Spongius Hypertrophic Cardiomyopathy in Patients With Mutations in the Four-and-a-Half LIM Domain 1 Gene

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Background—X-linked myopathy with postural muscle atrophy is a novel X-linked myopathy caused by mutations in the four-and-a-half LIM domain 1 gene (FHL1). Cardiac involvement was suspected in initial publications. We now systematically analyzed the association of the FHL1 genotype with the cardiac phenotype to establish a potential cardiac involvement in the disease.

Methods and Results—Seventeen male patients and 23 female mutation carriers were compared with healthy controls. Every patient underwent a comprehensive clinical and cardiovascular workup. ECG abnormalities occurred frequently in affected males and were less frequent in heterozygous females. Both male and female mutation carriers had increased myocardial mass (affected males=115.1±25.3 g/m²; heterozygous females=95.1±19.6 g/m²; controls=89.0±15.6 g/m² and 72.6±12.6 g/m², respectively) with increased wall thickness (typically midventricular and apical segments) mainly in affected males. Longitudinal systolic function was reduced in affected males (radial systolic strain: affected males=24.6±11.8%; male controls=43.2±14.8%; P=0.002). Diastolic dysfunction occurred in both affected males and heterozygous females. Cardiac MRI revealed a morphological hallmark of X-linked myopathy with postural muscle atrophy; a characteristic spongious structure and replacement fibrosis indicated by late enhancement could be detected in most affected males. X-linked myopathy with postural muscle atrophy was associated with reduced exercise capacity in affected males but not in heterozygous female mutation carriers.

Conclusions—X-linked myopathy with postural muscle atrophy patients consistently showed electrical, functional, and characteristic morphological cardiac abnormalities that translate into reduced exercise capacity. Reduced systolic and diastolic function is associated with a novel type of spongious hypertrophic cardiomyopathy. An unexpected finding was that some cardiac abnormalities were also present in heterozygous female mutation carriers. (Circ Cardiovasc Genet. 2012;5:490-502.)

Key Words: hypertrophic cardiomyopathy ■ FHL1 mutation ■ XMPMA ■ strain ■ strain rate

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Clinical Perspective on p 502

We and others identified the four-and-a-half LIM domain 1 gene (FHL1) on chromosome Xq26.3 as the causative gene for this new genetic disorder. In an Austrian family we found an amino acid substitution, C224W, which segregated with the disease. Analysis of the protein by Western blotting with FHL1-specific antibodies indicated a striking reduction of FHL1 protein levels in skeletal muscle cells of affected individuals.
*FHL1* is expressed in both, skeletal and cardiac muscle, is abundant in oxidative fibers, and plays a role in sarcomere synthesis and assembly. FHL1 is a member of LIM-only proteins containing four-and-a-half domains with FHL-specific LIM consensus sequence C-X_{6-21}-H-X_{6-8}-C-X_{6-17}-C-X_{6-7}. LIM domains are cysteine rich, double zinc-binding structures consisting of 2 subdomains, each responsible for binding 1 Zn^{2+} ion.

Mutations at conserved cysteines that are involved in zinc binding have a highly deleterious effect on the tertiary structure of the protein. In vitro studies demonstrated that mutations or changes in the amino-acid sequence can eliminate the stability of the LIM tertiary structure. In the muscle LIM protein (MLP or CSR2P3), which is known to be causative for hereditary hypertrophic cardiomyopathy, the mutation of a Zn^{2+}-coordinating cysteine residue ablates the Zn^{2+} binding within the LIM domain, destabilizing the protein to proteolysis and reducing its protein–protein interactions. Thus, mutations affecting the Zn^{2+}-complexing property of *FHL1* likely cause hypertrophy of skeletal and cardiac muscles. In fact, we recently described patients with mutations in the C-terminus of *FHL1* presenting with XMPMA displaying hypertrophic cardiomyopathy and rhythm abnormalities.

A number of protein-binding partners including myosin-binding protein C bind to different LIM domains within *FHL1*. Because mutations in myosin-binding protein C are the second-most common cause of familial hypertrophic cardiomyopathy, the *FHL1* gene might be a strong candidate for hereditary and sporadic hypertrophic cardiomyopathy (HCM). However, the morphological expression and the clinical presentation of this hitherto unknown cardiomyopathy in patients with XMPMA are completely uncharacterized. A detailed assessment of the cardiac manifestations associated with *FHL1* cardiomyopathy should provide further knowledge of the cause and pathobiology of the disease. We therefore characterized potential cardiac manifestations in patients and carriers with mutations in the C-terminus of the *FHL1* gene. To this end, we recruited additional families and family members from our previous reports. We performed comprehensive cardiac assessment as well as genetic testing for *FHL1* mutations. This allowed us to describe, for the first time, morphological and functional alterations of the heart in hemizygous male mutation carriers and the impact on cardiac function in heterozygous females in comparison with control family members.

**Methods**

**Study Population**

A total of 85 study participants were recruited from 4 Austrian families and 7 unrelated German families (Figure 1). Male study subjects (n=17; age 38±15 years) hemizygous for mutations in *FHL1* were identified, displaying the clinical features of XMPMA, partly reported in Schoser et al. Additionally, all female first-degree relatives, including the mothers of the index patients (n=23; age 52±18 years), who were heterozygous for mutations in *FHL1*, were examined and genealogical data were collected. The affected male subjects were also compared with 22 healthy wild-type male controls and the heterozygous females were compared with 23 healthy females without the mutation, all recruited from the affected families. Care was taken to recruit controls from similar age ranges (37±14 years; Table 1). Because it was not possible to recruit female control individuals from the families with the same mean age as the heterozygous females, we adjusted for age in the analyses. All patients provided informed consent for genotype assessment, cardiac phenotyping, and imaging including digital data storage. The study was approved by the Ethics Committee of the Medical University of Graz.

**Molecular Genetic Analysis**

Genomic DNA was extracted from blood samples using standard procedures. PCR and subsequent sequencing of all coding exons of *FHL1* including exon/intron boundaries was performed as described in Windpassinger et al. Briefly, polymerase chain reaction products were sequenced using the BigDYEv3 ET Terminator Cycle Sequencing Kit (Perkin-Elmer, Applied Biosystems Inc.). Sequencing reactions were run on the ABI Prism3100 DNA Analyzer (Perkin-Elmer, Applied Biosystems Inc.). and the data were collected with the ABI DATA COLLECTION software version 1.1. Subsequently, sequences were analyzed using the mutation detection software Seqscape version 2.1.1 (Applied Biosystems, Foster City, CA).

**Clinical Investigations**

All participants underwent detailed identical clinical and cardiovascular examinations. Clinical neurological assessment was performed by neurologists specialized in neuromuscular disorders. Technical analysis included a 12-lead ECG, long-term Holter recording (Pathfinder Del Mar Reynolds Medical Ltd., Irvine CA; mean recording time 2.4 days), and serum chemistry analysis. Comprehensive echocardiography and cardiac magnetic resonance imaging (CMRI) studies were performed on the same day. Spiroergometry (Ganshorn Powercure, Niederlauer, Germany) was carried out on all except 3 patients, who were excluded because of substantial muscular weakness. Patients with risk factors for coronary artery disease (CAD) underwent coronary angiography (n=5) or coronary computed tomography angiography (n=9). None of those patients had significant CAD.

**Blood Sampling and Assay**

In all study participants (n=85) blood samples were drawn and analyzed for routine laboratory parameters and organ-specific enzyme isoforms, indicating cardiac, musculoskeletal, and liver involvement. Blood samples were drawn from the antecubital vein after at least 30 minutes of supine rest. Troponin T and N-terminal pro-B-type natriuretic peptide (NT-proBNP) were measured by electrochemiluminescence on an Elecsys 2010 analyzer (Roche Diagnostics).

**Electrocardiography**

Standard 12-lead electrocardiograms were recorded on the day of the echocardiographic examination and examined for standard interval measurements, ST-T segment abnormalities, Q-waves, and left ventricular (LV) voltage. The ST-T wave segments were studied for the presence or absence of T-wave inversions, and, when present, the maximum T-wave depth in any lead was recorded in mm. We defined LVH by calculating the Sokolow-Lyon index and by the Romhilt-Estes (RE) point score.

