International Journal of Cardiology xxx (2020) xxx

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Impact of sex on timing and clinical outcome of septal myectomy for obstructive hypertrophic cardiomyopathy

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ARTICLE INFO

Article history:
Received 28 January 2020
Received in revised form 29 July 2020
Accepted 17 August 2020
Available online xxxx

Keywords:
Hypertrophic cardiomyopathy
Septal myectomy
Sex differences
Survival analysis

ABSTRACT

Background: Sex disparities are common in hypertrophic cardiomyopathy (HCM). Previous research has shown that at time of myectomy, women are older, have greater impairment of diastolic function and more advanced cardiac remodeling. The clinical impact of these differences is unknown.
Method: This study included 162 HCM patients (61% men) who underwent septal myectomy. Time to treatment was calculated in relation to symptom onset and diagnosis. Pre- and post-operative echocardiographic data were collected. Sex differences were assessed at baseline and in time-to-event survival analyses for the composite endpoint of all-cause mortality, cardiac transplantation, re-intervention and aborted sudden cardiac death.
Results: Women were generally older at time of myectomy (57 vs. 49 years, $p < 0.01$), with similar time to treatment as measured from symptom onset (2.3 [1.3–6.0] vs. 2.8 [1.1–5.3] years, $p > 0.05$), but a shorter time since diagnosis compared to men (2.6 [1.2–7.0] vs. 4.3 [2.4–8.3] years, $p = 0.02$). Mean wall thickness and left atrial diameter were the same for men and women, but were higher in women when correcting for body surface area (absolute: 20 vs. 19 mm, 48 vs 46 mm, $p \geq 0.05$; corrected: 9.7 vs. 11.2 mm/m^2, 23.4 vs. 26.3 mm/m^2, $p < 0.01$). After 5.9 [3.0–9.1] years, 15% of men and 8% of women had reached the composite endpoint ($p > 0.05$).
Conclusion: In conclusion, although women present later in life and seem to have more advanced disease on echocardiography, time until myectomy was similar and clinical outcomes after myectomy are favourable for both men and women.

1. Introduction

Hypertrophic cardiomyopathy (HCM) is the most prevalent inherited cardiac disease, with an estimated prevalence of 0.2–0.5% of the general population [1]. In HCM patients, the presence of left ventricular outflow tract (LVOT) obstruction is associated with significant morbidity and mortality [2,3]. Septal reduction therapy is the primary treatment modality for patients suffering from drug-refractory symptoms for obstructive HCM. Recent research has shown that women are older and have more advanced disease at time of myectomy, as reflected through a greater impairment of diastolic function and more fibrosis on microscopy [4]. These findings are in unison with the older age of diagnosis and more symptomatic clinical presentation often observed in women with HCM, and are a possible indication of a delay in surgical treatment of women [5–8]. A potential consequence of this is worse clinical outcome after myectomy. However, previous research has shown that women with HCM start to exhibit symptoms later in life [9]. Whether these age differences are therefore truly secondary to diagnostic or therapeutic delays, rather than a reflection of an inherently different disease process, is unknown. To better understand the temporal differences between men and women, we aimed to quantify and compare time until myectomy in relation to symptom onset and diagnosis date. Furthermore, in this study we aimed to compare pre- and perioperative clinical characteristics as well as postoperative outcome and survival of men and women undergoing septal myectomy.

Abbreviations: AMLE, anterior mitral valve leaflet extension; HCM, hypertrophic cardiomyopathy; LV, left ventricle; LVOT, left ventricular outflow tract; NYHA, New York Heart Association; MWT, maximal wall thickness; SAM, systolic anterior motion of the mitral valve; SCD, sudden cardiac death; TTE, transthoracic echocardiography.

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https://doi.org/10.1016/j.ijcard.2020.08.059

2. Patients and methods

2.1. Study design

We identified 162 patients who underwent septal myectomy without concomitant cardiac surgery between 2000 and 2019 in the Erasmus Medical Center. The diagnosis of HCM was based on a maximal wall thickness (MWT) ≥15 mm (≥13 mm in first-degree relatives with HCM), not explained by loading conditions, in accordance with the guidelines [10]. Patients with HCM phenocopies, such as Anderson-Fabry disease, Danon disease, Noonan syndrome, amyloidosis, or other confirmed metabolic or mitochondrial disorders or malformation syndromes were excluded. Patients were candidates for myectomy based on 1) a peak LVOT gradient ≥50 mmHg at rest or after provocation and 2) presence of unacceptable symptoms despite maximally tolerated medical therapy, including beta-blocking agents and calcium channel blockers [10]. The study conforms to the principles of the Declaration of Helsinki. All subjects gave informed consent for inclusion in the registry and local institutional review board approval was obtained.

