficiencies, and tachycardia (tachycardiomyopathy). For the latter four disorders, no sex differences in the prevalence and severity of cardiomyopathy have been reported so far. In particular,

autoimmune diseases (e.g. Kawasaki disease and Churg–Strauss syndrome) are generally more common in females, but there are no data on cardiac involvement in established cases being different between the two sexes.

Myocarditis

Myocarditis is a common cause of DCM and may arise from infective, toxic, or immune sources. The involved pathogenetic pathways are known to be modulated by sex hormones, resulting in differences between the sexes in their cardiac response to inflammatory injury.[50] Indeed, mouse models show that myocarditis occurs more often in male than in female mice, and also that it is more severe in male mice.[54,55] These findings are in accordance with observational studies in humans that show a higher prevalence in males.[56–59]

Alcohol-induced cardiomyopathy Excessive alcohol consumption is myotoxic through various mechanisms[60] and associated with the development of cardiomyopathy.[61] In experimental studies on the effect of alcohol on cardiomyocytes, male animals showed more functional and structural myocardial impairment while female animal hearts were less affected.[62,63] However, in humans, females seem to have a higher sensitivity to the cardiotoxic effects of ethanol than males.[64,65] Urbano-Márquez et al.[61] demonstrated that there was no difference in the prevalence of DCM between the sexes, but females required a lower total lifetime dose of ethanol to develop the disease.

Peripartum cardiomyopathy

By its very nature, peripartum cardiomyopathy is a form of DCM confined to females.[65] It typically occurs between the last month before childbirth and the first 5 months thereafter.[66] Although the exact aetiology remains to be fully elucidated, Hilfiker-Kleiner et al. have identified a central pathophysiological role for the hormone prolactin in an animal model of peripartum cardiomyopathy,

and have introduced bromocriptine, a dopamine D2 receptor agonist, as a potential cure.[67] More specifically, their findings suggest that peripartum oxidative stress triggers the proteolysis of prolactin into a smaller 16 kDa fragment, which in turn has detrimental proinflammatory, antiangiogenic, and proapoptotic effects.[68] Of note, the occurrence of peripartum cardiomyopathy in families with DCM, the presence of DCM in family members of patients with peripartum cardiomyopathy, and the identification of mutations in these families suggest a role for genetic factors and raise the likelihood that peripartum cardiomyopathy can be an 'unmasked' form of familial DCM.[69–71]

Arrhythmogenic right ventricular cardiomyopathy

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is characterized by global or regional right ventricular dysfunction, which is caused by progressive right ventricular adipose and fibrous replacement of the myocardium. Besides histological proof of these structural changes, which may also affect the left ventricle, the diagnosis is based on functional abnormalities, including conduction disturbances and arrhythmias, in addition to the presence of right ventricular dysfunction.[10] In >50% of cases, ARVC can also be found in relatives, pointing to inherited disease in the majority of cases. Inheritance of ARVC is predominantly autosomal dominant, involving various genes encoding intercalated disc proteins, such as plakophilin and other proteins of the cardiac desmosomes.[72] In addition, mutations in genes encoding non-desmosomal proteins can be involved, including transforming growth factor-β3, the cardiac ryanodine receptor, tmem43, titin, α-catenin, desmin, and phospholamban.[73] However, autosomal recessive transmission has also been described related to mutations in genes encoding plakoglobin and desmoplakin.[74] Sex differences in the prevalence, phenotypes, and clinical courses of ARVC have been described. It is more prevalent in males than females, with an approximate ratio of 3:1.[75] In a group of 171 consecutive ARVC patients, Bauce et al.[76] found more severe disease expression in males than females, as indicated by larger right ventricular volumes, lower right ventricular EF, and more severe LV involvement. Moreover, ECG