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**Figure 1.** Schematic representation of family members enrolled in the study. A total of 85 participants from 8 families with cases of XMPMA were phenotyped.
Table 1. Baseline Characteristics and Laboratory Analyses

<table>
<thead>
<tr>
<th></th>
<th>Male Hemizygous</th>
<th>Male Controls</th>
<th>P Value</th>
<th>Female Heterozygous</th>
<th>Female Controls</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>38±15</td>
<td>37±14</td>
<td>0.855</td>
<td>52±18</td>
<td>40±12</td>
<td>0.007</td>
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<tr>
<td>History of</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>3 (18%)</td>
<td>0 (0%)</td>
<td>0.074*</td>
<td>9 (39%)</td>
<td>0 (0%)</td>
<td>0.001*</td>
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<tr>
<td>Hyperlipidemia</td>
<td>3 (18%)</td>
<td>14 (64%)</td>
<td>0.008*</td>
<td>9 (39%)</td>
<td>2 (9%)</td>
<td>0.035*</td>
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<tr>
<td>CAD</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>na</td>
<td>2 (9%)</td>
<td>0 (0%)</td>
<td>0.489*</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>14 (82%)</td>
<td>0 (0%)</td>
<td>&lt;0.001*</td>
<td>12 (52%)</td>
<td>0 (0%)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Functional class</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NYHA I</td>
<td>3 (18%)</td>
<td>22 (100%)</td>
<td>&lt;0.001</td>
<td>11 (48%)</td>
<td>23 (100%)</td>
<td></td>
</tr>
<tr>
<td>NYHA II</td>
<td>14 (82%)</td>
<td>0 (0%)</td>
<td>&lt;0.001</td>
<td>11 (48%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>NYHA III</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>na</td>
<td>1 (4%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>ALT U/L</td>
<td>59.1±20.5</td>
<td>30.7±12.4</td>
<td>&lt;0.001</td>
<td>26.0±13.4</td>
<td>24.2±11.3</td>
<td>0.418</td>
</tr>
<tr>
<td>AST U/L</td>
<td>57.5±20.4</td>
<td>26.0±4.2</td>
<td>&lt;0.001</td>
<td>28.2±7.8</td>
<td>22.9±7.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CK U/L</td>
<td>870 (208, 3565)</td>
<td>130 (62, 302)</td>
<td>&lt;0.001</td>
<td>110 (53, 596)</td>
<td>95 (14, 331)</td>
<td>0.249</td>
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<tr>
<td>Myoglobin, ng/mL</td>
<td>200.6 (60.4, 355.9)</td>
<td>26.6 (20.9, 49.9)</td>
<td>&lt;0.001</td>
<td>38.9 (20.9, 112.6)</td>
<td>26.9 (21.0, 50.5)</td>
<td>0.003</td>
</tr>
<tr>
<td>Trop-T, ng/mL</td>
<td>0.18 (0.0, 0.39)</td>
<td>0.0 (0.0, 0)</td>
<td>&lt;0.001</td>
<td>0.0 (0.0, 0)</td>
<td>0.0 (0.0, 0)</td>
<td>na</td>
</tr>
<tr>
<td>NT-proBNP, pg/mL</td>
<td>149.0 (3.0, 782.0)</td>
<td>3.2 (2.0, 76.0)</td>
<td>&lt;0.001</td>
<td>114.0 (2.0, 2271.0)</td>
<td>70.0 (15.0, 211.0)</td>
<td>0.665</td>
</tr>
</tbody>
</table>

CAD indicates coronary artery disease; NYHA, New York Heart Association; ALT, alanine aminotransferase; AST, aspartate aminotransferase, CK, creatine kinase; CK-MB, creatine kinase muscle brain; Trop T, troponin T, NT-proBNP, B-type natriuretic peptide; and na, not available.

*Data are shown as unadjusted mean-standard deviation or median (min, max) for continuous variables and absolute and relative frequencies for categorical variables; P values are adjusted for family clustering.

**Analyzed using Fisher exact test.**

Standard Echocardiographic Measurements

Echocardiography (GE, Vivid 7 Dimension BT06) was performed according to the guidelines of the American Society of Echocardiography and images stored digitally for subsequent analysis. Data on LV septal, posterior and maximal wall thickness, and ejection fraction (EF) were assessed; LV mass and left atrial volumes were determined by established criteria. Left atrial dilation was defined as either atrial dilation in the apical 4 chamber view by 2D measurement and in the apical views by biplane measurement of the left atrial volume (left atrial volume index >28 mL/m² body surface area). We also characterized the degree of valvular regurgitation and pulmonary artery pressure. Diastolic function was assessed as previously described, by pulse wave and tissue Doppler (E wave velocity, A wave velocity, E to A ratio, É, E to É ratio, and the deceleration time). The velocity of the early diastolic septal mitral annulus É wave was analyzed to assess the early diastolic transmural velocity/mitral annular velocity ratio (E/É), as an estimate of diastolic function.

Color Doppler Myocardial Imaging for Regional Ventricular Function

Real-time 2-dimensional color Doppler myocardial imaging data (Echopac dimension 06, GE Ultrasound) were recorded from the interventricular septum, the LV lateral, anterior, and posterior wall using a standard apical 4- and 2-chamber view as well as the apical long axis view to evaluate longitudinal function (ie, myocardial shortening in systole and lengthening in diastole). To assess radial function of the infarct border zone (to measure myocardial thickening in systole and thinning in diastole), parasternal short axis views were used. Color Doppler myocardial imaging data were analyzed using dedicated software (TVI R, GE, USA). Longitudinal strain rates (SR) in the basal, mid, and apical segments of each wall and radial SRs of the infarct border zone were estimated by measuring the spatial velocity gradient. SR profiles were averaged over 3 consecutive cardiac cycles and integrated over time to derive natural strain profiles using end-diastole as the reference point. From the resulting SR and strain curves, peak systolic SR and systolic strain (ε) were measured. Data for the longitudinal function are presented as the mean of the interrogated wall. The intraobserver variability (expressed in percentage of the mean) for this method has been published previously, and averaged 10% for SR and 11% for strain.

Magnet Resonance Imaging

Cine-MRI was carried out in 56 study subjects: affected males (n=16), heterozygous females (n=20), and male controls (n=20). Six study subjects could not be examined because of claustrophobia, missing consent, or other specific contraindications for MRI, as was the case for 1 affected male with a sinus Valsalva aneurysm treated with stent. Analysis of LV EF was done by manual segmentation of the endocardial and epicardial borders of the end-diastolic and end-systolic frame, as previously described. Additionally, cardiac morphology was depicted by T2-weighted transversal Haste images and by short axis view T1-weighted Turbo Spin Echo sequences. The late enhancement (LE) technique (8 mm slice thickness, breathhold, short and long heart axis) was applied to detect changes of tissue integrity in LV myocardium. Images were acquired 10 to 15 minutes after the injection of gadopentetate dimeglumine (Magnevist, Schering, Berlin, Germany; 0.2 mmol/kg of body wt) using an inversion recovery sequence (field of view 240 × 320 mm²; matrix 165 × 256).

Spiroergometry

Spiroergometry was performed in 82 patients using a standardized protocol. Three patients (1 affected male, 2 female carriers) were excluded because of physical weakness. All participating patients performed symptom limited cardiopulmonary exercise testing on an electromagnetically braked cycle ergometer with a progressively increasing work-rate (10 W.min⁻¹). Heart rate and pulse oximetry were monitored continuously and blood pressure was taken noninvasively every 3 minutes. The maximum work rate was recorded. Oxygen uptake (Vo2), minute ventilation, and CO2 output were calculated.
breath by breath, interpolated and averaged over 10-second periods. Peak oxygen uptake (peak \( V_{O_2} \)) and oxygen pulse (\( O_2 \)-pulse) were calculated as described by Wassermann et al.\(^{15} \)

**Autopsy**

We searched the pathology archives for autopsy reports including description of the hearts of deceased patients with XMPMA. We were given the names by relatives who had known these deceased patients. Only 1 patient with this skeletal myopathy (which was unknown in 1980) was found to have been autopsied with an examination of the heart.

**Statistical Analysis**

Descriptive statistics were used to characterize the study population. For continuous variables mean and standard deviation or median, minimum and maximum were displayed, and for categorical variables, the number of observations and relative frequencies, respectively. The analyses focused on estimating putative associations between the carriers of the FHL1 gene and outcomes regarding echocardiographic findings (and strain data). To account for clustering of observations within families, GEE models were used. An exchangeable working correlation matrix was assumed to account for correlation within families and a robust variance estimator was used. For each continuous outcome, the normality assumption was assessed. Outcomes for which the empirical distribution showed substantial positive skewness were log transformed before analysis. Echocardiographic findings (and strain data) were adjusted for hypertension for men and hypertension and age for women. Binary variables with small number of observations were compared using Fisher exact test. All analyses were done using Stata 9 (StatCorp)

**Results**

**Mutation Analysis of FHL1**

We found 4 different mutations in the FHL1 gene in our study population. As in our previous analyses\(^7\) the most frequent mutation was C224W, which we identified in 12 males (hemizygous) and in 19 females (heterozygous). The C224W mutation was found in the large Austrian kindred and 4 out of the 7 German families. The mutations H246Y, V280M, and A168GfsX195 were each present in 1 family (H246Y in an affected male and his carrier mother; V280M and A168GfsX195 each in 2 affected males and their carrier mothers). Altogether we identified 17 hemizygous male and 4 out of the 7 German families. The mutations H246Y, V280M, and A168GfsX195 were each present in 1 family (H246Y in an affected male and his carrier mother; V280M and A168GfsX195 each in 2 affected males and their carrier mothers). Altogether we identified 17 hemizygous male and 23 heterozygous female mutation carriers. All 3 isoforms of FHL1 and the corresponding protein domain structures are shown in Figure 2A. The positions of mutations affecting isoform FHL1A, as reported in Chen et al.\(^{16} \) are shown in Figure 2B.

