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# Sex-related differences in cardiomyopathies

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ABSTRACT

Cardiomyopathies (CMPs) are a heterogeneous group of heart muscle diseases with several different phenotypes defined as myocardial disorders in which the heart muscle is structurally and functionally abnormal in the absence of coronary artery disease, hypertension, valvular heart disease and congenital heart disease sufficient to explain the observed myocardial abnormality. CMPs can be classified into one of the following, i.e. hypertrophic CMP (HCM), dilated CMP (DCM), arrhythmogenic right ventricular CMP (ARVC), restrictive CMP (RCM), and unclassified CMPs.

Although an increasing number of CMPs are now recognized to have a genetic basis, single mutations are associated with phenotypic variability and may cause not only a specific CMP, but also several different CMPs. Recently, it has become evident that, along with environmental interactions, age and sex may affect the penetrance of disease genes thus determining the phenotypic expression of CMPs. Noteworthy, an increasing body of data indicates that sex plays an important role in various forms of CMPs. The mode of inheritance may affect the sex-related occurrence of CMPs. Also, sex is a relevant determinant of the clinical manifestation of CMPs, and sex-related characteristics can be found in all forms. Sex-specific aspects of clinical disease expression as well as potential modes of inheritance should be therefore taken into proper consideration in order to improve the diagnostic work-up and treatment strategy of CMPs in both sexes.



## 1. Introduction

The importance of sex differences is being increasingly recognized in cardiovascular medicine [1]. Multiple studies have shown substantial differences between males and females in ischemic heart disease, in terms of predisposing factors, disease manifestation, diagnostic work-up, management and prognosis. Sex differences in heart failure and cardiac arrhythmias have been reported, as well. Similarly, the clinical presentation of many cardiomyopathies (CMPs) is influenced by sex, and therefore sex should be taken into proper account in order to improve the diagnostic work-up and the management of CMP. There are still many unanswered questions, however, and further research is clearly needed. Specifically, the modifying role of sex hormones as well as sex issues have not been often taken into adequate consideration. Failure to account for sex and sex may therefore translate into less than adequate care of men and women with CMPs [2].

The present overview is intended as an expert focus on the sex-related differences in CMPs. Our aim is to highlight current knowledge about the prevalence of CMPs in women and discuss novel information on sex variations in epidemiology, symptoms, pharmacology, and treatment (Table 1).

## 2. Classification of cardiomyopathies

The term CMP was originally proposed by Brigden in order to define non-coronary myocardial diseases, a group of diseases for which knowledge was very limited [3]. In 1980, the World Health Organization/International Society and Federation of Cardiology (WHO/ISFC) Task Force published the first report on the 'definition and classification of CMPs' [4]. In 1995, a novel WHO/IFSC Task Force proposed a new consensus classification in which CMPs were defined as "disease of the myocardium associated with cardiac dysfunction" and were classified according to anatomy and physiology [5]. In 2006, a writing committee of the American Heart Association published a Scientific Statement stating, for the first time, that pathological myocardial processes and dysfunction that are a direct consequence of other

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**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) |
| Non-familial | – | – |
| Dilated cardiomyopathy | | |
| Familial DCM (mainly autosomal dominant, occasionally X-linked) | Higher prevalence, more severe manifestation, and worse outcome | – |
| Non-familial | | |
| Arrhythmogenic right ventricular cardiomyopathy | | I |
| Familial (mainly autosomal dominant, occasionally autosomal recessive) | Higher prevalence, more severe manifestation | CDs more effective |
| Non-familial | – | – |
| Restrictive cardiomyopathy | | |
| Familial (autosomal dominant, autosomal recessive or X-linked) | Better survival | Higher prevalence |
| Non-familial | – | Related to endomyocardial fibrosis |

cardiovascular abnormalities should not be included as cardiomyopathies [6]. Subsequently, the CMPs were referred to as hypertrophic CMP (HCM), dilated CMP (DCM), arrhythmogenic right ventricular CMP (ARVC), restrictive CMP (RCM), and unclassified CMPs [7].