2.2. Surgical technique

In our center, patients with enlarged anterior mitral valve areas (>12 cm^2) are often treated by combining septal myectomy with anterior mitral valve leaflet extension (AMLE). Both surgical techniques have been described previously [11,12]. In short, after employment of standard cardiac surgery techniques aortotomy is performed, allowing partial resection of the septum towards the apex, leftwards of the imaginary line between the nadir of the right coronary cusp. An autologous pericardial patch is then placed across the bending point of the mitral valve to stiffen the anterior mitral valve leaflet, extending its width, shifting the centrally located chordae laterally. As the chordae are stretched and erected, leaflet coaptation is increased. Force of blood flow against the leaflet (which is proportional to its area) is increased, decreasing SAM and mitral regurgitation. The decision to perform AMLE was based initially on pre-operative echocardiographic assessment of the mitral valve leaflet area with the final decision made by the surgeon perioperatively, based on visual inspection and epicardial echocardiographic assessment of the mitral valve, its leaflet area and papillary muscle length. Surgical results are assessed with transesophageal echocardiography immediately after weaning from cardiopulmonary bypass, at a systolic blood pressure of ≥100 mmHg.

2.3. Clinical evaluation

Pre- and post-operative clinical assessment included medical history and transthoracic echocardiography (TTE). Medical history included assessment of symptom status according to the New York Heart Association (NYHA) classification and medication status. Time-to-treatment was measured from symptom onset and from date of HCM diagnosis, the former being defined by the first occurrence of symptoms associated with and judged to be caused by HCM (i.e. chest pain, dyspnea, fatigue, palpitations, syncope or cardiac arrest) in the absence of another more likely explanation. Both variables were considered missing when an exact year could not be determined.

TTE was generally performed a month before surgery, at discharge following myectomy, three months later and thereafter at yearly intervals. TTE studies were analyzed according to the guidelines [10,13,14]. Peak LVOT gradient was measured in rest and after provocation (particularly the Valsalva maneuver) using Doppler echocardiography and by applying the modified Bernoulli equation, which is defined as $P = 4v^2$, where P is the peak gradient and v equals blood velocity. Left ventricular (LV) systolic function was categorized as good (LV ejection fraction >51%), mildly reduced (LV ejection fraction 41% to 51%), moderately reduced (LV ejection fraction 30% to 40%), and poor (LV ejection fraction <30%) [13]. LV diastolic function was categorized as normal, abnormal relaxation, pseudonormal, or restrictive filling, based on Doppler mitral inflow pattern parameters including early (E) and late (A) LV filling velocities, E/A ratio, and tissue Doppler-derived septal early diastolic velocities (e') [14].

Genetic counselling and testing is routinely offered to HCM patients visiting the cardiogenetic outpatient clinic of the Erasmus MC and is described previously [15]. Before 2012, genetic testing was based on direct sequencing targeting a subset of mutations (≤11 genes) associated with HCM. Thereafter, next-generation sequencing covering a panel of >48 cardiomyopathy-associated genes was used, and since 2018 we employed whole-exome sequencing. Genetic analysis in family members of pathogenic gene mutation carriers targeted the gene mutation identified in the proband.

2.4. Follow-up

Follow-up information was obtained at routine visits at the HCM outpatient clinic or from hospitalization records in case of complications. Registered complications include peri-operative death, conduction disorders requiring pacemaker implantation, iatrogenic ventricular septal defect, pericardial effusion requiring pericardiocentesis, mediastinitis and stroke. Mortality status and causes of death were obtained from the hospital records, from general practitioners and by consulting civil registries. Endpoints included all-cause mortality, HCM-related mortality, cardiac transplantation, (aborted) sudden cardiac death (SCD) and repeat septal reduction therapy. Mortality was considered HCM-related in case of SCD, death caused by heart failure, post-operative death after an HCM intervention and stroke-related death. SCD was defined as (1) instantaneous and unexpected death in patients who were previously in a stable clinical condition, or nocturnal death with no antecedent history of worsening symptoms; (2) resuscitation after cardiac arrest; or (3) appropriate implantable cardioverter-defibrillator intervention. Patients who were lost to follow-up were censored at time of last follow-up.

2.5. Statistical analysis

Values were expressed as mean ± standard deviation, median [interquartile range] or number (%). Continuous data were assessed for normality by inspecting Q-Q plots and using the Shapiro-Wilk test, and were analyzed using the Student's *t*-test or Mann-Whitney *U* test, as appropriate. Categorical data were compared using Pearson's χ^2 test. Univariable and multivariable Cox proportional hazard regression analyses were used to assess the effect of sex and other baseline variables on time until the composite endpoint. All baseline variables were considered as potential predictors, but sex was entered into the multivariable model regardless of its performance in univariable analysis to account for potential suppressor effects from other independent variables. To allow us to discern potential differences between men and women in regard to disease progression, surrogate markers of disease progression (e.g. atrial fibrillation, systolic and diastolic dysfunction, time from disease onset) were favored over other candidate predictors. Model assumptions were assessed by inspecting Schoenfeld and Martingale residuals. Survival curves were constructed according to the Kaplan-Meier method, and comparisons were performed using the log-rank test. We performed a secondary analysis by stratifiying the group above and below the median time of surgery and compared age and time until myectomy for men and women, in order to ascertain possible temporal differences. All testing was two-tailed and p values <0.05 were considered statistically significant. All statistical analyses were performed using SPSS version 22 (IBM Corp., Armonk, New York) and R version 3.6.2 (https://cran.r-project.org/).