**Clinical Analysis**

Phenotypic analysis of all affected males (n=17) indicated the presence of typical neurological and musculoskeletal deficits associated with XMPMA. All 23 female carriers were clinically asymptomatic, but on closer examination 3 female C224W mutation carriers showed mild neurological symptoms (increased finger-ground distance when bending forward, mild contractures, and rigid spine similar to the affected males).

Clinical symptoms potentially indicative of cardiac involvement are listed in Table 1. The major cardiac symptom at presentation was dyspnea, as classified according to the New York Heart Association (NYHA) functional classification. The 7 most severely affected males with C224W mutation presented with palpitations. There was no evidence of CAD in affected males; however, 3 with C224W mutation had a history of hypertension (mean age 55 years; range, 49–64; SD, 7.9; median, 52) and hyperlipidemia. The prevalence of hypertension was higher in heterozygous females (n=9, mean age 68.8 years, range 42–78, SD=11.5, median 73), including 1 smoker and 2 obese females. There were no smokers among the affected males. Additionally, 2 female carriers presented with a history of CAD and stroke.

**Laboratory Analyses**

Analyses of serum chemistry indicated cardiac involvement: creatine kinase (CK) and MB fraction of CK (CK-MB), were increased, and cardiac troponin T (cTnT) was elevated by a factor of 16 in all 17 phenotypically affected males (Table 1). NT-proBNP was also significantly increased. Seven female mutation carriers had only slightly elevated NT-proBNP values, whereas other cardiac and noncardiac tests were within normal limits.

**Electrocardiography**

Twelve-lead electrocardiograms showed negative T-waves in 71% and Q-waves in 53% of affected males (Figure 3). The prevalence of ECG abnormalities was significantly higher in male mutation carriers than in controls (\( P<0.001 \)). Interestingly, 44% of the heterozygous female mutation carriers also exhibited negative T-waves and 17% showed Q waves, whereas no relevant ECG changes were observed in the female control group. Q-waves were present mainly in the legs II, III, aVL, aVF, and the precordial leads V5 and V6. The negative T-wave voltage in both females and males was similar (0[0–4] versus 0[0–4] mm). Only 2 affected males with C224W mutation met ECG criteria for LV hypertrophy by the Romhilt-Estes score, and none by the Sokolow-Lyon index. One heterozygous female carrier with C224W mutation had a positive Romhilt-Estes score and another with the same mutation had a positive Sokolow-Lyon index. A summary of the analysis of the ECG data is shown in Table 2. ECG Holter monitoring demonstrated sinus rhythm in all affected males, a short episode of asymptomatic nonsustained ventricular tachycardia in 2 of the affected males, and a high incidence of premature ventricular beats (13 [3–8142]/24 h) compared with male controls (4 [0–33]/24 h) \( P=0.007 \). Women with a FHL1 mutation also showed a significantly higher number of PVBs than healthy controls (12 [0–850] versus 0 [0–30]/24 h \( P=0.004 \)). Further, both men and women had pathologically prolonged QT and QTc intervals compared with healthy controls.

**Echocardiography**

**Global and Regional Ventricular Function**

All 85 study subjects had normal global LV EF: mean EF was 68.7, 68.3, 71.0, and 67.8% in male mutation carriers, male controls, female mutation carriers, and female controls, respectively. However, SR imaging revealed substantial regional LV function abnormalities (Figure 4 and Table 3; a detailed analysis of longitudinal and radial strain is given in online-only Data Supplement Tables I and II).
LV radial SR as a parameter for the velocity of systolic thickening of the inferolateral wall was lower in affected males than healthy male controls (1.37±0.56 versus 1.94±0.92 s⁻¹, respectively \(P=0.002\)). Figure 4 shows the pathological strain and SR areas matched to those myocardial segments displaying LE as a potential marker of myocardial fibrosis. Consistently, regional radial strain (\(\varepsilon\)) as a parameter for the total amount of systolic thickening of the inferolateral wall was significantly reduced in affected male patients compared with healthy male controls (24.63±11.78% versus 43.22±14.87%; \(P<0.001\)). Female mutation carriers did not show significant changes in radial strain and SR.

LV longitudinal SR as a marker for the velocity of systolic shortening of a segment was significantly reduced in the septal (−0.70±0.35 versus −1.09±0.36 s⁻¹; \(P=0.009\)), lateral (−0.84±0.49 versus −1.38±0.65 s⁻¹; \(P=0.004\)), anterior...
Figure 3. Typical ECG tracing in FHL1 cardiomyopathy. **Left:** ECG from a 24-year-old affected man showing pathological Q-waves in the inferior leads. **Right:** ECG tracing from a 54-year-old affected man showing pathological T-waves in the anterior leads V4-V6.

(−0.74±0.40 versus −1.10±0.44 s⁻¹; \(P=0.003\)), and inferior wall (−0.85±0.25 versus −1.39±0.52, \(P=0.001\)) in affected males when compared with healthy male controls. In addition, LV longitudinal ε as a parameter for the total amount of systolic shortening was significantly reduced in the septal (12.44±5.79% versus 19.57±3.96%; \(P<0.001\)), lateral (12.26±4.84% versus 18.89±5.22%, \(P<0.001\)), anterior (12.68±5.80% versus 20.31±5.38%; \(P<0.001\)), and inferior wall (14.41±4.03 versus 25.34±9.67, \(P≤0.001\)) when compared with healthy male controls. Left ventricle longitudinal strain and SR analysis did not reveal any significant changes in female mutation carriers.

**Diastolic Function**

Evidence of diastolic dysfunction was a common finding in male and female mutation carriers. Tissue Doppler derived E/é was significantly elevated in male mutation carriers as compared with controls. In addition, classical parameters of diastolic dysfunction, such as E/A, é, and left atrial volume were abnormal in mutation carriers (Table 3). There was a tendency for LA volume to be increased in mutation carriers, but this did not reach statistical significance.

**Structural Remodeling**

Echocardiography demonstrated substantial LV hypertrophy (to be classified as mild, according to Spirito et al) and cardiac remodeling in comparison with control male family members (Table 3). Maximal end-diastolic wall thickness was significantly higher in affected males than in male controls (16.0±1.4 versus 10.4±0.9 mm; \(P<0.001\)). Overall estimated LV mass was significantly higher in affected than in control males (115.1±25.3 versus 89.0±15.6 g/m²; \(P=0.003\)). Morphologically, the left ventricle showed asymmetric hypertrophy, and in particular, the middle part of the septum and the apex were thickened, as was the papillary muscle (Figure 5A). In this area, the structure of the heart muscle appeared nonhomogeneous: patients showed spongious structures in the septal wall and in the apex (Figure 5A) and in the posterolateral wall.

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**Table 2. ECG and Holter ECG Findings**

