Sex Differences in Left Ventricular Noncompaction in Patients With and Without Neuromuscular Disorders

Claudia Stöllberger,[a] Gerhard Blazek,[b] Maria Winkler-Dworak,[c] and Josef Finsterer[a]

[a]Krankenanstalt Rudolfstiftung, Wien, Austria
[b]Hanusch Krankenhaus, Wien, Austria
[c]Vienna Institute of Demography of the Austrian Academy of Sciences, Wien, Austria

Introduction and objectives. Left ventricular hypertrabeculation/noncompaction (LVHT/NC) is more prevalent in men and is frequently associated with neuromuscular disorders (NMDs). The aim of this study was to assess sex differences in: *a)* the location and extent of LVHT/NC; *b)* left ventricular function; *c)* cardiac symptoms; *d)* electrocardiographic findings; *e)* the prevalence of NMD; and *f)* mortality.

Methods. Between June 1995 and September 2006, 100 patients (mean age, 53 [15] years; range, 14–94 years, 29 female) were diagnosed echocardiographically with LVHT/NC. All underwent cardiologic investigation and were invited to undergo a neurologic examination.

Results. The neurologic examination showed normal results in 14 patients, 21 were diagnosed with a specific form of NMD, and 44 had an NMD of unknown etiology. The other 21 refused to undergo the examination. Women presented more often with LVHT/NC affecting the anterior wall (10% vs 0%; *P*<.05), the inferoposterior wall (28% vs 10%; *P*<.05), and the lateral wall (72% vs 31%; *P*<.001). In addition, on average 2.0 ventricular regions were affected in woman compared with 1.4 in men (*P*<.001). In contrast, apical LVHT/NC was slightly more common in men (97% vs 86%; *P*=.057). No differences were observed in age, symptoms, NMD prevalence, electrocardiographic findings, or mortality.

Conclusions. In adults with LVHT/NC, there were sex differences in the location and extent of the condition. However, these did not affect clinical, neurologic, echocardiographic or electrocardiographic parameters, or prognosis. The higher prevalence of LVHT/NC in males remains unexplained.

Key words: *Cardiomyopathy. Echocardiography. Sex differences. Neuromuscular disorders. Noncompaction.*

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Diferencias de sexo en la ausencia de compactación ventricular izquierda con y sin trastornos neuromusculares

Introducción y objetivos. La hipertrabeculación/ausencia de compactación ventricular izquierda (HACVI) es más prevalente en los varones y a menudo se asocia con trastornos neuromusculares (TNM). Este estudio se diseñó para valorar las diferencias por sexos de: *a)* la localización y la extensión de la HACVI; *b)* la función ventricular izquierda; *c)* los síntomas cardiacos; *d)* los hallazgos electrocardiográficos; *e)* la prevalencia de TNM, y *f)* la mortalidad.

Métodos. Entre junio de 1995 y septiembre de 2006, se diagnosticó HACVI mediante ecocardiograma a 100 pacientes (29 mujeres; media de edad: 53 ± 15 [intervalo: 14-94] años). Todos los pacientes fueron sometidos a una exploración cardiológica e invitados a realizarse un examen neurológico.

Resultados. El estudio neurológico fue normal en 14 pacientes, a 21 personas se les diagnosticó un TNM específico, a 44 un TNM de etiología desconocida, y 21 pacientes rehusaron ser sometidos a un estudio neurológico. Las mujeres presentaron con más frecuencia una HACVI que afectaba a la pared anterior (el 10 frente al 0%; p < 0,05), a la posteroinferior (el 28 frente al 10%; p < 0,05) y a la lateral (el 72 frente al 31%; p < 0,001), además de HACVI que afectaba a 2 frente a 1,4 regiones ventriculares (p < 0,001). En contraste, los varones presentaban con una frecuencia ligeramente más elevada HACVI apical (el 97 frente al 86%; p = 0,057). No se detectaron diferencias con respecto a la edad, los síntomas, la prevalencia de TNM, los hallazgos electrocardiográficos ni la mortalidad.

