Sudden Cardiac Death in Women
Causes of Death, Autopsy Findings, and Electrocardiographic Risk Markers

BACKGROUND: Despite recent progress in profiling of risk for sudden cardiac death (SCD) and prevention and intervention of cardiac diseases, SCD remains a major cause of death. Among women, the incidence of SCD is significant, but lower than in men, particularly in the premenopausal and early postmenopausal years. Possibly, as a consequence of the difference in population burden, the mechanisms and risk markers of SCD are not as well defined for women. The aim of this study was to determine the autopsy findings and causes of death among women in a large SCD population. Additionally, we sought to classify prior ECG characteristics in male and female subjects with SCD.

METHODS: The Fingesture study has systematically collected clinical and autopsy data from subjects with SCD in Northern Finland between 1998 and 2017. The cohort consists of 5869 subjects with SCD. Previously recorded ECGs were available and analyzed in 1101 subjects (18.8% of total population; and in 25.3% of women).

RESULTS: Female subjects with SCD were significantly older than men: 70.1±13.1 years versus 63.5±11.8 years (mean ± standard deviation, P<0.001). The most frequently identified cause of death was ischemic heart disease in both sexes: 71.7% among women versus 75.7% among men, P=0.005. In contrast, women were more likely to have nonischemic cause of SCD than men (28.3% versus 24.3%, P=0.005). The prevalence of primary myocardial fibrosis was higher among women (5.2%, n=64) than in men (2.6%, n=120; P<0.001). Female subjects with SCD were more likely to have normal prior ECG tracings (22.2% versus 15.3% in men, P<0.001). A normal ECG was even more common among nonischemic female subjects with SCD (27.8% versus 16.2% in men, P=0.009). However, ECG markers of left ventricular hypertrophy, with or without repolarization abnormalities, were more common among women (8.2%; 17.9%) than in men (4.9%; 10.6%, P=0.036; P<0.001, respectively).

CONCLUSIONS: Women were considerably older at the time of SCD and more commonly had nonischemic causes. Women were also more likely to have a prior normal ECG than men, but an increased marker for SCD risk based on ECG criteria for left ventricular hypertrophy with repolarization abnormalities was more commonly observed in women.

Key Words: autopsy death, sudden, cardiac electrocardiography sex

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Sudden cardiac death (SCD) remains a major cause of death despite the recent progress in prevention and interventions of cardiac diseases. In previous studies of SCD epidemiology and risk factors, the rate of SCD has been considerably lower among women than among men.\(^1,2\) Therefore, information on SCD in women has been limited. The annual rate of SCD in women has been estimated to be almost half of that in men,\(^1,3\) and the differences are particularly striking in the middle-age premenopausal and early postmenopausal years. However, the decline of SCD incidence in women has been significantly slower than in men.\(^4\) It has been speculated that SCD would be a more heterogeneous disorder in women than in men, and that women would have more atypical presentation and would be less likely to have classical symptoms of cardiac diseases.\(^1\) As a consequence, underlying conditions associated with SCD risk have been thought to be more difficult to recognize, predict, and prevent among women.\(^6\)

As in men, coronary artery disease (CAD) risk factors are associated with an increased risk of SCD at a general population level among women.\(^1,5\) Smoking, hypertension, and diabetes are associated with a 2.5- to 4.0-fold risk of SCD in women\(^1\) and obesity (body mass index \(\geq 30\) kg/m\(^2\)) with moderately to markedly elevated risk of SCD\(^1,6\) and also with greater risk of SCD in women without a history of diagnosed CAD.\(^6\) However, there are some conflicting results in earlier studies on association of traditional risk factors of CAD and SCD among women,\(^7\) which is why new markers are needed for risk evaluation, especially among women.

Based on existing data, there are likely to be sex differences not only in risk factors but also in pathogenesis, symptoms, and awareness of SCD.\(^1\) Coronary artery disease is the most common cause for SCD in the Western world, but the data on cause of death among female subjects with SCD are very limited. In women, SCD seems to occur more often without previously known CAD.\(^1,2,7-10\) In prior studies, 37% of women with SCD had a prior cardiac disease, when in men, the comparable prevalence was 56%. In Framingham\(^2\) and other studies,\(^11\) 69% of women with SCD did not have a documented CAD event, and only 10% had symptoms of acute coronary syndrome weeks before death.\(^1\) In contrast, SCD is more commonly the first CAD-associated event among women,\(^6\) and women are more prone to have unrecognized prior myocardial infarction.\(^12\)

Autopsy has been regarded as the standard method for detecting underlying cardiac pathology leading to SCD, even though up to 30% of autopsies of subjects with SCD under the age of 35 years are negative for a structural heart disease basis. Because large autopsy-verified SCD reports on women are lacking, the aim of this study was to determine the autopsy findings and causes of death in women in a large SCD cohort. Additionally, we aimed to study the electrocardiographic findings in women with SCD and compare the results with male subjects with SCD.

**METHODS**

The data, analytical methods, and study materials will be made available to other researchers for the purpose of reproducing the results or replicating the procedure. Inquiries can be directed to the corresponding author.