CMPs are now considered as primarily genetic disorders of the myocardium associated with higher risk of life-threatening cardiac arrhythmias, heart failure, and sudden cardiac death [8]. The evolving knowledge in genomic medicine during the last decade has reshaped our understanding of CMPs as diseases of multifactorial nature and complex pathophysiology. Genetic testing in CMPs has subsequently grown from primarily a research tool into an essential clinical evaluation piece with important clinical implications for patients and their families. Indeed, current evidence supports the use of genetic testing in clinical practice to improve risk stratification for clinically affected patients and their at-risk relatives for hypertrophic, arrhythmogenic, and dilated CMPs. Understanding how to implement genetic testing and to evaluate at-risk family members, provide clinical implications of results as well as discuss limitations of genetic testing is essential to improving personalized care [7].

## 3. Sex-related penetrance of cardiomyopathies

Recently, it has become evident that, along with environmental interactions, age and sex are involved in determining the phenotypic expression of CMPs [9]. Noteworthy, an increasing body of data indicates that sex plays an important role in various forms of CMP, in terms of prevalence, clinical presentation and prognosis [8].

The mode of inheritance may affect the sex-related occurrence of CMPs. When the causative gene is located on the X-chromosome, inheritance is X-linked recessive. As a result, CMPs primarily affect males, as it occurs in case of muscular dystrophies (Becker's disease and Duchenne's disease) and metabolic disorders (Danon's disease and Fabry's disease) [8]. Women may also suffer from X-linked CMPs [10], but they generally show milder symptoms and signs of the disease. In most familial forms of CMP, inheritance is autosomal dominant, which should theoretically yield a similar occurrence in the two sexes [8]. Since this is not the case in several forms of CMPs, other non-genetic factors are clearly involved.

Among others, sex hormones seem to have profound effects on the prevalence and severity of CMPs [1]. Originally, a modifying role of the inter-relationship between oestrogen and testosterone has been suggested, thus explaining the lower prevalence of cardiovascular disease in the pre-menopausal phase [1]. The same is true for pregnancy conditions and complications, particularly eclampsia [11]. This has prompted a large body of animal investigations with the aim to study sex-related differences in sex hormones and their receptors and to the search for their underlying mechanisms. Experimental work has demonstrated that estrogens are involved in calcium handling and affect the metabolism of glucose, fatty acids, and nitric oxide, as well as the extracellular matrix turnover in different models of CMP [1]. Also, animal studies have shown that females have less fibrosis and more hypertrophy than males, thus experiencing a distinctive a cardiac remodelling pattern [12]. Overall, experimental data are consistent with a protective effect from oestrogens in females in the setting of hypertrophy and heart failure [2]. Conversely, no definitive data about the influence of oral contraceptives and/or pregnancies on the clinical course of CMPs in humans exist. There is an ongoing debate whether experimental animals are informative of human sex differences. It is well known that sex differences in animal models mimic those in humans imperfectly. Age, duration of disease exposure, sex hormone and growth hormone profiles, many forms of stressors, and other factors differ between animal models and humans. Furthermore, menopause is a human phenomenon that is difficult to study in animal models, and surgical ovariectomy is an imperfect proxy for physiological menopause [12].

Sex-specific differences in CMPs can be further affected by behavioural aspects of differences between the two sexs. Generally, females are more reluctant in seeking for medical help in case of symptoms compared with males, and physicians are perhaps less willing to perform diagnostic and therapeutic procedures in females. Thus, differences between males and females in terms of disease manifestation may thus be masked in female patients with CMP [13]. Also, CMPs are more commonly suspected or diagnosed in men than in women at time of cardiovascular screening for participation in sport or military activities [14–17]. Preventive identification of CMPs through systematic pre-participation screening including ECG has been shown to be an effective strategy for preventive identification of CPMs and is now common practice in most European countries and compulsory in Italy [14,15]. Screening protocols have been introduced also for evaluating unselected young males at time of military service [16,17].

## 4. Hypertrophic cardiomyopathy

HCM is a genetic heart muscle disease caused by a mutation in sarcomere protein genes. HCM has a prevalence of 0.2%, i.e. 1 case over 500 adults [18]. It is characterized by an increase in left ventricular wall thickness (hypertrophy), causing left ventricular outflow obstruction, diastolic dysfunction, myocardial ischemia, and mitral regurgitation. Clinical manifestation ranges from no or atypical symptoms to dyspnea, chest pain, palpitations, and syncope. Sudden cardiac death can represent the most devastating complication [18]. Newer genetic testing has been developed and can be used to identify asymptomatic family members with sarcomere mutation [19].

