Sex Differences in Left Ventricular Noncompaction in Patients With and Without Neuromuscular Disorders
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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 infero-posterior 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, neuologic, 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.

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 cardíacos; 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.

INTRODUCTION

Left ventricular hypertrabeculation/noncompaction (LVHT) is an increasingly recognized cardiac abnormality, frequently associated with neuromuscular disorders. In the majority of case series LVHT is more prevalent in males than females (Table 1). 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:

- location and extent of LVHT;
- left ventricular function;
- cardiac symptoms;
- electrocardiographic findings;
- prevalence of neuromuscular disorders; and
- 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 Stöllberger C et al. Sex Differences in Left Ventricular Noncompaction.
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 examination
comprising the history and a clinical neurological
examination. If there were indications for a
polyneuropathy an established screening program for
colorectal neoplasms 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 χ² 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
females; 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 >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 morbidity, 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 who 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>
<thead>
<tr>
<th>Characteristics</th>
<th>Total (n=100)</th>
<th>Male (n=29)</th>
<th>Female (n=71)</th>
</tr>
</thead>
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<tr>
<td>Age, mean (SD), y</td>
<td>53.3 (15.4)</td>
<td>52.4 (14.4)</td>
<td>55.4 (17.8)</td>
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<tr>
<td>Below median age, n (y)</td>
<td>50 (50.0)</td>
<td>38 (53.5)</td>
<td>12 (41.4)</td>
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<td>Indication for echocardiography</td>
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<tr>
<td>Heart failure, n (%)</td>
<td>54 (54.0)</td>
<td>38 (53.5)</td>
<td>16 (55.2)</td>
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<tr>
<td>Chest pain, n (%)</td>
<td>23 (23.0)</td>
<td>17 (23.9)</td>
<td>6 (20.7)</td>
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<td>Syncope, n (%)</td>
<td>8 (8.0)</td>
<td>5 (7.0)</td>
<td>3 (10.3)</td>
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<td>Myopathy, n (%)</td>
<td>7 (7.0)</td>
<td>7 (9.9)</td>
<td>0 (0)</td>
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<tr>
<td>Stroke/embolism, n (%)</td>
<td>3 (3.0)</td>
<td>1 (1.4)</td>
<td>2 (6.9)</td>
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<td>Hypertension, n (%)</td>
<td>3 (3.0)</td>
<td>2 (2.8)</td>
<td>1 (3.4)</td>
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<td>Family screening, n (%)</td>
<td>2 (2.0)</td>
<td>1 (1.4)</td>
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<td>Clinical characteristics</td>
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<tr>
<td>Neurologically normal, n (%)</td>
<td>14 (14.0)</td>
<td>7 (9.9)</td>
<td>7 (24.1)</td>
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<td>Specific neuromuscular disorder, n (%)</td>
<td>21 (21.0)</td>
<td>17 (23.9)</td>
<td>4 (13.8)</td>
</tr>
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<td>Neuromuscular disorder of unknown etiology, n (%)</td>
<td>44 (44.0)</td>
<td>28 (39.4)</td>
<td>16 (55.2)*</td>
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<td>Neurologically not investigated, n (%)</td>
<td>21 (21.0)</td>
<td>19 (26.8)</td>
<td>2 (6.9)</td>
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<td>Exertional dyspnea, n (%)</td>
<td>67 (67.0)</td>
<td>48 (67.6)</td>
<td>19 (65.5)</td>
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<td>Angina pectoris, n (%)</td>
<td>25 (25.0)</td>
<td>16 (22.5)</td>
<td>9 (31.0)</td>
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<td>Edema, n (%)</td>
<td>19 (19.0)</td>
<td>13 (18.3)</td>
<td>6 (20.7)</td>
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<tr>
<td>Palpitations/vertigo/syncope, n (%)</td>
<td>18 (18.0)</td>