abnormalities typical for ARVC and late potentials were more common in male than in female patients, which is consistent with more severe disease. Hodgkinson et al.[77] reported on the impact of implantable cardioverter-defibrillator (ICD) therapy in patients with a specific form of familial ARVC (ARVD5). In a group of 48 subjects at 50% a priori risk of inheriting ARVC (as defined by clinical, pedigree, and/or haplotype data), more males were classified as high risk, based on clinical events of sudden cardiac death or ventricular tachycardia, and the relative risk of early death was significantly higher in males than in females,[77] which is in line with other reports.[78,79] Bhonsale et al.[80] reported on 215 patients with arrhythmogenic right ventricular dysplasia/cardiomyopathy-associated mutations and found male sex to be an independent predictor of the first arrhythmic event on multivariable analysis. Finally, Merner et al.[81] identified the missense mutation in transmembrane protein 43 (TMEM43 c.1073C>T, p.S358L) as the cause of this fully penetrant, lethal form of ARVC. They also observed far more serious early events, such as heart failure and death, in males, which again clearly indicates an influence of sex. The cause of these sex differences in ARVC is unknown, but it has been shown that strenuous physical exertion in susceptible mice may elicit ARVC, and differences in physical exercise between males and females might thus play a role.[82]

Restrictive cardiomyopathy

Restrictive cardiomyopathy (RCM) refers to cardiomyopathy with the presence of restrictive ventricular physiology at normal or reduced ventricular volumes (systolic and/or diastolic of one or both ventricles), and normal wall thickness.[10]

Familial restrictive cardiomyopathy

Restrictive cardiomyopathy rarely occurs as a familial disease, but it can result from autosomal dominant, autosomal recessive, or X-linked inheritance. In most cases, transmission is autosomal

dominant, involving mutations in TNNI3[83] or DES[66,67] encoding troponin I and desmin,[84,85] respectively, the latter also being associated with conduction disorders and skeletal myopathy.[86,87] Infrequently, inheritance is autosomal recessive, for instance in the case of hereditary haemochromatosis being due to a mutation in HFE, the gene encoding human haemochromatosis protein, and leading to storage of iron in the myocardium. Reports on sex differences in familial RCM are scarce. Ammash et al.[88] reported on the experience of the Mayo Clinic in a group of 94 patients with idiopathic RCM, of whom 61% were females. Interestingly, despite the higher occurrence in the females, they showed significantly better survival than the males. However, Rivenes et al.[89] described a higher incidence of sudden cardiac death in girls with RCM.

Non-familial restrictive cardiomyopathy

Non-familial RCM mainly results from secondary endomyocardial or myocardial effects from various origins. The final common pathway is fibrotic tissue remodelling of the endocardium, such as is typical for endomyocardial fibrosis, hypereosinophilic syndrome, scleroderma, carcinoid heart disease, or anticancer therapies (radiation and cytostatic drugs). However, non-familial (AL/pre-albumin) amyloidosis and metastatic cancer infiltration of the myocardium may also result in RCM. A small, retrospective, single-centre study reported on a sample of 17 patients referred for surgery from 1971 to 1995 for endomyocardial fibrosis, and indicated that endomyocardial fibrosis was more common in females than in males.[90] However, no sex differences are known for hypereosinophilic syndrome, scleroderma, or carcinoid heart disease, nor for AL amyloidosis, in which cardiac involvement seems to be nearly equally distributed in both sexes.[33] Finally, RCM may also be due to radiation to the chest. Although there is substantial exposure bias (radiation to the chest being more common in females because of breast cancer), it is still not known whether RCM due to radiation is more common in females.

Unclassified cardiomyopathies

Familial unclassified forms

Non-compaction cardiomyopathy is a rare, structural myocardial disorder of acquired or congenital origin, characterized by prominent trabeculations and recesses in the LV walls. Non-compaction cardiomyopathy is often familial, and different genes are involved, in particular MYH7 and MYBPC3, which are also implicated in HCM.[10] In infants, X-linked inheritance may occur; however, an autosomal dominant pattern of inheritance is detectable in most adult non-compaction cardiomyopathy patients.[91] In a retrospective, single-centre study in 100 patients, Stöllberger et al.[92] described a higher prevalence of non-compaction cardiomyopathy in males, whereas females had more extensive disease. The outcomes were, however, comparable between males and females.