Familial HCM occurs as an autosomal dominant disorder in 50% of cases. A mutation in the sarcomere protein gene encoding for contractile elements of the heart has been found, with 6 different genes on at least 4 chromosomes being associated with HCM, and with a total of 50 different mutations being identified so far [18]. Familial HCM

spectrum includes sarcomeric HCM but also other inherited CMPs with LV hypertrophy: glycogen storage diseases, lysosomal storage diseases, familial transthyretine-related amyloidosis, carnitine deficiency, syndromic disorders, and mitochondrial CMPs [18]. The phenotypic expression of HCM may vary according to the mutation involved. The diverse clinical phenotype suggests the existence of some factors that modify disease presentation, and sex has been hypothesized to be one of the important factors affecting clinical manifestations [19].

Despite genetic inheritance does not follow sex predilection, there is a 2:1 predominance of HCM in male patients. Charron et al. evaluated patients with HCM in a French genotype population and found that penetrance was greater in males than in females (77% versus 58%) [20]. Reduced patient awareness and clinician bias are potential reasons of the sex-related differences in prevalence of HCM. In particular, the occurrence of sudden cardiac death in young male athletes with HCM may have corroborated the misconception that this disease affects more frequently and more severely men than women [21]. Besides these potentially important factors, delayed HCM diagnosis in women may be secondary to genetic and endocrine factors directly impacting phenotypic expression. For example, it has been suggested that reduced penetrance and delayed disease onset may be more common in female patients with certain sarcomeric gene mutations [22]. In addition, as in coronary artery disease, endocrine features associated with female sex may delay the development of the HCM phenotype or its clinical manifestations. This concept is supported by experimental work showing that estrogens have a protective effect on development of secondary myocardial hypertrophy [23].

With respect to sex differences in clinical manifestations, women are more frequently diagnosed as having HCM due to onset of symptoms, such as palpitation and dyspnea. Although the reasons for the sex differences in symptoms are unknown, medical screening system and clinician bias may be related to the different magnitude of symptoms. Out of clinical complications, there are not differences in atrial fibrillation and hospitalization for heart failure between males and females, whereas embolic events have been reported to be less common in females than males. Female sex is associated with a worse survival as compared with male sex [24]. As regards echocardiographic data, there are several differences between the two sexs. Apical HCM is predominant in males [22]. On the other hand, LV outflow obstruction is significantly more frequent in females, which in turn could be related to smaller LV size and higher LV contractility [24]. Although the mechanism of LV outflow tract gradient induction is complex and the mitral valve apparatus also contributes to obstruction by systolic anterior motion of the mitral leaflet [18], Sex-related differences in clinical outcome have been reported so far. Frequency of sudden cardiac death, i.e. the most catastrophic complication of the disease, is similar in both sexes [24–26]. Nevertheless, at cardiovascular magnetic resonance (CMR), women have greater late gadolinium enhancement than men indicating that they have larger extent of cardiac fibrosis, i.e. a major substrate for sudden cardiac death [27]. Female patients with HCM have a greater risk than male patients to experience congestive symptoms or die from heart failure [28,29]. These findings may be explained in part by the greater prevalence of LV outflow obstruction compared with male patients, which in turn could be related to smaller LV cavity dimensions [26]. Because outflow obstruction has been shown to be a possible predictor of adverse outcome due to heart failure in HCM, the more frequent occurrence of obstruction in female patients likely contributed importantly to their more adverse long-term outcome. Other possibilities include an enhanced susceptibility of female patients with HCM to the consequences of atrial fibrillation, including heart failure, embolic stroke, and LV remodelling. Finally, risk for heart failure-related clinical deterioration and death is greater in those female patients >50 years old as compared with those <50 years old or with male patients, thus suggesting that post-menopausal endocrine changes may impact on the clinical course of HCM, as previously shown in coronary artery disease [1].

The risk associated with pregnancy in women with HCM is an important, well-recognized clinical issue [30]. Available evidence indicates that maternal mortality is increased in patients with HCM compared with the general population. However, absolute maternal mortality is low and appears to be principally confined to women at a particularly high risk. In the presence of a favorable clinical profile, the progression of symptoms, atrial fibrillation, and syncope are also uncommon during pregnancy [31].