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3. Results

3.1. Study cohort

Baseline characteristics for men and women are presented in Table 1. On average, women were 8 years older at time of myectomy. In the full group, time until myectomy as measured from date of diagnosis was higher in men. Time until myectomy was similar in the subset of patients initially evaluated for symptoms. Year of symptom onset was missing in 14 (14%) men and 11 (18%) women, and the year of diagnosis was unknown in 1 man and 1 woman. Sex was not a predictor of missing symptom onset or diagnosis data (odds ratio for male sex 0.78 [0.33–1.84]).

More than a third of both men and women had a pathogenic sarcomeric gene variant. Female patients were more likely to have hypercholesterolemia and hypertension, and used angiotensin-converting enzyme-inhibitors or angiotensin II receptor blockers more often. When comparing absolute values, MWT and left atrial diameter were similar for men and women and LV end-diastolic diameter was higher in men. Corrected for body surface area (BSA), LV end-diastolic diameter was similar, but MWT and left atrial diameter were higher in women. Diastolic function was impaired in 84% of men and 94% of women ($p > 0.05$).

3.2. Surgical results

Globally, no differences were seen regarding post-operative results (Table 2). Clinical improvement (i.e. reduction in NYHA class ≥1) was achieved in the majority (≥94%) of both men and women. Echocardiographic results were slightly in favor of men, who had a lower median post-operative LVOT gradient and a higher relative gradient reduction. The LVOT obstruction was abolished in 91% of men and 81% of women, although this did not reach statistical significance. No differences were seen regarding length of stay and complication rate, both in total and for individual complications.

3.3. Clinical outcome

Unadjusted Kaplan-Meier survival curves for the composite endpoint of all-cause mortality, cardiac transplantation, repeat septal reduction therapy and aborted SCD are shown in Fig. 1A. After a median follow-up of 5.9 [3.0–9.1] years, 15% of men and 8% women had reached the composite endpoint (log-rank: $p = 0.27$), demonstrating similar survival after myectomy for both sexes. Age-adjusted survival rates diverged early in favor of women, although the difference was not significant ($p = 0.067$, Fig. 1B). Table 2 illustrates the occurrence of individual endpoints for men and women. In univariable Cox proportional hazard regression analyses, sex was not a predictor of outcome, whereas age, heart failure medication and degree of diastolic dysfunction were. Use of heart failure medication and diastolic dysfunction were significant predictors after multivariable adjustment (Table 3).

3.4. Temporal differences

To explore temporal differences whilst preserving sample size, we split the group below and above the median time of surgery (August 2012). Men were relatively overrepresented in both periods (before and after 2012: 56% vs. 67%, $p = 0.15$). There were no significant age differences comparing men and women separately between periods (men: 47 ± 13 vs. 52 ± 14 years, $p = 0.10$; women: 55 ± 17 vs. 58 ± 14 years, $p = 0.51$), although overall the recent group was several years older (50 ± 15 vs. 55 ± 15 years, $p = 0.047$). No differences were found when comparing time until myectomy in men before and after 2012 (from symptom onset: 3.7 [1.2–6.4] vs. 2.2 [1.1–4.5] years; from diagnosis: 6.0 [2.7–9.3] vs. 4.0 [2.0–7.4] years, $p > 0.05$ for both), nor in women before and after 2012 (from symptom onset: 2.9 [1.4–7.8]

Table 1
Clinical and echocardiographic variables for men and women at time of myectomy.