**Study Population**

The Fingesture population consisted of 5869 autopsied subjects with SCD (male \(n=4631, 78.9\%\); female \(n=1238, 21.1\%\); mean age, 65±12 years). Fingesture is designed to study systematically collected clinical and autopsy data of subjects with SCD in Northern Finland from 1998 to 2017. A medico-legal autopsy has been carried out in all subjects with SCD at the Department of Forensic Medicine, University of Oulu, Oulu, Finland, and the National Institute for Health and Welfare, Oulu, Finland. The autopsies were performed by experienced forensic pathologists (each performing over 100 autopsies per year) using contemporary guidelines for diagnosis of cause of death. Finnish law requires a medico-legal autopsy to be performed if the death is not because of a preexisting known disease, if the subject has not been treated by physicians during the last illness, or if the death is otherwise unexpected (Act on the Inquest Into the Cause of Death, 459/1973, 7th paragraph: Finnish law), which leads to highest autopsy rates in Finland compared to Western societies.\(^13\) A death was classified as sudden if it was either a witnessed event within 6 hours of the onset of symptoms or an unwitnessed death within 24 hours when the subject was last seen alive in a normal state of health. The current criteria...
for SCD were chosen to cover as many subjects with SCD as possible, considering that many subjects with SCD would be found dead and would have been missed with the 1-hour definition for SCD originally proposed by Hinkle and Thaler.14 All of the subjects are from a defined geographical area in Northern Finland.

If there was evidence of a noncardiac cause of the death, such as pulmonary embolism or cerebral hemorrhage, the death was classified as a noncardiac sudden death, and it was excluded from the SCD cohort. The cohort was further subcategorized into ischemic and nonischemic causes of SCD. The anatomic criteria for ischemic SCD included evidence of an active coronary artery process, defined as an acute intracoronary thrombus, plaque rupture or erosion, hemorrhage into a plaque or critical coronary stenosis (>75%) in major coronary artery. Subjects were classified as having a nonischemic cause of SCD if they did not fulfill the criteria for ischemic SCD. Precise definitions for nonischemic causes of SCD, including alcoholic, obesity- and hypertension-related cardiomyopathy and primary myocardial fibrosis (PMF), are presented in Table 1. More detailed methods of the Fingeresture study have been reported earlier by Kaikkonen et al.15

The study complies with the Declaration of Helsinki and was approved by the Ethics Committee of Northern Ostrobothnia Hospital District and the National Authority for Medicolegal Affairs (Valvira). Consent from next of kin was waived by the Ethics Committee since according to the Finnish law, medicolegal autopsy does not require consent.

**ECG Analysis**

Antemortem ECGs were collected from all subjects with one or more ECGs in their health records. ECGs were standard resting 12-lead recordings at a paper speed of 50 mm/s and a calibration of 1 mV per 10 mm. ECGs were analyzed independently by 2 investigators. The median time between the last available ECG prior to the event of SCD was 2 years (interquartile range, 0.28, 4.9 years).

Electrocardiographic analyses included standard interval measurements, including QRS and QTc duration. In addition, we analyzed inferolateral T-wave inversions and inferolateral early repolarization with a horizontal or descending ST-segment and QRS fragmentations. QRS durations were measured and classified as prolonged when the QRS was ≥110 ms. Inferolateral T-inversions were classified by coronary artery regions as inferior or lateral if there were at least 2 T-inversions ≥0.1 mV in at least 2 contiguous leads in the same region, specifically inferior leads (II, III, aVF) or lateral leads (I, aVL, V4–V6). Similarly, early repolarization was classified inferolateral if there were at least 2 slurred or notched J-point elevations ≥0.1 mV in inferior or lateral leads. ST-segment was classified as horizontal or descending if it was under 0.1 mV 100 ms after the QRS complex had ended. Two definitions of prolonged QTc were analyzed: QTc ≥460 ms among women and QTc ≥440 ms among men, and in the second definition, QTc ≥470 ms among women and QTc ≥450 ms among men were classified as prolonged. Marked QTc prolongation was defined as QTc over 490 ms in both men and women. Fragmented QRS (fQRS) complexes was classified by coronary artery regions as inferior, lateral, or anterior if there were at least 2 notched changes in QRS complex that could not be considered as early repolarization. The definition of fQRS required at least 2 fQRSs inferiorly, laterally, or anteriorly. Q-waves were classified by standard Minnesota criteria. Electrocardiographic markers of left ventricular hypertrophy (LVH) were measured by using the Cornell criteria (S-wave in V3 and R-wave in aVL >24 mm in men, and S in V3 and R in aVL >20 mm in women) and the Sokolow-Lyon criteria (tallest