Conclusiones. La HACVI en los adultos difiere según el sexo en cuanto a su localización y extensión, pero esto no afecta a los parámetros clínicos, neurológicos, electrocardiográficos o ecocardiográficos, ni tampoco al pronóstico. La prevalencia superior de HACVI en los varones continúa sin ser explicada.

Palabras clave: *Miocardiopatía. Ecocardiograma. Diferencias de sexo. Trastornos neuromusculares. Ausencia de compactación.*

Correspondence: Dra. C. Stöllberger,
Steingasse 31/18, A-1030 Wien, Austria,
E-mail: claudia.stoellberger@chello.at

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ABBREVIATIONS

LVHT: left ventricular hypertrabeculation/noncompaction
NMD: neuromuscular disorders

INTRODUCTION

Left ventricular hypertrabeculation/noncompaction (LVHT) is an increasingly recognized cardiac abnormality, frequently associated with neuromuscular disorders.[1] In the majority of case series LVHT is more prevalent in males than females (Table 1).[2-19] The reason for this difference in prevalence is unknown. If there are gender differences in patients with LVHT is also unknown. Thus, the following study in a case series of LVHT patients aimed to find out if there are gender differences regarding: *a*) location and extent of LVHT; *b*) left ventricular function; *c*) cardiac symptoms; *d*) electrocardiographic findings; *e*) prevalence of neuromuscular disorders; and *f*) mortality.

METHODS

All patients in whom LVHT was diagnosed in the echocardiographic laboratory of the Krankenanstalt Rudolfstiftung between June 1995 and September 2006 were included. The echocardiographic equipment was an Aloka 870 (June 1995 until April 1998), a Vingmed System Five (May 1998 until December 2005), and a Vivid 7 (since December 2005) with 2.5 to 3.6-MHz transducers. Two-dimensional and Doppler-echocardiographic criteria for the diagnosis of LVHT were: *a*) >3 trabeculations protruding from the left ventricular wall, distal to the papillary muscles, visible in 1 echocardiographic image plane, and *b*) intertrabecular spaces perfused from the ventricular cavity, as visualized on color Doppler imaging. In addition, all the patients fulfilled the criterion of >2 noncompacted/compacted layer in the most hypertrabeculated segment at end-systole.[16] Trabeculations were defined as structures with the same echogenicity as the myocardium and moving synchronously with the ventricular contractions.[20] In order to differentiate between trabeculations on the one side and false tendons or aberrant bands on the other side, the transducer had to be angulated and pictures in atypical views had to be obtained which best delineated LVHT. To obtain the technically best picture quality, the focus was adapted to the region of interest. The location of LVHT was assessed and categorized as apical if it involved the left ventricular apex and as anterior, lateral, or posterior-inferior, if it involved the anterior, lateral, or posterior-inferior segments of the left ventricular wall. The echocardiographic criteria remained the same during the whole study period. Measurements of left ventricular dimensions and wall thickness were performed in the parasternal short-axis view according to standard recommendations.[21] Assessment of left ventricular systolic function by calculation of the ejection fraction from the 2-dimensional picture was not feasible in several cases because the trabeculations impeded clear endocardial border tracing especially in the apical region. Thus, left

TABLE 1. **Gender Distribution in Case Series of Patients With Left Ventricular Hypertrabeculation/Noncompaction**

Author	Year	Cases, No.	Females, %	Age, Mean, Years	Country
Pignatelli[2]	2003	36	44	0.25	USA
Grillo[3]	2002	5	40	2	Italy
Neudorf[4]	2001	7	57	3	Germany
Burke[5]	2005	14	57	3.6	USA
Özkutlu[6]	2002	12	8	4	Turkey
Wald[7]	2004	22	59	4	Canada
Lilje[8]	2006	66	48	4	Germany
Ichida[9]	1999	27	44	5	Japan
Alehan[10]	2004	9	11	6	Turkey
Chin[11]	1990	8	38	8	USA
Hamamichi[12]	2001	6	50	17	Japan
Murphy[13]	2005	45	38	37	United Kingdom
Chung[14]	2004	9	56	40	Australia
deGroot[15]	2005	18	50	40	Netherlands
Oechslin[16]	2000	34	26	42	Switzerland
Lofiego[17]	2006	65	63	47	Italy/Netherlands
Sengupta[18]	2004	32	47	49	USA
Kawasaki[19]	2005	10	20	50	Japan
Present study	2006	100	29	53	Austria

ventricular systolic function was only assessed by calculation of the left ventricular fractional shortening from the M-mode picture.