Variable		Men (n = 99)	Women (n = 63)	P value
Age (y)		49 ± 14	57 ± 15	<0.01
NYHA class				0.78
I		1 (1%)	1 (2%)	
II		20 (21%)	12 (19%)	
III		75 (77%)	48 (76%)	
IV		1 (1%)	2 (3%)	
Atrial fibrillation		20 (20%)	12 (19%)	0.86
Hypertension		27 (27%)	29 (46%)	0.01
Hypercholesterolemia		18 (18%)	22 (35%)	0.02
Diabetes mellitus		9 (9%)	7 (11%)	0.67
Pathogenic DNA variant*		36 (41%)	17 (34%)	0.42
Beta-blockers		76 (77%)	47 (77%)	0.97
Calcium channel antagonists		41 (41%)	26 (43%)	0.88
Disopyramide		2 (2%)	2 (3%)	0.62
ACE inhibitors or angiotensin II receptor blockers		9 (9%)	16 (25%)	<0.01
Mineralocorticoid receptor antagonists		1 (1%)	4 (7%)	0.07
Diuretics		14 (14%)	11 (18%)	0.51
Implantable cardioverter-defibrillator		15 (15%)	7 (11%)	0.46
Time-to-treatment†				
Whole group (n = 149)	from symptom onset (y)	2.8 [1.1 – 5.3]	2.3 [1.3 – 6.0]	0.82
	from diagnosis (y)	4.3 [2.4 – 8.3]	2.6 [1.2 – 7.0]	0.02
Initial evaluation for symptoms (n = 89)	from symptom onset (y)	3.4 [1.4 – 6.2]	3.4 [1.7 – 7.0]	0.69
	from diagnosis (y)	3.0 [1.2 – 6.0]	1.7 [0.9 – 4.2]	0.25
Initial evaluation for other reasons (n = 60)	from symptom onset (y)	1.4 [0.6 – 4.4]	1.7 [0.9 – 2.7]	0.81
	from diagnosis (y)	7.5 [4.0 – 11.6]	3.1 [1.4 – 8.5]	0.01
Echocardiographic variables				
Peak resting or provoked LVOT gradient (mmHg)		82 ± 33	93 ± 34	0.04
Maximal wall thickness	absolute (mm)	20 ± 5	19 ± 5	0.58
	indexed (mm/m²)	9.7 ± 2.5	11.2 ± 4.6	<0.01
LA diameter	absolute (mm)	48 ± 7	46 ± 7	0.05
	indexed (mm/m²)	23.4 ± 3.6	26.3 ± 7.8	<0.01
LV end-diastolic diameter	absolute (mm)	45 ± 8	42 ± 5	0.01
	indexed (mm/m²)	22.2 ± 3.7	23.4 ± 3.0	0.09
Systolic function‡				0.80
	Good	88 (92%)	54 (89%)	
	Mildly reduced	7 (7%)	6 (10%)	
	Moderately reduced	1 (1%)	1 (2%)	
Diastolic function§				0.29
	Normal	16 (16%)	4 (6%)	
	Impaired relaxation	28 (29%)	22 (35%)	
	Pseudonormal relaxation	47 (48%)	33 (52%)	
	Restrictive	7 (7%)	4 (6%)	
Systolic anterior motion of the mitral valve		96 (98%)	62 (100%)	0.26
Mitral regurgitation				0.94
	No/trace	8 (8%)	5 (8%)	
	Mild/moderate	77 (80%)	47 (78%)	
	Severe	11 (12%)	8 (13%)	

Data are presented as number (percentage), mean ± SD or median [IQR]. *Proportion of genotype-positive patients of genetically tested group. †Date of symptom onset and diagnosis was available in 133 and 161 patients, respectively. 54 (54%) men and 35 (65%) women were initially evaluated for symptoms. Other reasons include family screening (7 [7%] men and 2 [4%] women) or incidental findings (33 [35%] men and 18 [33%] women). ‡Systolic function could not be assessed in 3 (3%) men and 2 (3%) women. § Diastolic function could not be assessed in 1 (1%) man. ACE = angiotensin converting enzyme, HCM = hypertrophic cardiomyopathy, LA = left atrial, LV = left ventricular, LVOT = left ventricular outflow tract, NYHA = New York Heart Association.

Please cite this article as: R. Huurman, A.F.L. Schinkel, P.L. de Jong, et al., Impact of sex on timing and clinical outcome of septal myectomy for obstructive hypertrophic cardiom..., International Journal of Cardiology, https://doi.org/10.1016/j.ijcard.2020.08.059

Table 2
Post-operative outcome after myectomy stratified according to sex.

Variable	Men (n = 99)	Women (n = 63)	P value
Improvement in symptoms*	82 (95%)	46 (94%)	0.71
Peak LVOT gradient (mmHg)†	10 [7–18]	19 [10–38]	0.001
LVOT gradient reduction (mmHg)†	65 [45–80]	68 [36–81]	0.91
LVOT gradient reduction (%)†	86 [69–92]	77 [55–86]	<0.01
Post-operative LVOT gradient ≥30 mmHg	9 (9%)	12 (19%)	0.07
AMLE performed‡	76 (78%)	38 (62%)	0.04
Complications	17 (18%)	9 (14%)	0.59
Peri-operative mortality	0 (0%)	1 (2%)	0.21
Mediastinitis	3 (3%)	0 (0%)	0.16
Ventricular septal defect	1 (1%)	0 (0%)	0.42
Pericardial effusion requiring drainage	14 (14%)	5 (8%)	0.39
Conduction disturbance requiring pacing	3 (3%)	3 (5%)	0.59
Stroke	0 (0%)	0 (0%)	–
Length of hospital stay (days)	8 [7–9]	9 [6–10]	0.46
Outcome			
Repeat septal reduction therapy	2 (2%)	0 (0%)	
Aborted sudden cardiac death	2 (2%)	0 (0%)	
All-cause mortality	10 (10%)	5 (8%)	
Peri-operative mortality	0 (0%)	1 (1%)	
Sudden cardiac death	1 (1%)	0 (0%)	
HCM-related death	0 (0%)	2 (3%)	
Non-cardiac death	3 (3%)	0 (0%)	
Unknown	6 (6%)	2 (3%)	
Cardiac transplantation	1 (1%)	0 (0%)	