<td>14 (19.7)</td>
<td>4 (13.8)</td>
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<tr>
<td>Diabetes mellitus, n (%)</td>
<td>15 (15.0)</td>
<td>9 (12.7)</td>
<td>6 (20.7)</td>
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<td>Arterial hypertension, n (%)</td>
<td>32 (32.0)</td>
<td>22 (31.0)</td>
<td>10 (34.5)</td>
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<tr>
<td>Heart failure, n (%)</td>
<td>71 (71.0)</td>
<td>50 (70.4)</td>
<td>21 (72.4)</td>
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<td>NYHA I, n (%)</td>
<td>8 (8.0)</td>
<td>4 (5.6)</td>
<td>4 (13.8)</td>
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<td>NYHA II, n (%)</td>
<td>16 (16.0)</td>
<td>14 (19.7)</td>
<td>2 (6.9)</td>
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<tr>
<td>NYHA III, n (%)</td>
<td>27 (27.0)</td>
<td>22 (31.0)</td>
<td>5 (17.2)</td>
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<td>NYHA IV, n (%)</td>
<td>20 (20.0)</td>
<td>10 (14.1)</td>
<td>10 (34.5)*</td>
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<td>ECG findings</td>
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<tr>
<td>No ECG abnormality, n (%)</td>
<td>9 (9.0)</td>
<td>6 (8.5)</td>
<td>3 (10.3)</td>
</tr>
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<td>2 or more ECG abnormalities, n (%)</td>
<td>49 (49.0)</td>
<td>36 (50.7)</td>
<td>13 (44.8)</td>
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<tr>
<td>Tall QRS complex, n (%)</td>
<td>39 (39.0)</td>
<td>31 (43.7)</td>
<td>8 (27.6)</td>
</tr>
<tr>
<td>ST/T wave abnormality, n (%)</td>
<td>39 (39.0)</td>
<td>28 (39.4)</td>
<td>11 (37.9)</td>
</tr>
<tr>
<td>Left bundle branch block, n (%)</td>
<td>23 (23.0)</td>
<td>14 (19.7)</td>
<td>9 (31.0)</td>
</tr>
<tr>
<td>Ventricular ectopic beats, n (%)</td>
<td>13 (13.0)</td>
<td>9 (12.7)</td>
<td>4 (13.8)</td>
</tr>
<tr>
<td>Pathologic Q waves, n (%)</td>
<td>8 (8.0)</td>
<td>5 (7.0)</td>
<td>3 (10.3)</td>
</tr>
<tr>
<td>Left anterior hemiblock, n (%)</td>
<td>7 (7.0)</td>
<td>5 (7.0)</td>
<td>2 (6.9)</td>
</tr>
<tr>
<td>Right bundle branch block, n (%)</td>
<td>5 (5.0)</td>
<td>4 (5.6)</td>
<td>1 (3.4)</td>
</tr>
<tr>
<td>Low voltage, n (%)</td>
<td>4 (4.0)</td>
<td>4 (5.6)</td>
<td>0 (0)</td>
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<tr>
<td>Sinustachycardia, n (%)</td>
<td>3 (3.0)</td>
<td>3 (4.2)</td>
<td>0 (0)</td>
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<td>WPW-syndrome, n (%)</td>
<td>3 (3.0)</td>
<td>2 (2.8)</td>
<td>1 (3.4)</td>
</tr>
<tr>
<td>Sum of ECG abnormalities, mean, (SD)</td>
<td>1.5 (0.8)</td>
<td>1.5 (0.8)</td>
<td>1.5 (0.9)</td>
</tr>
<tr>
<td>Echocardiographic findings</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Left ventricular enddiastolic diameter, mean (SD), mm</td>
<td>64.2 (12.6)</td>
<td>65.6 (12.0)</td>
<td>60.8 (13.8)*</td>
</tr>
<tr>
<td>Left ventricular fractional shortening, mean, (SD), %</td>
<td>23.1 (11.4)</td>
<td>23.1 (11.4)</td>
<td>23.1 (11.6)</td>
</tr>
<tr>
<td>Interventricular septal thickness, mean (SD), mm</td>
<td>12.4 (3.1)</td>
<td>12.5 (2.9)</td>
<td>12.0 (3.7)</td>
</tr>
<tr>
<td>Left ventricular posterior wall thickness, mean (SD), mm</td>
<td>12.4 (2.9)</td>
<td>12.6 (2.7)</td>
<td>12.0 (3.3)</td>
</tr>
<tr>
<td>Valvular abnormalities, n (%)</td>
<td>54 (54.5)</td>
<td>36 (51.4)</td>
<td>18 (62.1)</td>
</tr>
<tr>
<td>LVHT location</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Apex, n (%)</td>
<td>94 (94.0)</td>
<td>69 (97.2)</td>
<td>25 (86.2)</td>
</tr>
<tr>
<td>Anterior wall, n (%)</td>
<td>3 (3.0)</td>
<td>0 (0)</td>
<td>3 (10.3)*</td>
</tr>
<tr>
<td>Posterior-inferior wall, n (%)</td>
<td>15 (15.0)</td>
<td>7 (9.9)</td>
<td>8 (27.6)*</td>
</tr>
<tr>
<td>Lateral wall, n (%)</td>
<td>43 (43.0)</td>
<td>22 (31.0)</td>
<td>21 (72.4)*</td>
</tr>
<tr>
<td>LVHT extension, ventricular segments, mean (SD)</td>
<td>1.6 (0.7)</td>
<td>1.4 (0.6)</td>
<td>2.0 (0.9)*</td>
</tr>
</tbody>
</table>

SD indicates standard deviation; ECG, electrocardiogram; NYHA, New York Heart Association; WPW, Wolff-Parkinson-White.

*P < 0.05.

**P < 0.01.
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.\(^{5,14,15,16,19}\) 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 controlled 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 appriciate 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.

REFERENCES