## 5. Dilated cardiomyopathy

DCM is currently defined by the presence of left ventricular (LV) or biventricular dilatation and systolic dysfunction in the absence of abnormal loading conditions (hypertension, valve disease) or coronary artery disease sufficient to cause global systolic impairment [7,8]. The causes of DCM can be classified as genetic or non-genetic, but there are circumstances in which genetic predisposition interacts with extrinsic or environmental factors [32].

In at least one-third of the patients with idiopathic DCM, familial occurrence can be noted, pointing to inherited disease. 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 [33]. In addition, there are sex-related differences in the clinical manifestations of Duchenne and Becker muscular dystrophies that frequently show cardiac involvement. 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. Because of the compensatory function of the second, non-mutated X-chromosome, women have a lower chance of disease manifestation, but may also express the disease phenotype [7].

In general, familial DCM primarily affects males, with a reported male/female ratio of up to 1.5:1, despite the usual mode of inheritance, which is autosomal dominant. Herman et al. reported on various mutations in *TTN*, the gene encoding the sarcomeric protein titin, in 312 patients with idiopathic DCM, and found that adverse events occurred significantly earlier in males than in females carrying the *TTN* mutations [33]. Similarly, Van Rijsingen et al. observed sex differences in 269 patients with DCM due to mutations in the lamin A/C gene (*LMNA*), with men showing a greater prevalence of adverse events and higher mortality than women [34]. These results have been recently confirmed in a large series of 803 consecutive patients with DCM recorded in the Heart Muscle Disease Registry of Trieste, Italy [35]. During a median of 108 months follow-up, women showed a better long-term prognosis notwithstanding a presentation with a more advanced disease and a lower clinical-instrumental improvement on optimal medical therapy compared to men [35]. These results are in keeping with recent findings by Halliday et al. who evaluated the relationship between sex, age and outcome in 881 patients with DCM and found that women with DCM had better survival compared to men, partly due to less severe left ventricular dysfunction and a smaller scar burden [36]. These findings emphasize the current role of CMR that is a valuable tool for the evaluation of patients with, or at risk for, heart failure and has a growing impact on diagnosis, clinical management, and decision making of the various forms of DCM. Through its ability to characterize the myocardium by using multiple different imaging parameters, it provides insight into the etiology of the underlying pathologic process and its prognosis [37,38].

The subgroup of non-familial DCM comprises a variety of disorders, including CMPs due to myocarditis, alcohol abuse, peripartum CMP, autoimmune diseases, drug toxicity, nutritional deficiencies, and tachycardia (tachy-CMP). Although autoimmune diseases, i.e. Kawasaki disease and Churg–Strauss syndrome, are generally more common in females, there are no data on cardiac involvement in established cases being different between the two sexes [7].

Sex-related differences in the response to medical treatment have been reported in DCM patients with heart failure [39]. Women with heart failure respond better to beta-blockers, but have a worse prognosis with digoxin, than men. Angiotensin-converting-enzyme inhibitors and angiotensin-receptor blockers are equally effective in both sexes. Implantable cardioverter-defibrillator therapy might be associated with a lower survival benefit in women than in men with heart failure. Finally, women demonstrate a significantly more favorable echocardiographic response to cardiac resynchronization therapy than men, regardless of their heart failure functional class [39].

A form of DCM that occurs only in women is the so-called 'Peripartum CMP' (PPCM), which is a rare but potentially life-threatening disorder defined by the development of unexplained systolic heart failure towards the end of pregnancy or in the months following delivery [40]. A number of associations are reported including Afro-Caribbean ethnicity, older age, multiple pregnancy, and hypertension with or without pre-eclampsia. The etiology is complex and includes autoimmunity, fetal microchimerism, virus infection, stress activated cytokines and toxicity caused by an abnormal cleavage product of prolactin. Genetic predisposition seems important in some cases, with a recent report of familial DCM coexisting with PPCM or identification of DCM causative mutations in some PPCM women.

## 6. Arrhythmogenic right ventricular cardiomyopathy

Sex-related differences in epidemiology, pathogenesis, and clinical presentation have also been observed in several cardiac diseases complicated by ventricular arrhythmias such as ARVC.