### Table 1. Definitions for Nonischemic Causes of Sudden Cardiac Death

<table>
<thead>
<tr>
<th>Adjudicated Causes of Death</th>
<th>Descriptive Causes of Death From Autopsy</th>
<th>Autopsy Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>DCM</td>
<td>DCM</td>
<td>Left ventricular dilation with inadequate degree of LVH, in later stages pale and flabby myocardium and dilation of both ventricles and atria, unspecific fibrosis and focal atrophy/hypertrophy of myocytes.</td>
</tr>
<tr>
<td>Hypertrophic cardiomyopathy</td>
<td>HCM</td>
<td>Concentric LVH, with myocyte disarray accompanied by various degrees of interstitial fibrosis.</td>
</tr>
<tr>
<td>HOCM</td>
<td>LVH, with asymmetrical septal hypertrophy, myocyte disarray, and various degrees of interstitial fibrosis.</td>
<td></td>
</tr>
<tr>
<td>Right ventricular dysplasia/CM</td>
<td>ARVC</td>
<td>Right ventricular dilation, atrophy of the right ventricular myocardium with fibrofatty replacement of myocytes.</td>
</tr>
<tr>
<td>Other cardiomyopathies</td>
<td>PMF</td>
<td>Interstitial, diffuse, or patchy myocardial fibrosis without LVH, myocardial scarring, or other structural abnormalities without left ventricular hypertrophy (heart weight &gt;420 g) or any other apparent cause for fibrosis.</td>
</tr>
<tr>
<td>Hypertensive CM</td>
<td>Increased heart weight (420 g), LVH, unspecific fibrosis, other organ changes related to hypertension (eg, medial hypertrophy, intimal fibrosis/sclerosis in renal arterioles).</td>
<td></td>
</tr>
<tr>
<td>Alcoholic CM</td>
<td>Focal replacement fibrosis of the myocardium, LVH and increased heart weight (&gt;420 g). In later stages, signs of dilated cardiomyopathy, other organ changes related to excessive long-term alcohol consumption (eg, liver cirrhosis and/or severe steatosis, pancreatic fibrosis/calcifications).</td>
<td></td>
</tr>
<tr>
<td>CM associated with obesity</td>
<td>Heart weight increased over value predicted for normal body weight, LVH or both left and right ventricular wall hypertrophy, dilation of both atria and ventricles, excessive epicardial fat and fat infiltration of myocardium, obesity (body mass index &gt;30).</td>
<td></td>
</tr>
</tbody>
</table>

ARVC indicates arrhythmogenic right ventricular cardiomyopathy; CM, cardiomyopathy; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; HOCM, hypertrophic obstructive cardiomyopathy; LVH, left ventricular hypertrophy; and PMF, primary myocardial fibrosis.
R wave in V5 or V6 and S-wave in V1>35 mm) with or without concomitant strain pattern (T-wave inversion in lateral leads).

Statistical Analysis
To compare continuous variables of interest, Student t test was used. When comparing categorical variables between the groups of interest, Pearson chi-square test was used. Continuous variables are presented as mean±SD. All statistical analyses were performed using Statistical Package for Social Studies 21.0 (SPSS Inc, Chicago, IL). All reported P values are 2-sided. Values <0.05 were considered as statistically significant.

RESULTS
Characteristics and Cause of SCD
Clinical and autopsy data from 5869 subjects with SCD were collected between 1998 and 2017. The majority of the subjects with SCD were male (n=4631, 78.9% compared to 1238 women, 21.1%, P<0.001). Ischemic SCD was observed in 4392 cases (74.8%) and nonischemic SCD in 1477 (25.2%) cases. Although ischemic SCD was observed in 79.8% (n=3504), with only 20.2% women (n=888, P<0.005). A nonischemic cause was observed in 350 women (23.7%) and in 1127 men (76.3%, P=0.005). Among women, a nonischemic cause of SCD was more common (28.3%) than the proportion among men (24.3%, P=0.005). The prevalence differences between sexes and ischemic and nonischemic SCDs are shown in Figure 1. The prevalence of PMF was considerably higher among women than in men: 5.2% of women (n=64) versus 2.6% among men (n=120, P<0.001). Women with SCD were more likely to have no macroscopic findings at autopsy and normal histology than were men (0.6% versus 0.2%, P=0.015). Causes of death are presented in Table 2.

Characteristics of subjects with SCD by sex are shown in Table 3. Females with SCD were generally older than men: 70.1±13.1 versus 63.5±11.8 years, P<0.001. Women also had higher body mass index (28.1±7.4 versus 27.5±6.0 kg/m², P=0.001), more abdominal fat (3.2±1.8 versus 2.7±1.4 cm, P<0.001), and smaller heart weight (412±104 versus 501±128 g, P<0.001). Different levels of myocardial fibrosis were a common finding in both sexes, but more common in men than in women. The amount of fibrosis also seems to be more severe in men than in women, with any degree of fibrosis being observed in the ventricles of 92.4% of males with SCD, compared to 89.3% of female subjects (P<0.001). Substantial fibrosis was seen in 12.7% of men, compared to 7.8% of women (P<0.001). One out of 10 women with SCD did not have fibrosis (n=132, Table 2.