<table>
<thead>
<tr>
<th></th>
<th>Male Hemizygous</th>
<th>Male Controls</th>
<th>(P) Value</th>
<th>Female Heterozygous</th>
<th>Female controls</th>
<th>(P) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate, bpm</td>
<td>69.4±17.4</td>
<td>67.1±10.2</td>
<td>0.011</td>
<td>72.1±15.5</td>
<td>74.2±11.0</td>
<td>0.189</td>
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<tr>
<td>Sinus rhythm</td>
<td>17 (100%)</td>
<td>22 (100%)</td>
<td>n.a.</td>
<td>19 (83%)</td>
<td>23 (100%)</td>
<td>0.909*</td>
</tr>
<tr>
<td>QRS duration, ms</td>
<td>98.4±11.9</td>
<td>95.9±14.1</td>
<td>0.959</td>
<td>94.6±16.0</td>
<td>90.1±10.8</td>
<td>0.371</td>
</tr>
<tr>
<td>QT interval, ms</td>
<td>400.1±32.4</td>
<td>385.8±28.9</td>
<td>0.022</td>
<td>404.9±33.8</td>
<td>381.1±28.4</td>
<td>0.061</td>
</tr>
<tr>
<td>QTc, ms</td>
<td>427.7±27.2</td>
<td>406.0±27.3</td>
<td>&lt;0.001</td>
<td>432.2±35.3</td>
<td>418.8±19.0</td>
<td>0.013</td>
</tr>
<tr>
<td>Any negative T-wave</td>
<td>12 (71%)</td>
<td>0 (0%)</td>
<td>&lt;0.001*</td>
<td>10 (44%)</td>
<td>6 (26%)</td>
<td>0.353*</td>
</tr>
<tr>
<td>No of negative T-waves</td>
<td>3 (10%)</td>
<td>0 (0, 0)</td>
<td>&lt;0.001</td>
<td>0 (0, 0)</td>
<td>0 (0, 2)</td>
<td>0.060</td>
</tr>
<tr>
<td>Maximal negative T-wave, mm</td>
<td>0 (0, 4)</td>
<td>0 (0, 0)</td>
<td>0.008</td>
<td>0 (0, 4)</td>
<td>0 (0, 2)</td>
<td>1.000</td>
</tr>
<tr>
<td>Any Q wave (s)</td>
<td>9 (53%)</td>
<td>0 (0%)</td>
<td>&lt;0.001*</td>
<td>4 (17%)</td>
<td>0 (0%)</td>
<td>0.470*</td>
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<tr>
<td>Ventricular tachycardia</td>
<td>2 (12%)</td>
<td>0 (0%)</td>
<td>0.184*</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>n.a.</td>
</tr>
<tr>
<td>Prior atrial fibrillation, any</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>n.a.</td>
<td>3 (15%)</td>
<td>0 (0%)</td>
<td>0.107*</td>
</tr>
<tr>
<td>PVB (24 h)</td>
<td>13 (8, 8142)</td>
<td>4 (0, 33)</td>
<td>0.007</td>
<td>12 (0, 850)</td>
<td>0 (0, 30)</td>
<td>0.004</td>
</tr>
<tr>
<td>Positive Sokolow criteria</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>n.a.</td>
<td>1 (4%)</td>
<td>0 (0%)</td>
<td>1.000*</td>
</tr>
<tr>
<td>Positive RE-criteria</td>
<td>2 (12%)</td>
<td>0 (0%)</td>
<td>0.184*</td>
<td>1 (4%)</td>
<td>0 (0%)</td>
<td>1.000*</td>
</tr>
</tbody>
</table>

QTc indicates corrected QT interval; PVB, premature ventricular beats; and RE, Romhilt-Estes.

Data are shown as unadjusted mean±standard deviation or median (min, max) for continuous variables and absolute and relative frequencies for categorical variables; For men, \(P\) values are corrected for blood pressure and family clustering; for women, \(P\) values are corrected for age, blood pressure and family clustering.

*Analyzed using Fisher exact test.
(Figure 5B). In the right ventricle 7 patients had pronounced trabecularization and 10 demonstrated RV hypertrophy. Unlike classical hypertrophic cardiomyopathy,18 our patient population generally showed asymmetrical hypertrophy of the septum, especially of the middle part and of the apex combined with the spongious appearance of myocardial structure. Notably, about half of heterozygous female mutation carriers demonstrated some degree of LV hypertrophy, but the majority depicted the classical concentric remodeling pattern (Table 3). Left ventricle remodeling was associated with increased atrial volume and size in affected males.

Only 1 female (77 years of age), heterozygous for C224W, did have borderline EF, severely elevated pulmonary artery pressure, and moderate tricuspid regurgitation. Seven additional subjects

![Figure 4. Comparison of the significantly pathological strain and strain rate areas with the late enhancement areas in the MRI of affected males. The different colors encode strain and strain rate values. Color encoding according to color bars at the bottom.](http://circgenetics.ahajournals.org/)

<p>| Table 3. Echocardiographic Findings Associated With Mutations in FHL1 Genes |
|---------------------------------------------------------------|----------|----------|----------|----------|----------|----------|</p>
<table>
<thead>
<tr>
<th>Male Hemizygous</th>
<th>Male Controls</th>
<th>Female Heterozygous</th>
<th>Female Controls</th>
<th>P Value</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Structural remodeling</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LV end-diastolic diameter, mm</td>
<td>45.3±4.0</td>
<td>48.6±5.0</td>
<td>0.034</td>
<td>42.9±4.8</td>
<td>45.5±4.4</td>
</tr>
<tr>
<td>Septal wall thickness, basal, mm</td>
<td>11.3±1.7</td>
<td>10.3±0.8</td>
<td>0.054</td>
<td>11.2±1.6</td>
<td>9.2±1.3</td>
</tr>
<tr>
<td>Septal wall thickness, mid, mm</td>
<td>14.8±1.7</td>
<td>10.3±0.8</td>
<td>&lt;0.001</td>
<td>11.7±1.8</td>
<td>9.3±1.6</td>
</tr>
<tr>
<td>Posterior wall thickness, mm</td>
<td>10.1±1.7</td>
<td>10.0±0.8</td>
<td>0.797</td>
<td>10.6±2.1</td>
<td>7.8±0.7</td>
</tr>
<tr>
<td>Max. apical wall thickness, mm</td>
<td>15.6±1.5</td>
<td>10.3±0.8</td>
<td>&lt;0.001</td>
<td>11.8±2.0</td>
<td>9.3±1.6</td>
</tr>
<tr>
<td>Max wall thickness, mm</td>
<td>16.0±1.4</td>
<td>10.4±0.9</td>
<td>&lt;0.001</td>
<td>11.8±2.0</td>
<td>9.4±1.5</td>
</tr>
<tr>
<td>Concentric hypertrophy</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>n.a.</td>
<td>10 (44%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Asymmetric hypertrophy</td>
<td>17 (100%)</td>
<td>0 (0%)</td>
<td>&lt;0.001*</td>
<td>4 (17%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>LV mass index, g/m²</td>
<td>115.1±25.3</td>
<td>89.0±15.6</td>
<td>0.003</td>
<td>95.1±19.6</td>
<td>72.6±12.6</td>
</tr>
</tbody>
</table>

Functional remodeling

| Ejection fraction, % | 68.7±6.8 | 68.3±4.7 | 0.867 | 71.0±8.6 | 67.8±4.1 | 0.009 |
| LA volume index, mL/m² | 32.6±13.6 | 24.4±5.7 | 0.156 | 35.7±14.6 | 26.8±4.0 | 0.125 |
| e′, m/s | 0.07±0.02 | 0.09±0.03 | <0.001 | 0.08±0.02 | 0.10±0.03 | 0.025 |
| E/e′ | 10.1±1.9 | 8.9±2.3 | 0.002 | 9.8±3.3 | 9.1±3.3 | 0.241 |
| Any diastolic dysfunction | 11 (65%) | 1 (5%) | 0.006* | 16 (69%) | 4 (17%) | 0.010* |
| Elevated PASP >30 mm Hg | 3 (18%) | 0 (0%) | 0.074* | 5 (22%) | 0 (0%) | 0.049* |
| Significant valvular heart disease | 0 (0%) | 0 (0%) | n.a. | 2 (9%) | 0 (0%) | 0.489* |
| Pericardial effusion | 4 (18%) | 0 (0%) | 0.029* | 1 (4%) | 0 (0%) | 0.1000* |
| Sinus of valsalva aneurysm | 2 (12%) | 0 (0%) | 0.184* | 0 (0%) | 0 (0%) | n.a. |

LV indicates left ventricular; LA, left atrial; and PASP, pulmonary artery systolic pressure.

Data are shown as unadjusted mean±standard deviation for continuous variables and absolute and relative frequencies for categorical variables.

For men, P values are corrected for blood pressure and family clustering; for women, P values are corrected for age, blood pressure, and family clustering.

*Analyzed using Fisher exact test.
(3 affected males, 4 female carriers) with the C224W mutation had slightly elevated pulmonary artery pressure (ages of males 50, 52, and 42 years; ages of females, 73, 76, 73 and 78 years).

The 2 males (aged 19 and 29 years) with the A168GfsX195 mutation both exhibited an aneurysm of the sinus of Valsalva; 1 of them had had surgical repair at age 27 (as previously reported).2

Pericardial Effusion

Analysis of 5 subjects with the C224W mutation revealed small pericardial effusions of unknown origin (4 affected males, 1 female carrier; ages of males, 50, 64 and 42 years; age of the female, 23 years).

Cardiac MRI
cMRI was obtained from 16 affected males and confirmed extended findings from echocardiography: Although global systolic function, as assessed by EF, was normal in affected males and females (68.7±6.8% and 71.0±8.6%, respectively), a novel type of cardiomyopathy was observed in affected males. The novel cardiomyopathy was characterized by 3 main findings that included (1) asymmetrical midventricular/apical hypertrophy (Figures 6B and 7C); (2) LE as a marker of fibrosis (Figure 6A and 3) a nonhomogeneous, spongiforme myocardial structure demarcated by hypointense intramural areas (Figure 7A–C) resembling the spongious structure on echocardiography (as shown in Figure 5A and 5B).