All patients underwent a baseline cardiologic examination at which they were asked for their family history, medical history, cardiovascular symptoms, and its duration. A clinical examination was carried out and a 12-lead ECG was registered. ECG abnormalities were registered according to previously published criteria.[22] Family screening was not performed systematically.

All patients were invited for a neurological investigation comprising the history and a clinical neurological examination. If there were indications for a polyneuropathy an established screening program for polyneuropathy including blood, cerebrospinal fluid investigation, and sometimes nerve biopsy was carried out. If there were indications for a myopathy a screening for myopathy was initiated, including muscle enzymes, electromyography, and occasionally muscle biopsy. Informed consent was obtained from all patients.

Patients included between June 1995 and December 2004, were contacted by telephone between February and April 2005.[23] Patients included later were contacted by telephone in March 2007. It was assessed if the patient was alive or not. In cases in whom no information could be obtained, the local registration office was contacted. If the patient was dead, the patient's general practitioner was contacted to assess the cause of death. In cases dying at hospitals, the hospital departments were contacted to obtain information about the terminal diseases and the cause of death.

Statistical Analysis

Group comparisons for differences of mean values from noncategorical data were done by using the *t* test. Contingency table methods, including the χ^2 test and, if necessary, the 2-sided Fisher exact test, were used to analyze categorical data. Equality of survivor functions was tested using the log-rank test. All statistical analysis were performed by using the statistical software package STATA (Stata Statistical Software: Release 8.2. College Station, TX, USA).

RESULTS

During the study period 36 933 transthoracic echocardiographic examinations have been carried out in the echocardiographic laboratory of the KA Rudolfstiftung. LVHT was diagnosed in 100 patients (29 female; mean age, 53 [15]; range, 14-94 years). Ninety-three of these cases, diagnosed until December 2005, have been published previously.[24]

Coronary angiography was performed in 56 (56%) patients and showed a >50% stenosis in 6. In 57 patients (57%), LVHT was confined to a single part of the left ventricular wall, mainly the apical. In 33 patients (33%) it involved 2 segments, in 8 patients (8%) it involved 3 segments, and in 2 patients 4 segments. LVHT did not involve the interventricular septum in any of the patients. Abnormalities of 1 or more valves were found in 54 patients (54%) and were mitral regurgitation (n=48), tricuspid regurgitation (n=25), calcific aortic regurgitation (n=12), aortic stenosis (n=4), and Ebstein's anomaly (n=1). The degree of regurgitation or stenosis was mild to moderate, and was due to ventricular dilatation in most of the cases.

Seventy-nine patients (79%) underwent at least 1 neurological investigation, the remaining 21 patients refused. A specific NMD was diagnosed in 21 patients (metabolic myopathy, n=14; Leber's hereditary optic neuropathy, n=3; myotonic dystrophy, n=2; Becker muscular dystrophy, n=1; and Duchenne muscular dystrophy, n=1). A NMD of unknown etiology was diagnosed in 44 patients. All of these 44 patients were either symptomatic or had elevated muscle enzymes, or abnormal electromyograms. Most of the patients underwent muscle biopsy which did not show a specific muscle disorder but only nonspecific myopathic changes. The neurological investigation was normal in 14 patients.

Indications for echocardiography, neurologic, and cardiovascular comorbidity, electrocardiographic, and echocardiographic findings are listed in Table 2. Females were more often in NYHA IV stages of heart failure. Females had more extensive LVHT than males, affecting more often the anterior, posterior-inferior, and lateral wall. Males on the contrary had LVHT affecting the apex slightly more often than females (97% vs 86%, *P*=.057).