<table>
<thead>
<tr>
<th>Causes of Death by Sex</th>
<th>Men</th>
<th>Women</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischemic death*</td>
<td>75.7 (3504)</td>
<td>71.7 (888)</td>
<td>0.005</td>
</tr>
<tr>
<td>HTA CMP</td>
<td>6.7 (310)</td>
<td>7.3 (90)</td>
<td>0.475</td>
</tr>
<tr>
<td>Obesity CMP</td>
<td>5.7 (264)</td>
<td>6.1 (76)</td>
<td>0.558</td>
</tr>
<tr>
<td>Alcoholic CMP</td>
<td>5.3 (244)</td>
<td>4.0 (49)</td>
<td>0.060</td>
</tr>
<tr>
<td>PMF*</td>
<td>2.6 (120)</td>
<td>5.2 (64)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Valve disease*</td>
<td>1.1 (53)</td>
<td>1.9 (23)</td>
<td>0.049</td>
</tr>
<tr>
<td>DCM</td>
<td>1.0 (46)</td>
<td>0.5 (6)</td>
<td>0.090</td>
</tr>
<tr>
<td>Myocarditis*</td>
<td>0.9 (40)</td>
<td>1.6 (20)</td>
<td>0.020</td>
</tr>
<tr>
<td>HCM</td>
<td>0.7 (34)</td>
<td>0.4 (6)</td>
<td>0.343</td>
</tr>
<tr>
<td>Missing information</td>
<td>0.1 (3)</td>
<td>0.1 (3)</td>
<td>0.082</td>
</tr>
<tr>
<td>Normal finding*</td>
<td>0.2 (8)</td>
<td>0.6 (7)</td>
<td>0.015</td>
</tr>
<tr>
<td>Anomalies</td>
<td>0.1 (4)</td>
<td>0.1 (1)</td>
<td>0.952</td>
</tr>
<tr>
<td>ARVC*</td>
<td>0.0 (1)</td>
<td>0.4 (5)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

ARVC indicates arrhythmogenic right ventricular cardiomyopathy; CMP, cardiomyopathy; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; HTA, hypertension; and PMF, primary myocardial fibrosis.

*Significant differences (P<0.05) between men and women.

Table 3. Characteristics of Sudden Cardiac Death Victims by Sex

<table>
<thead>
<tr>
<th>Characteristics of Sudden Cardiac Death Victims by Sex</th>
<th>Men</th>
<th>Women</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Continuous variables, mean±SD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (y)*</td>
<td>63.5±11.8</td>
<td>70.1±13.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI (kg/m²)*</td>
<td>27.5±6.0</td>
<td>28.1±7.4</td>
<td>0.001</td>
</tr>
<tr>
<td>Abdominal fat (cm)*</td>
<td>2.7±1.4</td>
<td>3.2±1.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Heart weight (g)*</td>
<td>501±128</td>
<td>412±104</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Categorical variables, prevalence, % (n)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior scar</td>
<td>43.2 (1958)</td>
<td>44.9 (546)</td>
<td>0.313</td>
</tr>
<tr>
<td>Fibrosis (any degree)*</td>
<td>92.4 (4277)</td>
<td>89.3 (1104)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>None*</td>
<td>7.5 (348)</td>
<td>10.7 (132)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mild*</td>
<td>28.7 (1327)</td>
<td>32.6 (404)</td>
<td>0.006</td>
</tr>
<tr>
<td>Moderate</td>
<td>51.0 (2363)</td>
<td>48.9 (605)</td>
<td>0.178</td>
</tr>
<tr>
<td>Substantial*</td>
<td>12.7 (590)</td>
<td>7.8 (96)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

BMI indicates body mass index.

*Significant differences (P<0.05) between men and women.
10.7%, P<0.001), while in men the corresponding percentage was 7.5% (n=348, P<0.001).

Circumstances Surrounding SCDs
Among all SCDs, 85% were unwitnessed in men, and 83% in women were unwitnessed. In ischemic SCD, the proportion of unwitnessed death was even higher in men than in women (91% versus 87%, P=0.049; Table 4). SCD in women occurred indoors more often than in men (92% versus 82%, P<0.001, respectively). SCD occurred during exercise more often in men than in women (11% versus 2%, P<0.001, respectively). The excess of SCD during exercise in men compared to women was even greater for those with ischemic SCDs (13% versus 3%, P<0.001, respectively). SCD occurred during exercise more often in men than in women (92% versus 82%, P<0.001, respectively). At the same time, the overall decreasing (Figure 3) to 2007 (P=0.004), and to 72.4% between 2008 to 2012 (P=0.016), and to 72.4% between 2013 to 2017 (P=0.004; Figure 3). This phenomenon was also present in both women and men, although there was some fluctuation in prevalence among women during the last 10 years. However, among men, the trend was overall decreasing (Figure 3). At the same time, the overall proportion of nonischemic deaths increased in women and in men (Figure 3).

Sex-Related Electrocardiographic Differences Among Subjects With SCD
Antemortem ECGs were recorded in 1101 subjects, among whom 279 (25.3%) were women and 822 (74.7%, P=0.005) were men. Differences in the prevalence of ECG changes were compared between the sexes and ischemic and nonischemic groups. At least one ECG abnormality was found in 84.7% of males with SCD and 72.8% of females with SCD (P<0.001). The mean QRS duration in men was 101.8±22.8 ms and in women, 93.9±22.8 ms (P<0.001; Table 5). ECG findings that were more common in men than in women were QRS durations >110 ms (24.5% versus 13.6%, in men and women, respectively, P<0.001), total fQRS (55.6% versus 46.2%, P=0.007), and inferior fQRS (44.2% versus 35.5%, P=0.011).