All affected male patients showed asymmetric LV hypertrophy; the majority of them (11 out of 16) had midventricular accentuated LV hypertrophy as well as apical hypertrophy; in most patients (11 out of 16) the right ventricle also showed some degree of hypertrophy. Seven out of 16 male patients showed a nonhomogeneous, spongiforme myocardial structure, especially in the midventricular and apical wall segments (Figure 7A–7C). Hypointense intramural areas were round, with a size of 1 to 2 mm, or elongated, with a size of up to 6 mm. These patients had no pronounced trabecularization; the morphological pattern is thus not compatible with noncompaction.

cMRIs were also performed in 20 heterozygous female mutation carriers: 4 out of 14 nonhypertensive women demonstrated mild morphological abnormalities with accentuated trabecularization of the right ventricle (1 out of 14) and LV (1 out of 14), focal midventricular hypertrophy (1 out of 14), and minor pericardial effusion (1 out of 14).

Spiroergometry

All 82 subjects underwent symptom-limited exercise testing. Affected males were characterized by an impaired exercise capacity as indicated by a significantly lower maximal workload (watts); affected males = 130.0±39.2; male controls = 181.6±44.5; P=0.031; 95% CI −39.4 (−75.3 to −3.5). Maximum oxygen uptake (VO₂max) was reduced in affected males compared with controls: 22.17±8.04 mL/(min*kg) versus 27.28±5.77 mL/(min*kg), P=0.011. After adjusting for hypertension, differences in VO₂ max were no longer statistically significant. Exercise capacity in heterozygous female carriers was not impaired compared with healthy controls.

Autopsy

Postmortem examination of 1 heart (male, age 48 years; death, 1980) was reported to show marked cardiac hypertrophy; heart weight was 480 g, trabeculae and papillary muscle of the left ventricle were mildly hypertrophic (18 mm), and the right ventricle was also hypertrophic (7 mm). The coronary vessels were sclerotic, the lumen sometimes narrowed. The heart muscle was rather dry and coarsely fibrous; in the ventricular septum there was a necrosis the size of a small lentil undergoing transformation to scar tissue. No further necrosis or callosities were reported. Endocardium, tendon cords, and valves were delicate. The autopsy findings are consistent with cardiomyopathy. Although mutation analyses were never performed for this proband, we could refer this phenotype to the familial C224W mutation.

Discussion

We describe here a new type of hypertrophic cardiomyopathy presenting in patients with mutations in the C-terminal FHL1 protein associated with the skeletal myopathy, XMPMA. The main findings of this novel cardiomyopathy are (1) midventricular and apical hypertrophy, intramural fibrosis and spongious structures; (2) abnormal diastolic function and regional
systolic function, especially in the hypertrophic segments; (3) common ECG abnormalities with pathological Q-waves and negative anterior T-waves; and (4) reduced exercise capacity.

To date, there have been 9 publications reporting a total of 27 different FHL1 mutations, associated with clinical findings including XMPMA, rigid spine syndrome, scapuloperoneal myopathy, reducing body myopathy, and Emery-Dreifuss muscular dystrophy.19 Although hypertrophic cardiomyopathy and rhythm abnormalities were mentioned in these studies, a detailed evaluation of the cardiac phenotype is not available. Also, the majority of earlier reports focus on mutations that occur within the first 3 LIM domains, putatively impacting all 3 FHL1 isoforms (A, B, & C), we report here on the cardiac involvement of mutations that occur in the C-terminal region of FHL1, and thus the FHL1 isoform C would still be preserved, whereas only isoforms A (except for V280M) and B would be affected. In a transgenic mouse model for FHL1 with mutations in LIM domain 2 (affecting isoforms FHL1 A, B, and C), it was found that there was no change in slow-twitch (soleus plantaris) and fast-twitch (extensor digitorum longus) enriched skeletal muscle contractility,5 but the heart was not examined in this study. We observe here in patients with mutations in LIM domain 4 (affecting only FHL1 A and B) a cardiomyopathy with midventricular and apical hypertrophy, fibrosis, spongious structure, and impaired diastolic and systolic function, possibly linked to the decrease in level of expression and functioning of FHL1 A and FHL1 B molecules.

LV Morphology

Previous studies have touched on the relationship between FHL1 and cardiomyopathy.1,2,20,21 Knoblauch et al21 described LV hypertrophy, cardiac fibrosis and hypertension in affected male patients, and Gueneau et al20 reported hypertrophic cardiomyopathy with conduction defects and arrhythmias in all index cases. Based on our previous report,2 the number of families and cases was increased, and the cardiac phenotype, as well as its functional consequences, was thoroughly and systematically evaluated. Schoser et al2 investigated 10 affected men, 2 mildly affected women, and 6 mothers of the index patients from 7 families of Germany, Austria, and Croatia. None of the affected males had overt clinical cardiac rhythm disturbance or cardiomyopathy. In 2 men, a rare aneurysm of the sinus of Valsalva was found and treated by surgery. Three male patients suffered from exercise-induced fatigue and respiratory insufficiency; 1 of them died from respiratory failure at 47 years of age. In 1 affected female carrier, cardiac rhythm alterations were found late in life. To our knowledge, our report is the first to comprehensively describe the cardiac phenotype of patients with FHL1 mutation at the morphological and functional levels.

All phenotypically affected males (ie, for all 4 of the FHL1 mutations identified) showed asymmetric septal hypertrophy, with the thickest parts in the middle of the septum and in the apex. The extent of hypertrophy of the left ventricle was similar for all known mutations in the C-terminus of FHL1 described so far.

Seventeen percent of the heterozygous females also demonstrated asymmetrical septum hypertrophy, albeit less pronounced than their male counterparts, indicating that female mutation carriers can also display mild structural abnormalities caused by the genetic defect in FHL1. XMPMA is clearly an X-linked recessive disorder and the presence of a cardiac phenotype in some female carriers is consistent with this
mode of inheritance. Hence, a definition of dominant inheritance with reduced penetrance or expressivity is in our opinion not appropriate.

Another typical morphological finding in affected males was LE in the left ventricle, as a marker for myocardial fibrosis.\textsuperscript{22,23} The underlying mechanism for this mainly intramural pattern of LE is unknown. A pathology related to classic obstructions of the large coronary arteries is unlikely as CAD was excluded in our patients and ischemic necrosis usually starts in the subendocardium. However, as in other hypertrophic cardiomyopathies, a small vessel disease leading to focal chronic ischemia might be the reason for this localized fibrosis. This may also explain the fibrous regions observed in the autopsy report from 1980. The observed intramural pattern of LE resembles that of nonischemic cardiomyopathies.\textsuperscript{23–25} Moreover, this typical pattern of LE does not correspond to a specific coronary territory.

The hallmark of this newly identified hypertrophic cardiomyopathy is a spongious appearance of the LV myocardium that was seen in nearly half of the affected males in all wall segments, including the apex. This morphological pattern is not compatible with noncompaction, because none of our patients had a NC/C ratio (noncompacted to compacted myocardium) of >2 or 2.3 in diastole as described in Petersen et al.\textsuperscript{26} Additionally, the cardiac phenotype does not meet the classic criteria for hereditary HCM in its most various forms, but rather shows a divergent form of HCM with midventricular accentuation of the hypertrophy including spongious structure.

**Left Ventricular Function**

Global LV function was normal, but regional LV function was impaired in all affected males compared with the control group. The most severely affected segments were the inferolateral, septal, and anterior walls. These segments with functional abnormalities also showed, in general, the most prominent morphological changes. Hence, our data suggest that morphological changes coincide with, and may partly underlie, functional abnormalities. For screening of families, regional functional abnormalities are important because only
by this assessment can subtle systolic dysfunction be identified. When focusing on regional myocardial function, it was evident that both systolic SR, which is related to regional contractility, and systolic strain, which is influenced by regional stroke volume, are reduced. In addition, these 2 functional abnormalities could be detected in the longitudinal and radial direction, suggesting a cardiomyopathy with complex myocardial dysfunction.