Non-familial unclassified forms

Tako-Tsubo cardiomyopathy (or 'stress cardiomyopathy') is an abrupt, transient, LV apical ballooning syndrome, mimicking myocardial infarction despite normal coronaries on angiography.[10] The pathogenesis of this relatively frequent disorder seems to be catecholamine-driven, transient myocardial dysfunction, and Tako-Tsubo cardiomyopathy usually has a benign prognosis.[93] Interestingly, Tako-Tsubo cardiomyopathy occurs preferentially in females, in particular post-menopausal females.[94,95] Although disease presentation has been reported to be similar between the sexes, Tako-Tsubo cardiomyopathy is more often triggered by emotional stressors in females and physical stressors (e.g. severe pain or acute illness) in males.[96] In the case of a physical stressor, clinical disease manifestation is usually more severe, with shock or cardiac arrest,[97] which might point to a biologically less well-established physical stress resistance in male than in female hearts.[98] The pathophysiological explanation for the epidemiological and clinical sex differences in Tako-Tsubo cardiomyopathy is unclear, but sex differences in the response to various kinds of

myocardial stress have been well established experimentally and suggest that sex hormones have some influence.[99] Accordingly, Brenner et al.[100] analysed the levels of sex hormones in post-menopausal women with Tako-Tsubo cardiomyopathy and age-matched females, with and without myocardial infarction, and found significantly higher oestrogen levels at hospital admission in Tako-Tsubo cardiomyopathy patients.

Discussion

Cardiomyopathies constitute a group of disorders encompassing a wide variety of specific diseases, but the available evidence indicates that significant sex differences are present in many cardiomyopathies. The most salient findings are summarized in Table 1. Although it is hard to generalize, hypertrophic and arrhythmogenic forms of cardiomyopathies appear to be more prominent in males, in terms of both prevalence and severity, whereas in dilated forms of cardiomyopathy the distribution varies depending on the specific (genetic) subtype. For example, DCM due to myocarditis or familial disease is more prominent in males, but females more often suffer from Tako-Tsubo cardiomyopathy. In addition, peripartum cardiomyopathy is an established form of DCM in females. Although the causes of sex interaction with the manifestation of cardiomyopathy are diverse and individual, several factors may play a role, some of which we have already alluded to above.

Table 1. Sex characteristics and differences between cardiomyopathies

	Males	Females
Hypertrophic cardiomyopathy		
Familial		
HCM (autosomal dominant)	Higher prevalence	Older at diagnosis, more outflow obstruction, worse symptoms (progression)
Danon's disease (X-linked)	Primarily affected, onset before adulthood	Onset in adulthood
Fabry's disease (X-linked)	Primarily affected, more severe manifestation	Usually mild manifestation
Familial transthyretine-related amyloidosis (autosomal dominant)	Higher prevalence, more hypertrophy	More hypertrophy in post-menopause
Carnitine deficiency (autosomal recessive)	Rare	Preferentially diagnosed
Non-familial		
Athlete's heart	Higher prevalence, more hypertrophy	Rare
Senile systemic amyloidosis	Higher prevalence, predominantly in elderly	Rare
Dilated cardiomyopathy		
Familial		
DCM (mainly autosomal dominant, occasionally X-linked)	Higher prevalence, more severe manifestation, and worse outcome	
Non-familial		
Myocarditis	Higher prevalence, more severe manifestation	
Alcohol-induced cardiomyopathy	Higher prevalence	Earlier manifestation
Peripartum cardiomyopathy		Exclusively in females
Arrhythmogenic right ventricular cardiomyopathy (mainly autosomal dominant, occasionally autosomal recessive)	Higher prevalence, more severe manifestation	ICDs (probably) less effective
Restrictive cardiomyopathy		
Familial (autosomal dominant, autosomal recessive or X-linked)	Better survival	Higher prevalence
Non-familial		Related to endomyocardial fibrosis
Unclassified		
Familial		
Left ventricular non-compaction (mainly autosomal dominant, occasionally X-linked)	Higher prevalence	Typical regional affection, more extensive disease
Non-familial		
Tako-Tsubo cardiomyopathy		Higher prevalence, predominantly in post-menopause