The presence of any Q-waves was almost twice as frequent in men than in women (15.6% versus 8.2%, P=0.002, respectively). The mean QTc duration was 439.5±39.8 ms in men and 438.2±37.7 ms in women, an overall small difference that was not biologically or statistically significant (P=0.623; Table 5). However, QTc >440 ms or >450 ms in men was a markedly more prevalent finding (44.8%, P<0.001, and 34.4%, respectively) than QTc over 460 ms and 470 ms in women (22.6%, P<0.001, and 17.2%, P<0.001, respectively). Markedly prolonged QTc (>490 ms) was equally prevalent among female and males with SCD (8.2% versus 9.9%, P=0.427, respectively). An interesting difference in frequency of ECG changes between the sexes was criteria for LVH, which were markedly more prevalent in women (17.9%) than in men (10.6%, P<0.001). In addition, LVH combined with repolarization abnormalities was a more common finding in women (8.2%) than in men (4.9%, P=0.036). All ECG analyses are presented in Table 5.

Subgroup analyses of subjects with ischemic and nonischemic SCD revealed that most of the ECG findings paralleled those observed in the total SCD population, with a few exceptions. Among subjects with ischemic SCD (Table 6), men had significantly more pathological Q-waves (19.3%) than did women (9.4%, P<0.001). This difference was somewhat larger than that observed in the total SCD data. Additionally, among subjects with nonischemic SCD (Table 7), LVH with repolarization abnormalities was seen in significantly more women than men (10.2% versus 4.6%, P=0.038, respectively).

Table 4. Circumstances During Sudden Cardiac Death in Both Sexes

<table>
<thead>
<tr>
<th>Circumstance</th>
<th>Men</th>
<th>Women</th>
<th>Ischemic Men</th>
<th>Ischemic Women</th>
<th>Nonischemic Men</th>
<th>Nonischemic Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Witnessed, % (n)</td>
<td>15 (680)</td>
<td>17 (205)</td>
<td>16 (576)</td>
<td>18 (160)</td>
<td>9 (104)</td>
<td>13 (45)*</td>
</tr>
<tr>
<td>Unwitnessed, % (n)</td>
<td>85 (3950)</td>
<td>83 (1033)</td>
<td>84 (2927)</td>
<td>82 (728)</td>
<td>91 (1023)</td>
<td>87 (305)*</td>
</tr>
<tr>
<td>Indoors, % (n)</td>
<td>82 (3791)</td>
<td>92 (1143)+</td>
<td>80 (2802)</td>
<td>82 (1818)</td>
<td>88 (989)</td>
<td>93 (325)+</td>
</tr>
<tr>
<td>Outdoors, % (n)</td>
<td>18 (836)</td>
<td>8 (95)+</td>
<td>20 (608)</td>
<td>8 (70)+</td>
<td>12 (138)</td>
<td>7 (25)+</td>
</tr>
<tr>
<td>During exercise, % (n)</td>
<td>11 (4135)</td>
<td>2 (1210)+</td>
<td>13 (449)</td>
<td>3 (26)+</td>
<td>4 (47)</td>
<td>1 (2)+</td>
</tr>
</tbody>
</table>

*P<0.05; †P<0.01 compared to men. Unwitnessed indicates found dead.
Proportion of Cardiac and Noncardiac Causes of Sudden Death

Attributable to the protocol of the study, we do not have information on noncardiac causes of sudden death in the total cohort. Nevertheless, we were able to perform a subgroup analysis within autopsy-verified subjects with sudden death in year 2016. Sudden death occurred in 960 autopsied subjects, of which 593 (143 women and 450 men) were of natural causes, excluding accidents, suicides, and homicides. Cardiac cause for SCD was detected in 355 subjects (60%). Among women, SCD was a significantly more common cause of sudden death than in men (69% versus 57%, \( P = 0.009 \), respectively). Among noncardiac cause for sudden death, only gastrointestinal tract hemorrhage had a significantly higher proportion among men (6.7%, \( n = 30 \)) compared to women (0.7%, \( n = 1 \); \( P = 0.005 \) between men and women). Among noncardiac causes for sudden death without significant difference between women and men, intracranial hemorrhage or stroke occurred in 4.0% (\( n = 24 \); 4 women/20 men), vascular events such as aortic dissection or rupture, or acute ischemia in 2.5% (\( n = 15 \); 2 women/13 men), and pulmonary embolism/other venous thromboembolism in 1.5% (\( n = 9 \); 2 women/7 men).

DISCUSSION

The incidence of SCD was considerably lower in women than in men, which is consistent with observations in earlier studies.\(^1,2\) In our study, a significant majority of SCDs were ischemic, which is also consistent with previous studies,\(^16,17\) as was the observation that nonischemic SCD was more common among women than men.\(^1,7,10\) However, it is interesting to note that, within nonischemic SCD subgroup, there was a significantly higher prevalence of PMF as the cause of death among women with SCD compared to men. In addition, it was surprising to note a higher prevalence of voltage criteria for LVH, with and without associated repolarization abnormalities (ie, strain patterns), among women. Nonetheless, a large number of subjects with SCD, both among men and women, could not have been detected to be at specific risk of SCD based solely on ECG abnormalities, because one-fifth of women in the ischemic
SCD subgroup and almost one-third of women in the nonischemic SCD group had normal ECGs.