It can be assumed that these pathologies cause myocardial injury not by classic large vessel ischemia, but perhaps by a small vessel disease that increases cTnT concentrations in the circulation. The 16-fold increase in the cTnT value observed in all affected males is remarkable, and might be considered a crucial marker for the diagnosis of XMPMA cardiomyopathy. Such high levels have never been reported in other dystrophic myopathies. The origin of the highly elevated cTnT may be predominantly of cardiac origin; however, it cannot be ruled out that, to some extent, it may also come from degenerating skeletal muscle. There are some reports on the specificity of cTnT as expression of mRNA of the cardiac isoforms of troponin T and I in myopathic skeletal muscle was found.\(^27,28\) In fact, the second-generation cTnT assay showed increased cTnT values in 50% of Duchenne’s muscular dystrophy patients without clinical evidence of cardiac involvement.\(^29\)

Sixty-five percent of the hemizygous males and 69% of the heterozygous female mutation carriers showed impaired diastolic function, which may explain the dysnea observed in the affected patients. This may be related to LV hypertrophy and interstitial fibrosis as detected by MRI imaging. \(^{FHL1}\) mutations may also play a role in vascular remodeling underlying the development of pulmonary hypertension. In fact, proteomic analyses showed that \(^{FHL1}\) was upregulated in lung tissues of animal models as well as in samples from patients with idiopathic pulmonary hypertension.\(^30\) Our patient collective included a female individual with C224W mutation and primary severely increased pulmonary hypertension concomitant with right ventricular hypertrophy. Seven additional subjects with the C224W mutation had slightly elevated pulmonary artery pressure. In consequence, future work needs to address in more detail this potential relationship.

Electrocardiographical Assessment
In this study, all males affected with \(^{FHL1}\) cardiomyopathy had abnormal electrocardiograms. More than 70% of the patients demonstrated inferior and posterolateral T-wave inversions; Q-waves occurred in more than 50% of patients. Holter ECG recording demonstrated a high incidence of ventricular premature complexes and nonsustained ventricular tachycardia (cycle length 300–320 ms) in 2 affected males with the C224W and the V280M mutations. A 23-year-old male patient with C224W mutation showed paroxysmal atrial tachycardias and atrial flutter. In addition, this subject experienced bradycardic episodes with second degree sinusatrial and atrioventricular block causing pauses up to 3 seconds.

Clinical Impact of XMPMA-Associated Cardiomyopathy
Patients with XMPMA should undergo cardiac phenotyping and risk assessment with laboratory testing, ECG, echocardiography, and cardiac MRI. The echocardiographic measurements of global LV function (ie, EF) and end-diastolic wall thickness are routine techniques to assess cardiac involvement, but cardiac impairment can be detected at earlier stages using advanced echocardiographic techniques, such as SR imaging. In our current study, regional deformation was measured, allowing description of regional heterogeneity of LV function. Using this technical approach the functional abnormalities could be matched to those myocardial segments displaying LE as a marker of myocardial fibrosis.

A further important point is the ECG, which was abnormal in most patients with XMPMA and \(^{FHL1}\) cardiomyopathy. On the resting 12-lead ECG, only 2 patients demonstrated criteria for LV hypertrophy, but nearly all patients showed abnormal Q-waves and symmetrical T-wave inversions.

The observations from this study provide insight into the phenotypic and pathological expression of \(^{FHL1}\) cardiomyopathy. Our data show that cardiological screening is an important tool for detecting signs of the disease early in the clinical course of XMPMA. The cardiological results for female carriers suggest that mild mutations in \(^{FHL1}\) might also occur in isolated forms of HCM and therefore screening for mutations in \(^{FHL1}\) of genetically undiagnosed HCM is indicated in cases with similar clinical presentation of the heart. Family screening, including cardiological check-up, should be initiated as soon as an index patient is positively tested for a mutation in \(^{FHL1}\). It remains to be determined whether the cardiac phenotype develops as the first clinical sign of XMPMA males (as it appears in women). If this finding can be confirmed, cardiac examination would be the best option for early recognition of clinical manifestations of (heterozygous) \(^{FHL1}\) mutations.

Treatment and Clinical Management of XMPMA-Associated Cardiomyopathy
The presence of diastolic dysfunction and fibrosis provides a possible target for therapeutic strategies of \(^{FHL1}\) cardiomyopathies. Treatments of symptomatic \(^{FHL1}\) cardiomyopathy may involve the use of antagonists of the renin-angiotensin-aldosterone system, as there is evidence that tissue-level angiotensin can modulate both myocardial relaxation and fibrosis.\(^31,32\) ACE inhibitors or AT1 antagonists were of benefit in animal models of hypertrophic cardiomyopathy.\(^31,35\) but caution is warranted because human data are not available.

Limitations
As heart muscle biopsies could not be taken from the patients for ethical reasons, immune histochemistry and the underlying histological morphology could not be studied. One patient with \(^{FHL1}\) mutation underwent RV biopsy for clinical reasons, but perforation occurred as a complication. Biopsy in patients with XMPMA-associated cardiomyopathy so may
bear a specific risk for perforation due to the spongy nature of the myocardium.

**Conclusions**

XMPMA caused by four-and-a-half LIM domain protein 1 (FHL1) is associated with a newly described spongy hypertrophic cardiomyopathy with distinct morphological, functional, and electric abnormalities. In affected males, systolic and diastolic dysfunction, midventricular and apical LV hypertrophy, myocardial fibrosis and spongy structure of the myocardium could be observed. Using regional SR imaging, functional abnormalities could be detected at an early stage of the disease. Although a cardiac phenotype is detectable in some female carriers of the FHL1 mutations reported here, the skeletal muscle phenotype of XMPMA is only present in males. Thus XMPMA should still be considered an X-linked recessive disorder rather than a dominant disorder with reduced penetrance and expressivity. These relatively mild symptoms can be explained by random X-linked inactivation. Cardiac phenotyping in XMPMA patients and family members should be performed for better risk stratification and initiation of preventive therapies.

**Acknowledgments**

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**Disclosures**

None.

**References**

7. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, et al. Chamber Quantification Writing Group; American Society of Echocardiography’s Guidelines and Standards Committee; European Association of Echocardiography. Recommendations for chamber quantification: a report from the American Society of Echocardiography’s Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. *J Am Soc Echocardiogr*. 2005;18:1440–1463.
CLINICAL PERSPECTIVE

Male patients with X-linked myopathy caused by mutations in the C terminus of the FHL1 gene show hypertrophic cardiomyopathy with midventricular and apical hypertrophy, replacement fibrosis, and spongious structure. This unique form of hypertrophic cardiomyopathy is reflected in electrical and functional abnormalities that can be identified at an early stage of disease with strain and strain rate imaging. An unexpected finding was that some cardiac abnormalities were also present in heterozygous female mutation carriers. We propose that all mutation carriers should undergo cardiological screening as early as possible, as the cardiological phenotype becomes apparent before neurological signs of disease can be diagnosed. Systematic cardiac phenotyping of patients and family members with mutations in FHL1 may allow better risk stratification and earlier initiation of management strategies.
Spongy Hypertrophic Cardiomyopathy in Patients With Mutations in the Four-and-a-Half LIM Domain 1 Gene


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## SUPPLEMENTAL MATERIAL

### Supplemental table 1:
Longitudinal and radial strain rate and strain data in hemizygous males and wild-type male controls