During follow-up investigation, the mortality rate of females and males did not differ (log-rank; *P*=.5940) (Figure 1). Of the 22 patients who had died during follow-up, 7 (32%) were female and 15 (68%) were male. The 22 patients had died due to cardiac failure (n=7, 2 females), sudden cardiac death (n=3, 2 females), malignancy (n=3, 1 female), pneumonia (n=4), abdominal sepsis (n=1, female), stroke (n=1, female), hepatic failure in cirrhosis (n=1), and pulmonary embolism (n=2). The rate of cardiac deaths was not different in females and males (57% vs 40%, *P*=.452). Of the 10 females, who were in NYHA class IV at the baseline investigation, 7 improved with pharmacotherapy, and 3 had died, 2 of them from heart failure, and 1 from stroke. Of the 10 males, who were in NYHA class IV at the baseline investigation, 6 improved with pharmacotherapy, and 4 had died, 2 of them from pneumonia, 1 from malignancy, and 1 from heart failure.

DISCUSSION

This study in the largest ever-described case series of patients with LVHT confirms male preponderance among adult LVHT patients. Furthermore, it shows for

TABLE 2. **Clinical, Electrocardiographic, and Echocardiographic Findings of 100 Patients With Left Ventricular Hypertrabeculation/Noncompaction According to Gender**

Characteristics	Total (n=100)	Male (n=29)	Female (n=71)
Age, mean (SD), y	53.3 (15.4)	52.4 (14.4)	55.4 (17.8)
Below median age, n (y)	50 (50.0)	38 (53.5)	12 (41.4)
Indication for echocardiography			
Heart failure, n (%)	54 (54.0)	38 (53.5)	16 (55.2)
Chest pain, n (%)	23 (23.0)	17 (23.9)	6 (20.7)
Syncope, n (%)	8 (8.0)	5 (7.0)	3 (10.3)
Myopathy, n (%)	7 (7.0)	7 (9.9)	0 (0)
Stroke/embolism, n (%)	3 (3.0)	1 (1.4)	2 (6.9)
Hypertension, n (%)	3 (3.0)	2 (2.8)	1 (3.4)
Family screening, n (%)	2 (2.0)	1 (1.4)	1 (3.4)
Clinical characteristics			
Neurologically normal, n (%)	14 (14.0)	7 (9.9)	7 (24.1)
Specific neuromuscular disorder, n (%)	21 (21.0)	17 (23.9)	4 (13.8)
Neuromuscular disorder of unknown etiology, n (%)	44 (44.0)	28 (39.4)	16 (55.2)[a]