A comprehensive analysis of SCD in a large community was recently reported by Tseng et al.\textsuperscript{18} The prevalence of different causes of death differed significantly from the observations in this study attributable to the differences in study protocol. In the study by Tseng et al,\textsuperscript{18} all SCDs were included in the analyses, and in this study, noncardiac causes of sudden death were excluded. Otherwise, the mean age and proportion of women in the SCD population were somewhat compatible. In addition, in this study, we used a specific classification of cardiomyopathy diagnosis as we have done in a previous report.\textsuperscript{16,19} This subcategorization relies primarily on histological analyses, which in many other societies is not a mandatory part of sudden death autopsy. Also, in the study by Tseng et al,\textsuperscript{18} the number of autopsied subjects with sudden death was 315, and the case selection process for autopsy in sudden death might cause a certain bias. In this study, 5869 autopsies were performed, and attributable to the law requirements in Finland, selection bias remains minimal. Nevertheless, in the subgroup analyses of sudden death in 2016 in our study, the numbers for SCD were quite similar to that of unwitnessed subjects with SCD in the study by Tseng et al,\textsuperscript{18} because in both, \(\approx40\%\) of sudden deaths were caused by noncardiac causes. Surprisingly, the proportion of SCD from all sudden deaths was significantly higher among women in our study.

The incidence of SCD increases in both sexes with age, especially after the age of 70 years,\textsuperscript{1,2,20} and in the transition to postmenopausal age among women. In our study, females with SCD were significantly older than males with SCD (70.1±13.1 versus 63.5±11.8 years). In previous studies, SCD has also been shown to occur \(\approx10\) years later in women than in men.\textsuperscript{2} Women were more likely to have no findings at autopsy than men in our study, even though this was surprisingly rare among subjects with SCD in our study (0.6\% versus 0.2\% in women and in men, respectively; \(P=0.015\)), compared to other studies. This might be attributable to the age of the populations in our study as a result of the inclusion criteria for Fingesture, as well as the meticulous histological examinations of the myocardium, which are a part of the standard procedure in autopsy in Finland. In addition, the differences between women and men may also result from some of the differences in pathogenesis and pathophysiology of SCD between the sexes. PMF has been recently suggested to be an alternate pathway of a spectrum of genetically associated cardiomyopathies.\textsuperscript{21} In this study, PMF was twice as common a cause of SCD among women as in men. This may, in part, be attributable to the significantly lower prevalence of CAD as a cause of SCD among women, thus amplifying the prevalence of other causes. However, the large difference in prevalence was not seen in many other nonischemic SCD causes.

Previously, we have reported characteristics of SCD in Fingesture data in 2011\textsuperscript{16} when a subset of 2661 subjects whose deaths occurred between 1998 and 2007 were analyzed. In the previous study, subjects with ischemic SCD were older than subjects with nonischemic SCD, but differences in age among sexes were not studied. Ischemic heart disease was the most common cause of death (78.2\%). The most common nonischemic cause of death was obesity cardiomyopathy (23.7\%), followed by alcoholic cardiomyopathy (19.0\%), hypertensive cardiomyopathy (15.5\%), and PMF (13.6\%). In the previous study, the majority of SCDs occurred at home with a higher proportion among subjects with nonischemic SCD compared to subjects with ischemic SCD, but dif-

<table>
<thead>
<tr>
<th>Categorical variables, prevalence, % (n)</th>
<th>Men</th>
<th>Women</th>
<th>(P) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any ECG abnormality*</td>
<td>84.7 (696)</td>
<td>72.8 (203)</td>
<td>(&lt;0.001)</td>
</tr>
<tr>
<td>QRS &gt;110 ms*</td>
<td>24.5 (201)</td>
<td>13.6 (38)</td>
<td>(&lt;0.001)</td>
</tr>
<tr>
<td>QTc &gt;440 (MV460 (W) ms*</td>
<td>44.8 (368)</td>
<td>22.6 (63)</td>
<td>(&lt;0.001)</td>
</tr>
<tr>
<td>QTc &gt;450 (MV470 (W) ms*</td>
<td>34.4 (283)</td>
<td>17.2 (48)</td>
<td>(&lt;0.001)</td>
</tr>
<tr>
<td>QTc &gt;490 ms, M and W</td>
<td>9.9 (81)</td>
<td>8.2 (23)</td>
<td>0.427</td>
</tr>
<tr>
<td>Q-waves*</td>
<td>15.6 (128)</td>
<td>8.2 (23)</td>
<td>0.002</td>
</tr>
<tr>
<td>Lateral*</td>
<td>3.2 (26)</td>
<td>0.7 (2)</td>
<td>0.025</td>
</tr>
<tr>
<td>Inferior*</td>
<td>9.9 (81)</td>
<td>5.7 (16)</td>
<td>0.036</td>
</tr>
<tr>
<td>Anterior*</td>
<td>4.7 (39)</td>
<td>1.8 (5)</td>
<td>0.030</td>
</tr>
<tr>
<td>T-wave inversions*</td>
<td>21.4 (176)</td>
<td>18.6 (52)</td>
<td>0.323</td>
</tr>
<tr>
<td>Inferior*</td>
<td>5.7 (47)</td>
<td>5.0 (14)</td>
<td>0.659</td>
</tr>
<tr>
<td>Anterior*</td>
<td>4.7 (39)</td>
<td>4.3 (12)</td>
<td>0.761</td>
</tr>
<tr>
<td>Inferolateral</td>
<td>19.0 (156)</td>
<td>16.1 (45)</td>
<td>0.287</td>
</tr>
<tr>
<td>Early repolarization</td>
<td>20.8 (171)</td>
<td>21.5 (60)</td>
<td>0.803</td>
</tr>
<tr>
<td>+Horizontal/descending ST-segment</td>
<td>19.8 (163)</td>
<td>21.1 (59)</td>
<td>0.636</td>
</tr>
<tr>
<td>QRS fragmentation*</td>
<td>55.6 (457)</td>
<td>46.2 (129)</td>
<td>0.007</td>
</tr>
<tr>
<td>Inferior*</td>
<td>44.2 (363)</td>
<td>35.5 (99)</td>
<td>0.011</td>
</tr>
<tr>
<td>Lateral*</td>
<td>26.0 (214)</td>
<td>20.8 (58)</td>
<td>0.079</td>
</tr>
<tr>
<td>Anterior*</td>
<td>20.3 (167)</td>
<td>16.1 (45)</td>
<td>0.125</td>
</tr>
<tr>
<td>LVH (Cornell)</td>
<td>10.6 (87)</td>
<td>17.9 (50)</td>
<td>0.001</td>
</tr>
<tr>
<td>LVH (Sokolow-Lyon)</td>
<td>5.1 (42)</td>
<td>4.3 (12)</td>
<td>0.589</td>
</tr>
<tr>
<td>LVH (Cornell)+ repolarization abnormalities*</td>
<td>4.9 (40)</td>
<td>8.2 (23)</td>
<td>0.036</td>
</tr>
<tr>
<td>LVH (Sokolow-Lyon)+ repolarization abnormalities</td>
<td>1.7 (14)</td>
<td>1.4 (4)</td>
<td>0.759</td>
</tr>
</tbody>
</table>