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<th></th>
<th>1. Males</th>
<th>2. Males</th>
<th>Estimated difference</th>
<th>P-value</th>
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<td>hemizygous</td>
<td>controls</td>
<td>95% CI</td>
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<tr>
<td>rad SRI 1.syst.peak 1/s</td>
<td>1.37 ± 0.56</td>
<td>1.94 ± 0.92</td>
<td>-0.52 (-0.86; -0.19)</td>
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<tr>
<td>rad SI_max_syst %</td>
<td>24.63 ± 11.78</td>
<td>43.22 ± 14.87</td>
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<td>long.SRI_inf sep basal 1.syst.Peak 1/s</td>
<td>-0.99 ± 0.36</td>
<td>-1.04 ± 0.28</td>
<td>0.07 (-0.27; 0.41)</td>
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<tr>
<td>long.SI sept basal max syst.%</td>
<td>16.66 ± 4.68</td>
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<tr>
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<td>12.44 ± 5.79</td>
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<td>-5.94 (-9.16; -2.71)</td>
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<td>-1.23 ± 0.38</td>
<td>-1.29 ± 0.47</td>
<td>0.09 (-0.13; 0.32)</td>
<td>.420</td>
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<tr>
<td>long.SI sept_apic_ max syst.%</td>
<td>20.80 ± 6.67</td>
<td>23.07 ± 6.17</td>
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<td>long.SRI_lat_basal 1.syst.Peak 1/s</td>
<td>-1.12 ± 0.28</td>
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<td>0.13 (-0.17; 0.42)</td>
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<td>Apical</td>
<td>Basal-Mid</td>
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<tr>
<td>---------------------------------------------</td>
<td>-------------</td>
<td>-------------</td>
<td>-------------</td>
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<tr>
<td>long.SI lat_basal max syst.%</td>
<td>16.82 ± 6.41</td>
<td>19.73 ± 7.32</td>
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<td>0.10 (-0.22; 0.42)</td>
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<td>18.89 ± 5.22</td>
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<td>-0.84 ± 0.49</td>
<td>-1.38 ± 0.65</td>
<td>0.45 (0.14; 0.76)</td>
<td>.004</td>
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<tr>
<td>long.SI lat_apic_ max syst.%</td>
<td>10.08 ± 4.71</td>
<td>17.07 ± 5.44</td>
<td>-5.44 (-7.64; -3.23)</td>
<td>&lt;.001</td>
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<tr>
<td>long.SRI_anterior_basal 1.syst.Peak 1/s</td>
<td>-1.27 ± 0.55</td>
<td>-1.46 ± 0.43</td>
<td>0.21 (0.02; 0.40)</td>
<td>.030</td>
</tr>
<tr>
<td>long.SI ant_basal max syst.%</td>
<td>17.19 ± 6.02</td>
<td>24.02 ± 7.96</td>
<td>-7.27 (-12.10; -2.43)</td>
<td>.003</td>
</tr>
<tr>
<td>long.SRI_anterior_mid 1.syst.Peak 1/s</td>
<td>-0.74 ± 0.40</td>
<td>-1.10 ± 0.44</td>
<td>0.35 (0.12; 0.58)</td>
<td>.003</td>
</tr>
<tr>
<td>long.SI ant_mid_ max syst.%</td>
<td>12.68 ± 5.80</td>
<td>20.31 ± 5.38</td>
<td>-7.89 (-10.20; -5.57)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>long.SRI_anterior_apical_ 1.syst.Peak 1/s</td>
<td>-0.89 ± 0.53</td>
<td>-1.25 ± 0.50</td>
<td>0.41 (0.14; 0.68)</td>
<td>.003</td>
</tr>
<tr>
<td>long.SI ant_apical_ max syst.%</td>
<td>13.09 ± 6.06</td>
<td>18.93 ± 4.71</td>
<td>-5.66 (-8.42; -2.89)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>long.SRI_inf_basal_ 1.syst.Peak 1/s</td>
<td>-1.26 ± 0.42</td>
<td>-1.53 ± 0.37</td>
<td>0.28 (0.03; 0.53)</td>
<td>.030</td>
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<tr>
<td>long.SI inf_basal max syst.%</td>
<td>21.63 ± 5.84</td>
<td>26.75 ± 10.08</td>
<td>-5.06 (-11.21; 1.09)</td>
<td>.107</td>
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<tr>
<td>long.SRI_inf_mid 1.syst.Peak 1/s</td>
<td>-0.85 ± 0.25</td>
<td>-1.39 ± 0.52</td>
<td>0.55 (0.25; 0.85)</td>
<td>.001</td>
</tr>
<tr>
<td>long.SI inf_mid_ max syst.%</td>
<td>14.41 ± 4.03</td>
<td>25.34 ± 9.67</td>
<td>-11.18 (-13.92; -8.44)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>long.SRI_inferior_apical_ 1.syst.Peak 1/s</td>
<td>-1.70 ± 0.53</td>
<td>-1.89 ± 0.35</td>
<td>0.16 (-0.17; 0.50)</td>
<td>.337</td>
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<tr>
<td>Parameter</td>
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<td>Mean ± SD</td>
<td>Estimated Difference</td>
<td>p-value</td>
</tr>
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<td>----------------------</td>
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</tr>
<tr>
<td>long.SI inf_apical_max syst.%</td>
<td>24.63 ± 6.68</td>
<td>32.16 ± 5.63</td>
<td>-7.26 (-11.17; -3.36)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>long.SRI_anterior_septum_basal 1.syst.Peak 1/s</td>
<td>-0.81 ± 0.32</td>
<td>-1.27 ± 0.71</td>
<td>0.50 (0.08; 0.91)</td>
<td>.021</td>
</tr>
<tr>
<td>long.SI ant_septum_basal max syst.%</td>
<td>11.53 ± 3.12</td>
<td>21.97 ± 6.89</td>
<td>-10.32 (-13.19; -7.45)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>long.SRI_anterior_septum_mid 1.syst.Peak 1/s</td>
<td>-1.27 ± 0.38</td>
<td>-1.12 ± 0.25</td>
<td>-0.11 (-0.34; 0.13)</td>
<td>.361</td>
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<tr>
<td>long.SI ant_septum_mid_ max syst.%</td>
<td>18.66 ± 7.70</td>
<td>22.00 ± 3.88</td>
<td>-3.84 (-7.64; -0.04)</td>
<td>.048</td>
</tr>
<tr>
<td>long.SRI_anterior_septum_apical_1.syst.Peak 1/s</td>
<td>-1.14 ± 0.44</td>
<td>-1.12 ± 0.41</td>
<td>-0.08 (-0.44; 0.29)</td>
<td>.684</td>
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<tr>
<td>long.SI ant_septum_apical_ max syst.%</td>
<td>16.24 ± 5.90</td>
<td>20.57 ± 5.10</td>
<td>-4.08 (-8.41; 0.25)</td>
<td>.065</td>
</tr>
<tr>
<td>long.SRI_posterior_basal_1.syst.Peak 1/s</td>
<td>-1.37 ± 0.44</td>
<td>-1.53 ± 0.48</td>
<td>0.16 (-0.10; 0.41)</td>
<td>.226</td>
</tr>
<tr>
<td>long.SI posterior_basal_ max syst.%</td>
<td>17.14 ± 6.26</td>
<td>24.09 ± 6.12</td>
<td>-7.49 (-11.88; -3.10)</td>
<td>.001</td>
</tr>
<tr>
<td>long.SRI_posterior_mid_1.syst.Peak 1/s</td>
<td>-0.89 ± 0.55</td>
<td>-1.36 ± 0.49</td>
<td>0.47 (0.11; 0.82)</td>
<td>.010</td>
</tr>
<tr>
<td>long.SI posterior_mid_ max syst.%</td>
<td>12.81 ± 5.74</td>
<td>25.66 ± 11.67</td>
<td>-11.87 (-16.91; -6.84)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>long.SRI_posterior_apical_1.syst.Peak 1/s</td>
<td>-1.02 ± 0.34</td>
<td>-1.46 ± 0.47</td>
<td>0.42 (0.16; 0.67)</td>
<td>.001</td>
</tr>
<tr>
<td>long.SI posterior_apical_ max syst.%</td>
<td>15.16 ± 4.82</td>
<td>24.73 ± 6.59</td>
<td>-8.90 (-12.09; -5.70)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Long, longitudinal; SRI, strain rate s\(^{-1}\); SI, strain %; 1.syst.peak, first strain rate peak; inf sept, inferoseptal; lat, lateral, lat_apic, lateral apical; apic, apical; ant, anterior; inf, inferior; post, posterior; ant_septum, anteroseptal;

Data are shown as unadjusted mean ± standard deviation; Estimated differences, 95% CIs and p-values were calculated with GEE models, adjusting for blood pressure and family clustering.
### Supplemental table 2:
Longitudinal and radial strain rate and strain data in heterozygous females and wild-type female controls