Data are presented as number (percentage), mean ± SD or median [IQR]. *defined as a reduction of ≥1 New York Heart Association functional class, assessed at routine follow-up after 3 months. †measured on transthoracic echocardiography at routine follow-up after 3 months. ‡unknown in 1 man and 2 women. AMLE = anterior mitral leaflet extension; HCM = hypertrophic cardiomyopathy; LVOT = left ventricular outflow tract.

vs. 2.0 [1.3–4.1] years; from diagnosis: 2.8 [1.4–7.0] vs. 2.4 [0.9–6.9] years, p > 0.05 for both).

4. Discussion

This study demonstrates that, despite apparent differences at time of surgery, survival after myectomy is the same for both men and women after a median follow-up of 6 years. The most prominent differences found in our study are that women are 8 years older at time of surgery, that they seem to exhibit more advanced disease on echocardiography, and that both pre- and post-operative LVOT gradients were higher in women. Time until myectomy was similar in men and women.

4.1. Sex differences

This study was primarily conducted following the results of a recent study done by Nijenkamp et al., which was done on a subset of patients of our current cohort [4]. In that study, tissue of the ventricular septum of 27 women and 44 men was obtained during myectomy, after which isometric force measurements, protein analyses and histomorphological analyses were performed. Their findings were in part similar to the current results, with women being older at time of surgery and having higher indexed echocardiographic indices. Additionally, there was more interstitial fibrosis comparing women to men, altogether indicating more severe diastolic impairment on a cellular level and, as such, more severe disease at time of myectomy. These findings may indicate a delayed treatment in women, potentially influencing clinical outcomes following myectomy. The current findings demonstrate that, in a cohort of 99 men and 63 women, no differences in clinical outcome exist after a median follow-up of 6 years.

Potential sex differences concerning survival after myectomy have been investigated by several studies [5,16,17]. A recent study by Meghji et al. on 2506 patients demonstrated worse survival in women in their unadjusted analysis [16]. However, this difference was not found after adjustment for baseline characteristics. In contrast, Woo et al. found female sex to be an independent predictor of mortality in 338 patients [17]. The reasons for the differing results are unclear. Two findings are notable: first, all patients included in the latter study underwent surgery before 2002. Under the assumption that women are recognized and diagnosed at a later age (and thus later in their disease process), it is possible that studies conducted earlier in time will have a higher proportion of late-diagnosed women compared to contemporary research performed on data of an era in which more awareness of sex-specific biases exists. It must be noted that in their study, female sex was only a predictor of outcome after multivariable adjustment (and not in univariable analysis), which could signify that female sex asserts its effects on outcome by mediating other variables (e.g. age) rather than by its own association with outcome. Furthermore, surgical technique and experience as well as post-operative care will likely have improved in this time (which is reflected in the study by Meghji et al. by improved survival following more recent surgery), although we do not consider it likely that this alters sex related differences. Second, in the study by Meghji et al., similar to our results, the median age of women was several years higher compared to men. As age was the strongest predictor of mortality in their adjusted analysis, the sex difference seen in the unadjusted analysis likely stems from this age gap.

Interestingly, in their study and in that of Rowin et al., similarly reporting on sex differences in a large HCM center, women undergoing septal myectomy had more advanced symptoms compared to men (respectively NYHA III/IV 91% vs 85% and a mean NYHA class 2.4 ± 0.7 vs 2.1 ± 0.8), a finding not reproduced in our study. There is no obvious explanation for this difference, especially since both European and American guideline recommendations on timing of myectomy are similar [10,18]. Potential differences in NYHA assessment might be of importance, as we reported NYHA class at last assessment prior to surgery, and in both other studies it seems possible that this was done at an earlier moment. Differences in referral patterns can similarly be relevant and the influence of sample size can also not be excluded. Regardless, since a higher NYHA class was an independent predictor of adverse outcome in the study by Meghji et al., this represents an important topic both in the appreciation of sex differences and in general HCM care. The question remains whether survival would improve if women (but also men) are diagnosed and treated earlier in the disease process, when there is a lower symptomatic burden. Performing septal reduction therapy at an earlier stage (i.e. in patients with NYHA II symptoms) is a topic worthy of consideration, but this would require methods of identifying patients with a higher risk of progressing to severe symptoms, which we currently lack.