LVH indicates left ventricular hypertrophy; M, men; and W, women. *Significant differences (\(P<0.05\)) between men and women.

Table 5. Prevalence of Electrocardiographic Risk Markers for All Sudden Cardiac Death Victims by Sex
ferences between sexes were not studied. Among subjects with nonischemic SCD, the slight majority of the deaths occurred during 12-hour periods between midnight and noon, when in subjects with ischemic SCD, half occurred during daytime.14,16 In the present study, the circumstances surrounding SCD were somewhat different between men and women. In men, significantly more SCDs occurred during exercise, and most of these were caused by ischemic cardiac disease which, in part, explains the sex difference in this aspect, because women had significantly less ischemic SCD than men. In addition, women were more likely to experience SCD during the night (midnight to 6 AM) than men, and this difference was accentuated among women with a nonischemic cause of SCD (Figure 2). The percentage of un-

Table 6. Prevalence of Electrocardiographic Risk Markers for Ischemic Sudden Cardiac Death Victims by Sex

<table>
<thead>
<tr>
<th>Continuous variables, mean±SD</th>
<th>Men</th>
<th>Women</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>QTc (ms)*</td>
<td>437.3±39.4</td>
<td>439.9±38.0</td>
<td>0.440</td>
</tr>
<tr>
<td>QRS duration (ms)*</td>
<td>102.4±22.7</td>
<td>94.5±21.4</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

| Categorial Variables, prevalence, % (n)*| Any ECG abnormality* | QRS >110 ms* | QTc >440 (M)/460 (W) ms* | QTc >450 (M)/470 (W) ms* | QTc ≥490 ms, M and W | Q-waves* | Lateral | Inferior* | Anterior | T-wave inversions | Inferior | Anterior | T-wave inversions | Lateral | Inferior | Anterior | Inferolateral | Early repolarization | +Horizontal/descending ST-segment | QRS fragmentation* | Inferior* | Lateral | Anterior | LVH (Cornell)* | LVH (Sokolow-Lyon)* | LVH (Cornell)+repolarization abnormalities | LVH (Sokolow-Lyon)+ repolarization abnormalities |
|-----------------------------------------|---------------------|--------------|--------------------------|--------------------------|------------------------|-----------|---------|-----------|---------|-------------------|---------|---------|-------------------|---------|---------|---------|-------------|----------------------|----------------------|----------------------|-----------|---------|---------|-------------|----------------|---------------------|----------------------|----------------------|
| Men                                     | 85.2 (442)          | 26.0 (135)   | 42.2 (219)               | 32.4 (168)               | 9.2 (48)              | 19.3 (100)| 3.1 (16) | 12.3 (64) | 6.2 (32) | 23.7 (123)        | 17.7 (92) | 6.6 (34) | 4.8 (25)          | 21.0 (109) | 21.2 (110)| 20.6 (107) | 55.9 (290)  | 44.3 (230)          | 25.0 (130)           | 19.3 (100)           | 19.3 (100) | 13.3 (33) | 2.5 (3) | 10.0 (53)   | 5.4 (28)  | 5.0 (26)           | 1.9 (10)            | 0.6 (1)                  | 0.224     | 0.039   | 0.318     | 0.025       | 0.171       | 0.148     | 0.024     | 0.148     | 0.024     | 0.171     | 0.148     | 0.024     | 0.148     | 0.024     | 0.171     | 0.148     | 0.024     | 0.148     | 0.024     | 0.171     |
| Women                                   | 73.1 (125)          | 16.4 (28)    | 26.9 (46)                | 18.7 (32)                | 8.2 (14)              | 9.4 (16)  | 0.6 (1)  | 6.4 (11)  | 2.3 (4)  | 19.3 (33)          | 13.5 (23) | 6.4 (11) | 5.3 (9)           | 16.4 (28) | 22.2 (38) | 22.2 (38) | 46.8 (80)   | 38.0 (65)           | 19.3 (33)           | 14.6 (25)           | 14.6 (25) | 13.3 (33) | 5.9 (3) | 22.8 (39) | 1.7 (1)   | 7.0 (12)           | 0.6 (1)            | 0.1               | 0.432     | 0.148   | 0.038     | 0.125       | 0.171       | 0.148     | 0.038     | 0.148     | 0.038     | 0.171     | 0.148     | 0.038     | 0.148     | 0.038     | 0.171     | 0.148     | 0.038     | 0.171     | 0.148     | 0.038     | 0.171     |