Neurologically not investigated, n (%)	21 (21.0)	19 (26.8)	2 (6.9)
Exertional dyspnoea, n (%)	67 (67.0)	48 (67.6)	19 (65.5)
Angina pectoris, n (%)	25 (25.0)	16 (22.5)	9 (31.0)
Edema, n (%)	19 (19.0)	13 (18.3)	6 (20.7)
Palpitations/vertigo/syncope, n (%)	18 (18.0)	14 (19.7)	4 (13.8)
Diabetes mellitus, n (%)	15 (15.0)	9 (12.7)	6 (20.7)
Arterial hypertension, n (%)	32 (32.0)	22 (31.0)	10 (34.5)
Heart failure, n (%)	71 (71.0)	50 (70.4)	21 (72.4)
NYHA I, n (%)	8 (8.0)	4 (5.6)	4 (13.8)
NYHA II, n (%)	16 (16.0)	14 (19.7)	2 (6.9)
NYHA III, n (%)	27 (27.0)	22 (31.0)	5 (17.2)
NYHA IV, n (%)	20 (20.0)	10 (14.1)	10 (34.5)[a]
ECG findings			
No ECG abnormality, n (%)	9 (9.0)	6 (8.5)	3 (10.3)
2 or more ECG abnormalities, n (%)	49 (49.0)	36 (50.7)	13 (44.8)
Tall QRS complex, n (%)	39 (39.0)	31 (43.7)	8 (27.6)
ST/T wave abnormality, n (%)	39 (39.0)	28 (39.4)	11 (37.9)
Left bundle branch block, n (%)	23 (23.0)	14 (19.7)	9 (31.0)
Ventricular ectopic beats, n (%)	13 (13.0)	9 (12.7)	4 (13.8)
Pathologic Q waves, n (%)	8 (8.0)	5 (7.0)	3 (10.3)
Left anterior hemiblock, n (%)	7 (7.0)	5 (7.0)	2 (6.9)
Right bundle branch block, n (%)	5 (5.0)	4 (5.6)	1 (3.4)
Low voltage, n (%)	4 (4.0)	4 (5.6)	0 (0)
Sinustachycardia, n (%)	3 (3.0)	3 (4.2)	0 (0)
WPW-syndrome, n (%)	3 (3.0)	2 (2.8)	1 (3.4)
Sum of ECG abnormalities, mean, (SD)	1.5 (0.8)	1.5 (0.8)	1.5 (0.9)
Echocardiographic findings			
Left ventricular enddiastolic diameter, mean (SD), mm	64.2 (12.6)	65.6 (12.0)	60.8 (13.8)[a]
Left ventricular fractional shortening, mean, (SD), %	23.1 (11.4)	23.1 (11.4)	23.1 (11.6)
Interventricular septal thickness, mean (SD), mm	12.4 (3.1)	12.5 (2.9)	12.0 (3.7)
Left ventricular posterior wall thickness, mean (SD), mm	12.4 (2.9)	12.6 (2.7)	12.0 (3.3)
Valvular abnormalities, n (%)	54 (54.5)	36 (51.4)	18 (62.1)
LVHT location			
Apex, n (%)	94 (94.0)	69 (97.2)	25 (86.2)
Anterior wall, n (%)	3 (3.0)	0 (0)	3 (10.3)[a]
Posterior-inferior wall, n (%)	15 (15.0)	7 (9.9)	8 (27.6)[a]
Lateral wall, n (%)	43 (43.0)	22 (31.0)	21 (72.4)[b]
LVHT extension, ventricular segments, mean (SD)	1.6 (0.7)	1.4 (0.6)	2.0 (0.9)[b]