<table>
<thead>
<tr>
<th></th>
<th>3. Females heterozygous</th>
<th>4. Females controls</th>
<th>Estimated difference</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>rad SRI 1.syst.peak 1/s</td>
<td>1.70 ± 0.76</td>
<td>1.94 ± 0.62</td>
<td>-0.11 (-0.06; 0.28)</td>
<td>.212</td>
<td></td>
</tr>
<tr>
<td>rad SI_max_syst %</td>
<td>35.89 ± 12.33</td>
<td>46.42 ± 13.71</td>
<td>-3.42 (-8.92; 2.08)</td>
<td>.222</td>
<td></td>
</tr>
<tr>
<td>long.SRI_inf sep_basal 1.syst.Peak 1/s</td>
<td>-1.07 ± 0.22</td>
<td>-1.22 ± 0.42</td>
<td>0.11 (-0.01; 0.23)</td>
<td>.083</td>
<td></td>
</tr>
<tr>
<td>long.SI sept_basal max syst.%</td>
<td>19.84 ± 4.97</td>
<td>20.42 ± 6.87</td>
<td>0.36 (-1.53; 2.24)</td>
<td>.709</td>
<td></td>
</tr>
<tr>
<td>long.SRI_sep_mid_ 1.syst.Peak 1/s</td>
<td>-0.97 ± 0.56</td>
<td>-1.07 ± 0.33</td>
<td>-0.003 (-0.35; 0.34)</td>
<td>.986</td>
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</tr>
<tr>
<td>long.SI sept_mid_ max syst.%</td>
<td>19.06 ± 4.61</td>
<td>18.04 ± 5.65</td>
<td>2.17 (-1.05; 5.40)</td>
<td>.186</td>
<td></td>
</tr>
<tr>
<td>long.SRI_sept_apic_ 1.syst.Peak 1/s</td>
<td>-1.24 ± 0.32</td>
<td>-1.25 ± 0.38</td>
<td>-0.09 (-0.33; 0.15)</td>
<td>.475</td>
<td></td>
</tr>
<tr>
<td>long.SI sept_apic_ max syst.%</td>
<td>23.81 ± 6.57</td>
<td>22.49 ± 5.49</td>
<td>3.11 (-1.33; 7.55)</td>
<td>.170</td>
<td></td>
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<tr>
<td>long.SRI_lat_basal 1.syst.Peak 1/s</td>
<td>-1.19 ± 0.33</td>
<td>-1.37 ± 0.41</td>
<td>0.14 (-0.01; 0.28)</td>
<td>.071</td>
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<tr>
<td>long.SI lat_basal max syst.%</td>
<td>20.81 ± 8.20</td>
<td>22.41 ± 6.75</td>
<td>-0.28 (-4.68; 4.12)</td>
<td>.902</td>
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<tr>
<td>long.SRI_lat_mid_ 1.syst.Peak 1/s</td>
<td>-1.04 ± 0.42</td>
<td>-0.88 ± 0.38</td>
<td>-0.11 (-0.24; 0.01)</td>
<td>.062</td>
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<td>Measure</td>
<td>Mean 1</td>
<td>Mean 2</td>
<td>p-value</td>
<td>Effect Size</td>
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<tr>
<td>long.SI lat_mid_ max syst.%</td>
<td>17.61 ± 5.49</td>
<td>18.16 ± 4.40</td>
<td>-0.76 (-3.32; 1.80)</td>
<td>.561</td>
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<tr>
<td>long.SRI_lat_apic_1. syst.Peak 1/s</td>
<td>-1.16 ± 0.40</td>
<td>-1.27 ± 0.65</td>
<td>-0.03 (-0.27; 0.21)</td>
<td>.814</td>
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<tr>
<td>long.SI lat_apic_ max syst.%</td>
<td>17.55 ± 5.18</td>
<td>16.77 ± 6.24</td>
<td>3.20 (0.84; 5.58)</td>
<td>.008</td>
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<tr>
<td>long.SRI_anterior basal 1.syst.Peak 1/s</td>
<td>-1.38 ± 0.77</td>
<td>-1.49 ± 0.39</td>
<td>0.01 (-0.47; 0.50)</td>
<td>.959</td>
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<tr>
<td>long.SI ant basal max syst.%</td>
<td>20.39 ± 7.39</td>
<td>24.19 ± 5.42</td>
<td>-2.22 (-7.58; 3.13)</td>
<td>.416</td>
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<tr>
<td>long.SRI_anterior_mid 1.syst.Peak 1/s</td>
<td>-1.07 ± 0.41</td>
<td>-1.07 ± 0.49</td>
<td>-0.04 (-0.21; 0.12)</td>
<td>.613</td>
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<tr>
<td>long.SI ant_mid_ max syst.%</td>
<td>18.64 ± 4.67</td>
<td>19.85 ± 5.57</td>
<td>0.07 (-4.96; 5.10)</td>
<td>.979</td>
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<td>long.SRI_anterior_apical_ 1.syst.Peak 1/s</td>
<td>-1.14 ± 0.47</td>
<td>-0.89 ± 0.65</td>
<td>-0.38 (-0.54; -0.22)</td>
<td>&lt;.001</td>
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<tr>
<td>long.SI ant_apical_ max syst.%</td>
<td>17.69 ± 4.28</td>
<td>14.02 ± 7.83</td>
<td>6.04 (1.45; 10.64)</td>
<td>.010</td>
<td></td>
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<tr>
<td>long.SRI_inf_basal_ 1.syst.Peak 1/s</td>
<td>-1.33 ± 0.32</td>
<td>-1.56 ± 0.52</td>
<td>0.22 (0.02; 0.41)</td>
<td>.028</td>
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<tr>
<td>long.SI inf_basal max syst.%</td>
<td>24.20 ± 7.03</td>
<td>22.79 ± 6.99</td>
<td>2.62 (-3.38; 8.61)</td>
<td>.392</td>
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<tr>
<td>long.SRI_inf_mid 1.syst.Peak 1/s</td>
<td>-1.06 ± 0.27</td>
<td>-1.43 ± 0.58</td>
<td>0.27 (0.04; 0.49)</td>
<td>.019</td>
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<tr>
<td>long.SI inf_mid_ max syst.%</td>
<td>20.53 ± 7.89</td>
<td>23.01 ± 5.85</td>
<td>-1.31 (-6.41; 3.80)</td>
<td>.615</td>
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<tr>
<td>long.SRI_inferior_apical_ 1.syst.Peak 1/s</td>
<td>-1.47 ± 0.51</td>
<td>-1.60 ± 0.54</td>
<td>-0.10 (-0.39; 0.19)</td>
<td>.488</td>
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<tr>
<td>long.SI inf_apical_ max syst.%</td>
<td>26.83 ± 5.67</td>
<td>28.32 ± 9.42</td>
<td>0.04 (-5.35; 5.44)</td>
<td>.987</td>
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<tr>
<td>long.SRI_anterior septum_basal 1.syst.Peak 1/s</td>
<td>-0.90 ± 0.43</td>
<td>-1.31 ± 0.60</td>
<td>0.31 (-0.05; 0.68)</td>
<td>.087</td>
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<td>Description</td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
<td>Estimated Difference</td>
<td>p-value</td>
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</tr>
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<tr>
<td>long.SI ant_septum_basal max syst.%</td>
<td>17.14 ± 3.85</td>
<td>19.68 ± 4.61</td>
<td>-2.68 (-5.60; 0.24)</td>
<td>.071</td>
<td></td>
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<tr>
<td>long.SRI_anterior_septum_mid 1.syst.Peak 1/s</td>
<td>-0.99 ± 0.24</td>
<td>-1.17 ± 0.38</td>
<td>0.19 (0.04; 0.34)</td>
<td>.012</td>
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<tr>
<td>long.SI ant_septum_mid_ max syst.%</td>
<td>19.06 ± 3.95</td>
<td>20.99 ± 5.08</td>
<td>-1.76 (-4.97; 1.44)</td>
<td>.272</td>
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<tr>
<td>long.SRI_anterior_septum_apical_1.syst.Peak 1/s</td>
<td>-0.99 ± 0.40</td>
<td>-0.96 ± 0.38</td>
<td>-0.18 (-0.46; 0.11)</td>
<td>.218</td>
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<tr>
<td>long.SI ant_septum_apical_ max syst.%</td>
<td>19.56 ± 6.16</td>
<td>19.78 ± 6.64</td>
<td>1.04 (-2.02; 4.10)</td>
<td>.505</td>
<td></td>
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<tr>
<td>long.SRI_posterior_basal_1.syst.Peak 1/s</td>
<td>-1.43 ± 0.59</td>
<td>-1.54 ± 0.59</td>
<td>-0.004 (-0.29; 0.28)</td>
<td>.974</td>
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<tr>
<td>long.SI posterior_basal_ max syst.%</td>
<td>20.77 ± 9.85</td>
<td>23.46 ± 7.64</td>
<td>4.95 (2.88; 7.01)</td>
<td>&lt;.001</td>
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<tr>
<td>long.SRI_posterior_mid_1.syst.Peak 1/s</td>
<td>-1.14 ± 0.68</td>
<td>-1.70 ± 1.89</td>
<td>0.60 (-0.11; 1.30)</td>
<td>.097</td>
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<tr>
<td>long.SI posterior_mid_ max syst.%</td>
<td>20.17 ± 5.94</td>
<td>23.01 ± 6.89</td>
<td>-2.16 (-6.89; 2.56)</td>
<td>.360</td>
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<td>long.SRI_posterior_apical_1.syst.Peak 1/s</td>
<td>-1.20 ± 0.44</td>
<td>-1.40 ± 0.71</td>
<td>0.11 (-0.20; 0.41)</td>
<td>.496</td>
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</tr>
<tr>
<td>long.SI posterior_apical_ max syst.%</td>
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<td>20.97 ± 7.76</td>
<td>-1.45 (-4.28; 1.38)</td>
<td>.314</td>
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</tr>
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</table>

Long, longitudinal; SRI, strain rate s⁻¹; SI, strain %; 1.syst.peak, first strain rate peak; inf sept, inferoseptal; lat, lateral; lat_apic, lateral apical; apic, apical; ant, anterior; inf, inferior; post, posterior; ant_septum, anteroseptal;

Data are shown as unadjusted mean ± standard deviation; Estimated differences, 95% CIs and p-values were calculated with GEE models, adjusting for age, blood pressure and family clustering.