Sex-related differences in HCM are gaining more interest in contemporary literature [6–9,19–23]. Women are often under-represented in HCM cohorts, giving rise to a myriad of potential explanations which include, but are not limited to, a diagnostic bias, referral bias, a decreased awareness of cardiovascular disease and accompanying symptoms in women both in patients and medical professionals, and biological differences in sex hormone receptor levels and gene expression. A near-universal finding in multiple cohorts is a higher age in women compared to men, whether this is at initial evaluation or at time of intervention [4–9,19,20]. The reasons for this age discrepancy as well as its implications in the context of diagnostic and therapeutic delays are controversial topics. In this study, men were diagnosed at a younger age relative to their time of surgery. This is likely explained by differences in the modes of presentation expanded upon in several studies, which give men more, earlier opportunities for the detection of HCM [5–8]. Importantly, this difference was not seen in the subset of patients initially evaluated for symptoms, which demonstrates that their clinical course is broadly similar as soon as they are identified as patients. Moreover, time from symptom onset until surgery was equal for men and women, which suggests that a hypothesized diagnostic bias does not confer a therapeutic delay. Dimitrow et al. found that age of symptom onset was later in HCM women compared to men (31 ± 12 vs. 27 ± 10 years) with women also being more likely to present beyond the

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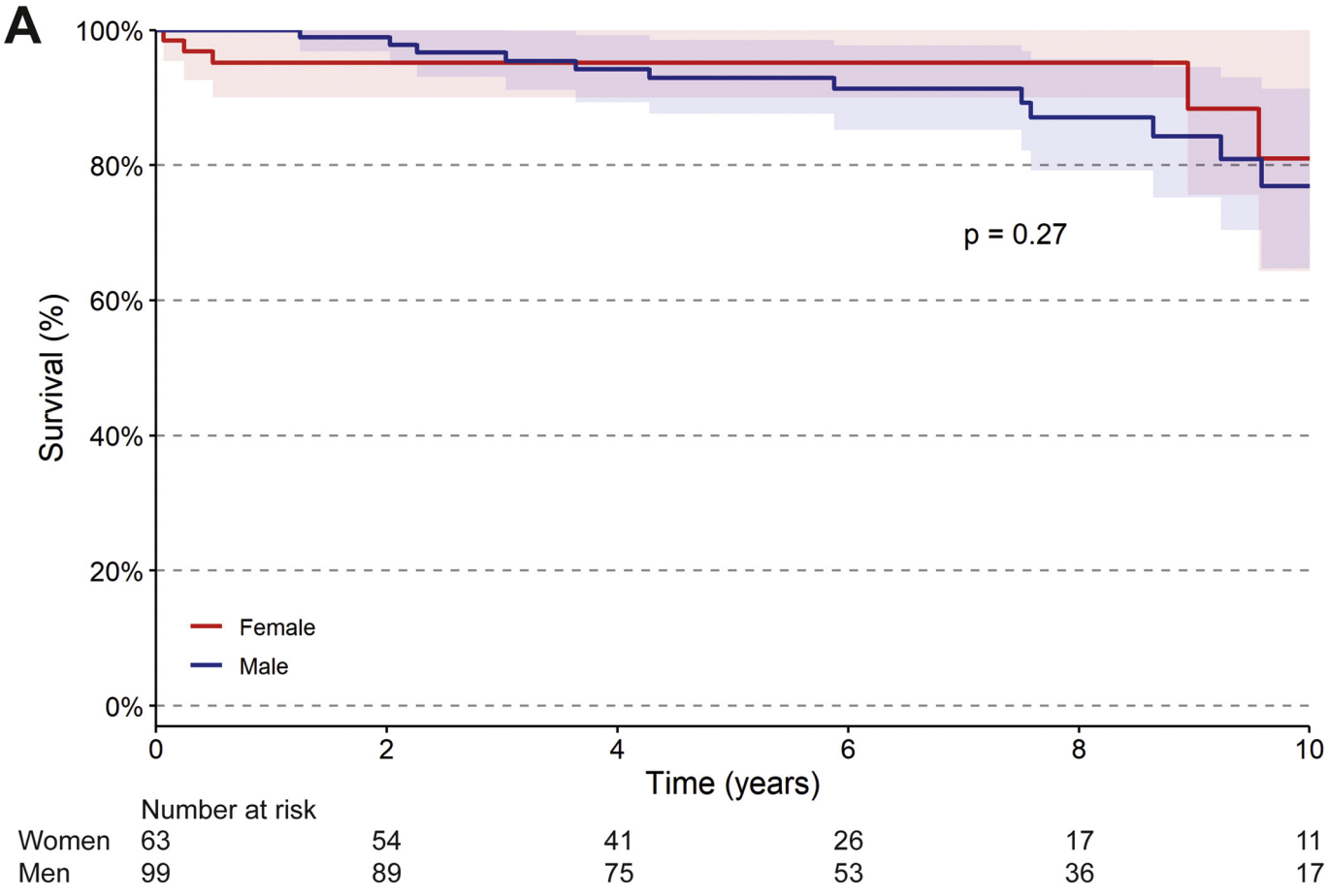