SD indicates standar deviation; ECG, electrocardiogram; NYHA, New York Heart Association; WPW, Wolff-Parkinson-White.
[a] $P<.05$.
[b] $P<.001$.

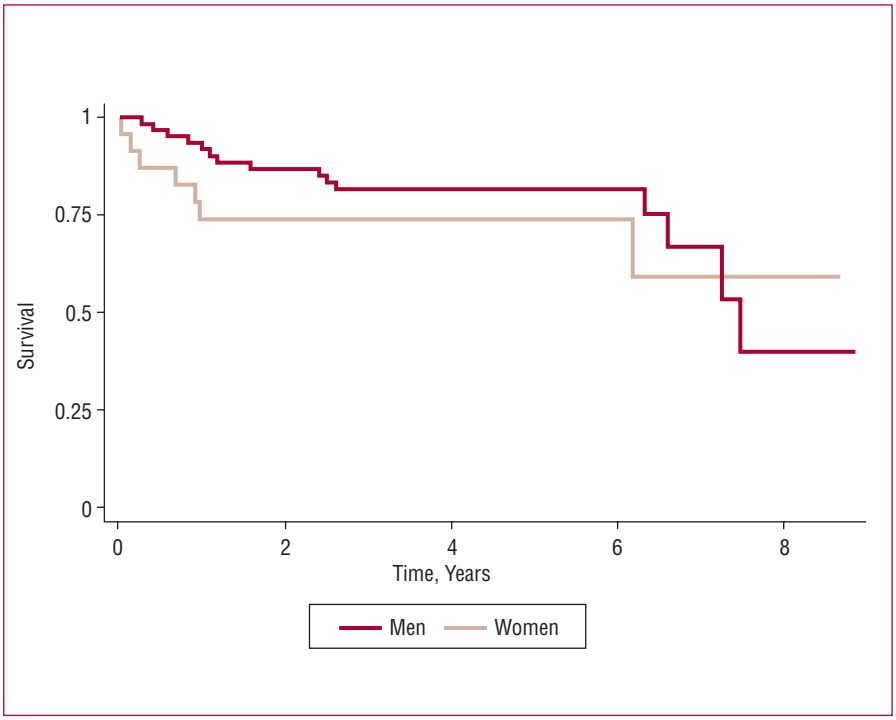

Figure 1. Survival curves of the patients of our series separated by sex.

the first time that LVHT location and extent, as assessed by echocardiography, differs between females and males and that females have more extensive LVHT. There were, however, no gender differences regarding cardiac and neuromuscular comorbidity as well as mortality.

The reason why LVHT is found more in males than females is unknown. We have the following hypotheses: *a*) LVHT may be associated with X-linked disorders thus favoring its occurrence in males; *b*) LVHT may be associated with genetically transmitted diseases, which occur more often in males than females; *c*) females with LVHT are more severely affected and eventually die earlier than males, thus leading to an underrepresentation of females in series of adults with LVHT; this hypothesis may be substantiated by some case series from children and adolescents who had a higher female ratio than case series from adults (Table 1); *d*) development of LVHT during lifetime may occur more often in males than females, thus leading to more males with LVHT in adult case series, so far, acquired LVHT has been described in 2 males but only 1 female of which all had a neuromuscular disorder[25-27]; *e*) LVHT may disappear more frequently in females than in males, so far, only 1 case of LVHT disappearance has been described in a female patient[28];and *f*) females with heart failure may be referred for echocardiography less often than males.[29] The higher proportion of females in advanced stages of heart failure when LVHT was diagnosed may support this assumption, suggesting that females were only referred for echocardiography if their condition was severely affected.

To explain the differences in location and extent of LVHT we have the following hypotheses: *a*) gender differences may occur in the amount and distribution of hormone receptors on myocardiocytes; *b*) differences exist in the hemodynamic and physiologic properties between the heart of males and females, the female heart has to endure enormous physiologic changes during pregnancy[30,31]; *c*) there might be differences in the adaptive mechanisms to volume load and decreased contractility between male and female hearts; and *d*) the molecular consequences of the mutations could be different in males and females.[32]

Despite these gender differences in extent and location of LVHT surprisingly there were no differences regarding clinical, neurologic, electrocardiographic, and echocardiographic findings. Furthermore, females with LVHT did not have a worse prognosis than males. Thus, possibly location and extent of LVHT do not have a clinical or hemodynamic impact. However, as can be seen in Figure 1, the survival curves begin to diverge around the seventh year. Therefore, it could be inferred that the length of the follow-up in our patients is still too short, and that we have to continue the follow-up. Other studies of patients with LVHT had a shorter duration of follow-up or did not look for gender differences.[2,3,6,7,9,10,13,16,19] In our patients with LVHT the prognosis, so far, has been shown to be dependent on cardiac and neuromuscular comorbidity.[33]

Limitations of the Study

These are that for quantification of LVHT only the ventricular walls and not the commonly used 16-segment model was applied, that left ventricular dimensions were not adjusted by body surface area, and that systolic function was only assessed by the left ventricular fractional shortening. No search for neuromuscular diseases have been performed in a control group. We concentrated our efforts on the neuromuscular comorbidity and no systematic investigations have been carried out, if LVHT was associated with other extracardiac diseases. Due to the small number of patients, no multivariate analysis regarding survival could be carried out. Furthermore, the relatively high age of our patients compared with other LVHT series does not allow to applicate our conclusions to other age groups.

CONCLUSION

This study shows that LVHT in adults differs significantly between females and males concerning location and extent without affecting clinical, neurologic, echocardiographic, or electrocardiographic parameters. Gender dependency of LVHT location and extent seems to have no prognostic impact. The higher prevalence of LVHT in males remains unexplained.

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