First, the mode of inheritance may affect the sex ratio of cardiomyopathy manifestation. In a subset of familial cardiomyopathies, the mode of inheritance is X-linked recessive, i.e. the causative gene is located on the X-chromosome. As a result, these cardiomyopathies primarily affect males: examples are the muscular dystrophies (Becker's disease and Duchenne's disease) and metabolic disorders (Danon's disease and Fabry's disease). Remarkably, females may also suffer from X-linked cardiomyopathies, although the signs and symptoms are usually only mild at most. This is due to random inactivation of the X-chromosome or just a gene dosage effect.[48,101] However, in most familial forms of cardiomyopathy, the inheritance is autosomal dominant,[10] which should theoretically result in a balanced sex distribution. Since this is not the case in several forms of these cardiomyopathies, we infer that other, non-genetic factors must be involved. Secondly, sex hormones seem to have profound effects on the prevalence and severity of cardiomyopathies. It is well established in different animal models that the response to volume- or pressure-induced myopathic stress is different in male and female hearts.[102–104] Females show a different remodelling pattern, with less fibrosis and more hypertrophy and preserved EF, as well as slower progression to heart failure compared with males.[105] Several studies have suggested a modifying role of the inter-relationship between oestrogen[106,107] and testosterone,[108] which can also be concluded from the considerably lower prevalence of cardiovascular disease in general in pre-menopausal compared with post-menopausal females and the earlier onset of cardiovascular disease in males.[109] Although the efficacy of hormone replacement therapy is still a matter of clinical research,[110] the sex hormonal (patho)physiological mechanisms are well established and also influence the manifestation of cardiomyopathies.[99,111] Oestrogen was thus shown to be involved in calcium handling and the metabolism of glucose, fatty acids, and nitric oxide, as well as extracellular matrix turnover, in different models of cardiomyopathies, together amounting to a protective effect from oestrogens in females in the setting of hypertrophy and heart failure.[99] However, Haines et al.[112] also demonstrated increased mortality of phyto-oestrogen-fed male mice in an HCM model, suggesting adverse effects

of oestrogen in HCM. The role of oestrogen in the pathogenesis of cardiomyopathy is particularly obvious in Tako-Tsubo cardiomyopathy, which occurs almost exclusively in post-menopausal women. Through effects on myocardial norepinephrine and calcium handling, with reduction of intracellular calcium accumulation, high oestrogen levels seem to protect pre-menopausal women against an overwhelming cardiomyopathic stress response.[113,114] The effects of testosterone on the manifestation of cardiomyopathies are less well established. Thirdly, gender effects may confound sex differences in cardiomyopathies. Whereas sex refers to biological differences between males and females, gender refers to the identity and behavioural aspects of differences between the sexes, and is subject to socio-cultural and psychological influences. In the general context of cardiovascular disease, it has been shown that females are more hesitant in seeking medical help in the case of symptoms compared with males, and that physicians are perhaps less willing to perform diagnostic and therapeutic procedures in females. It is readily conceivable that this also applies to subjects with a possible cardiomyopathy, in particular since many of these disorders are rare and symptoms and signs are often non-specific. As a result, differences between males and females in terms of disease manifestation may thus be either 'artificially' enlarged or obscured.

Conclusion

The manifestations of many cardiomyopathies are influenced by sex. In the diagnostic work-up of a subject presenting with a possible cardiomyopathy, the clinician should be aware of this issue. In addition, the patient's sex is also relevant for the therapeutic management and prognosis in the case of established disease. However, there are still many unanswered questions, and further research is clearly needed; in particular, the modifying role of sex hormones needs to be fully elucidated, as well as gender issues.

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