ARVC is characterized by global or regional right ventricular dysfunction, which is caused by progressive right ventricular adipose and fibrous replacement of the myocardium [41,42]. ARVC is a progressive hereditary CMP with a higher risk of ventricular arrhythmias and sudden cardiac death. It is characterized histologically by fibro-fatty replacement of RV myocardium with subsequent RV dilation and systolic dysfunction. Underlying pathogenesis is thought to be the mutation of several genes encoding desmosomes, which are responsible for cell to cell adhesion. Malfunctioning desmosomes leads to the initial phase of inflammation in affected myocardium with subsequent apoptosis and fibro-fatty replacement of the myocardium. In almost 50% of cases, ARVC can also be found in relatives, as the disease can be inherited in autosomal dominant form or autosomal recessive form [43].

Sex differences in the prevalence, phenotypes, and clinical courses of ARVC have been described [43–46]. It is more prevalent in males than females, with an approximate ratio of 3:1. The cause of these sex differences in ARVC is unknown, but differences in physical exercise between males and females might play a role. The two sexes differ in prevalence of abnormal ECG and presence of late potentials [42]. Moreover, men have larger right ventricular dimensions and practice competitive sports more frequently. However, sex is not associated with a high incidence of life-threatening ventricular arrhythmias. Therefore, the diagnosis of ARVC is less common in female patients, who present a higher prevalence of mild forms, whereas the degree of electrical instability does not differ significantly between sexes in affected subjects [43]. Given the incomplete genetic penetrance and variable phenotype, the clinical outcome of ARVC might be influenced by sex factors, as evidenced by the fact that a higher mortality rate and SCD have been documented in male patients compared with those documented in female patients with ARVC. Bhonsale et al. reported on 215 patients with ARVC-associated mutations and found male sex to be an independent predictor of the first arrhythmic event on multivariable analysis [44]. The missense mutation in transmembrane protein 43 (TMEM43 c.1073C > T, p.S358L) is the cause of this fully penetrant, lethal form of ARVC [45]. The mutation is associated with more serious early events, such as heart failure and death in males, which again clearly indicates an influence of sex. Recently, Lin et al. have found different characteristics of ventricular arrhythmias and substrate properties between men and women with ARVC [46]. Specifically, male sex and the presence of larger area of abnormal electrograms independently predicted recurrences of ventricular arrhythmias after radiofrequency catheter ablation.

Pregnancy seems to be well tolerated in patients affected by ARVC, but a programmed clinical protocol is mandatory particularly in the last trimester and puerperium, due to increased risk of ventricular arrhythmias [47].

## 7. Restrictive cardiomyopathy

Restrictive CMP (RCM) refers to CMP 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 [7,8]. Although the disease rarely occurs as a familial disease, RCM can result from autosomal dominant, autosomal recessive, or X-linked inheritance. In most cases, transmission is autosomal dominant, involving mutations in *TNNI3* or *DES* encoding troponin I and desmin, respectively, the latter also being associated with conduction disorders and skeletal myopathy. 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 [7,8].

Reports on sex differences in familial RCM are scarce. Long-term survival following surgery for endomyocardial fibrosis has been described in small series of patients [48]. Interestingly, despite the higher occurrence in the females, they showed significantly better survival than the males [49,50]. 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, hyper-eosinophilic 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. However, no sex differences are known for hyper-eosinophilic syndrome, scleroderma, or carcinoid heart disease, nor for AL amyloidosis, in which cardiac involvement seems to be nearly equally distributed in both sexes.

## 8. Conclusions

Incidence, causes, risk-factors, presentation of symptoms, diagnosis, treatment, response to treatment and prognosis, are all factors that differ significantly between women and men, and this for a large number of individual diseases and pathologies, including CMPs. Recently, it has become evident that, along with environmental interactions, age and sex may affect the penetrance of disease genes thus determining the phenotypic expression of CMPs.

In the present overview, we have focused on the sex-related differences in CMPs. A comprehensive review of the available scientific literature on sex-related differences in CMPs was beyond our scope. However, we highlighted current knowledge about the prevalence of CMPs in women and discussed novel information on sex variations in epidemiology, symptoms, pharmacology, and treatment. Noteworthy, evidence now exists that sex plays an important role in various forms of CMPs and that the mode of inheritance may affect the sex-related occurrence of CMPs. Also, sex is a relevant determinant of the clinical manifestation of CMPs, and sex-related characteristics can be found in all forms. Sex-specific aspects of clinical disease expression as well as potential modes of inheritance should be therefore taken into proper consideration in order to improve the diagnostic work-up and treatment strategy of CMPs in both sexes.

## Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

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