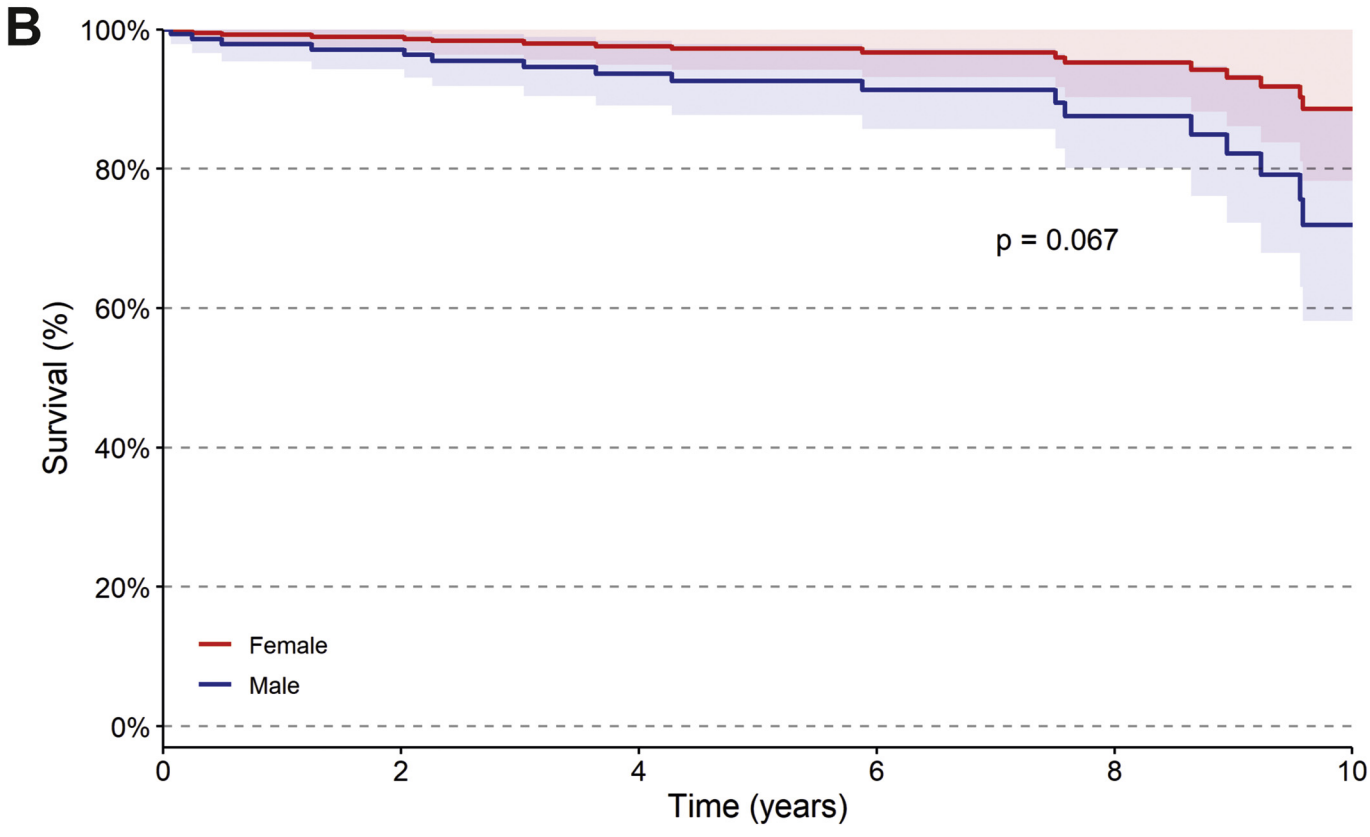

Fig. 1. Kaplan-Meier survival curves for the composite endpoint of all-cause mortality, cardiac transplantation, repeat septal reduction therapy and aborted sudden cardiac death stratified by sex. A, unadjusted survival curves for men (blue) and women (red). B, survival curves for men (blue) and women (red) adjusted (Cox-Kalbfleisch-Prentice) for age. No differences were seen regarding event-free survival after a median follow-up of 5.9 [3.0–9.1] years (unadjusted: $p = 0.27$, adjusted: $p = 0.067$). Shaded areas represent 95% confidence intervals. Prevalence of individual endpoints is shown in Table 2. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 3
Results of univariable and multivariable Cox proportional hazard regression analysis of baseline characteristics.

Variable	Univariable HR [95% CI]	P value	Multivariable HR [95% CI]	P value
Male sex	1.75 [0.63–4.85]	0.28	2.32 [0.79–6.83]	0.13
Age (y)	1.04 [1.00–1.07]	0.03	1.03 [0.99–1.07]	0.17
NYHA class ≥III	1.24 [0.57–3.33]	0.66		
Atrial fibrillation	1.71 [0.66–4.46]	0.27		
Hypertension	0.86 [0.31–2.39]	0.78		
Hypercholesterolemia	0.95 [0.32–2.86]	0.93		
Diabetes mellitus	1.23 [0.28–5.30]	0.79		
Pathogenic DNA variant	0.31 [0.09–1.07]	0.06		
Negative inotropic therapy*	0.38 [0.14–1.04]	0.06		
Heart failure therapy†	5.32 [2.03–13.94]	0.001	3.58 [1.29–9.93]	0.01
Implantable cardioverter-defibrillator	0.53 [0.12–2.30]	0.39		
Time from symptom onset (y)	0.97 [0.86–1.10]	0.60		
Time from diagnosis (y)	0.99 [0.91–1.08]	0.83		
Pre-operative peak LVOT gradient (mmHg)	1.00 [0.98–1.01]	0.68		
Maximal wall thickness				
absolute (mm)	1.03 [0.95–1.12]	0.50		
indexed (mm/m^2)	0.98 [0.88–1.09]	0.71		
LA diameter				
absolute (mm)	1.04 [0.98–1.11]	0.16		
indexed (mm/m^2)	1.00 [0.95–1.05]	0.99		
LV end-diastolic diameter				
absolute (mm)	1.03 [0.94–1.12]	0.57		
indexed (mm/m^2)	1.05 [0.89–1.24]	0.58		
Impaired systolic function	0.48 [0.06–3.70]	0.48		
Diastolic function‡			3.04 [1.38–6.70]	<0.01
Normal	reference			
Impaired relaxation	2.12 [0.42–20.72]	0.38		
Pseudonormal relaxation	3.72 [0.83–35.38]	0.09		
Restrictive	23.15 [3.80–250.71]	<0.001		
Systolic anterior motion of the mitral valve	0.17 [0.02–1.32]	0.09		
Mitral regurgitation				
No/trace	reference			
Mild/moderate	0.33 [0.10–1.04]	0.06		
Severe	0.37 [0.09–1.57]	0.18		

*includes beta-blockers, non-dihydropyridine calcium-channel antagonists and disopyramide. †includes angiotensin-converting enzyme inhibitors, mineralocorticoid receptor antagonists and diuretics, ‡univariable HR calculated using Firth's penalized maximum likelihood bias reduction method to account for data separation, treated as linear term in multivariable analysis. HR = hazard ratio; NYHA = New York Heart Association.

age of 40 [9]. Based on those results and our findings, we believe that the older age of women in our cohort is not purely a consequence of different forms of bias causing a treatment delay, and that it should be considered that the clinical course of HCM inherently implies a delayed disease onset in women.

4.2. Limitations

This study has several limitations. The retrospective nature of this study has inherent limitations, in particular regarding the time intervals measured until surgery. However, in an attempt to improve reliability, data was considered missing whenever no exact year of diagnosis or symptom onset could be ascertained. Furthermore, although the higher BSA-indexed echocardiographic parameters in women suggest more advanced disease, we underline the uncertainty that exists regarding the accuracy of using BSA when scaling cardiac size and advise caution in interpreting these results [24,25]. Also, importantly, the suggestion that HCM is more advanced in the female patients in our study is contradictory to the hypothesis that HCM manifests itself later in life in women, unless, for unknown reasons, female patients would be subject to an accelerated rate of disease progression. Of note, the finding that AMLE is performed more often in men could suggest that differences in body size impact clinical decision-making, as the decision to perform AMLE or not is at least in part dependent on visual inspection of the anatomy of the LV, mitral valve and papillary muscles. Whether this is indeed sex- and body size-specific and whether this would impact prognosis could not be reliably assessed in the current study and is a subject worthy of further scrutiny. Lastly, although we only included patients from 2000 onwards, we cannot exclude the possibility that our results were influenced by advances in diagnostic, surgical and other therapeutic techniques, or changes in the recognition of HCM diagnoses spanning two decades.

5. Conclusion

Women undergo septal myectomy later in life and seem to have more advanced disease on echocardiography. However, time until myectomy was not longer, suggesting that the age difference is not solely a function of treatment delay. Clinical outcomes after myectomy are favourable for both men and women.

Acknowledgments

None.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Grant support

None received

Declaration of Competing Interest

None.

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Please cite this article as: R. Huurman, A.F.L. Schinkel, P.L. de Jong, et al., Impact of sex on timing and clinical outcome of septal myectomy for obstructive hypertrophic cardiom..., International Journal of Cardiology, https://doi.org/10.1016/j.ijcard.2020.08.059