LVH indicates left ventricular hypertrophy; M, men; and W, women.

*Significant differences (P<0.05) between men and women.

Table 7. Prevalence of Electrocardiographic Risk Markers for Nonischemic Sudden Cardiac Death Victims by Sex

<table>
<thead>
<tr>
<th>Continuous variables, mean±SD</th>
<th>Men</th>
<th>Women</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>QTc (ms)</td>
<td>443.4±40.4</td>
<td>435.4±37.3</td>
<td>0.073</td>
</tr>
<tr>
<td>QRS duration (ms)*</td>
<td>100.7±23.0</td>
<td>93.1±24.9</td>
<td>0.004</td>
</tr>
</tbody>
</table>

| Categorial Variables, prevalence, % (n)*| Any ECG abnormality* | QRS >110 ms* | QTc >440 (M)/460 (W) ms* | QTc >450 (M)/470 (W) ms* | QTc ≥490 ms, M and W | Q-waves* | Lateral | Inferior* | Anterior | T-wave inversions | Inferior | Anterior | T-wave inversions | Lateral | Inferior | Anterior | Inferolateral | Early repolarization | +Horizontal/descending ST-segment | QRS fragmentation* | Inferior* | Lateral | Anterior | LVH (Cornell)* | LVH (Sokolow-Lyon)* | LVH (Cornell)+repolarization abnormalities | LVH (Sokolow-Lyon)+ repolarization abnormalities |
|-----------------------------------------|---------------------|--------------|--------------------------|--------------------------|------------------------|-----------|---------|-----------|---------|-------------------|---------|---------|-------------------|---------|---------|---------|-------------|----------------------|----------------------|----------------------|-----------|---------|---------|-------------|----------------|---------------------|----------------------|----------------------|
| Men                                     | 83.8 (254)          | 21.8 (66)   | 49.2 (149)               | 38.0 (115)               | 10.9 (33)             | 9.2 (28)  | 3.3 (10) | 5.6 (17)  | 2.3 (7)  | 17.5 (53)         | 12.5 (38) | 4.3 (13) | 4.6 (14)          | 15.5 (47) | 20.1 (61) | 18.5 (56) | 55.1 (167)  | 43.9 (133)          | 27.7 (84)           | 2.8 (3)              | 2.8 (3)   | 13.9 (15) | 2.3 (8) | 23.1 (25) | 18.5 (20) | 10.2 (31)           | 2.3 (8)            | 0.9 (1)                      | 0.371     | 0.697   | 0.371     | 0.355       | 0.432       | 0.485     | 0.409     | 0.485     | 0.409     | 0.355     | 0.432     | 0.485     | 0.409     | 0.355     | 0.432     | 0.485     | 0.409     | 0.355     | 0.432     | 0.485     | 0.409     |
| Women                                   | 72.2 (332)          | 9.3 (10)    | 15.7 (17)                | 14.8 (16)                | 8.3 (9)               | 6.5 (7)   | 0.9 (1)  | 4.6 (5)   | 0.9 (1)  | 17.6 (19)         | 13.9 (15) | 2.8 (3) | 2.8 (3)           | 15.7 (17) | 20.4 (22) | 19.4 (21) | 45.4 (49)   | 31.5 (34)           | 23.1 (25)           | 2.3 (8)              | 2.3 (8)   | 7.0 (12) | 2.8 (3) | 18.5 (20) | 18.5 (20) | 10.2 (11)           | 2.8 (3)            | 0.9 (1)                      | 0.697     | 0.451   | 0.697     | 0.485       | 0.371       | 0.485     | 0.409     | 0.485     | 0.409     | 0.371     | 0.485     | 0.409     | 0.371     | 0.485     | 0.409     | 0.371     | 0.485     | 0.409     | 0.371     | 0.485     | 0.409     |

LVH indicates left ventricular hypertrophy; M, men; and W, women.

*Significant differences (P<0.05) between men and women.
novel addition to the knowledge obtained from the previous studies.\textsuperscript{11–12}

Previously, the temporal patterns of causes for SCD have been analyzed in a subset of the Fingesture population gathered between 1998 and 2012.\textsuperscript{19} Among previously undiagnosed subjects with SCD, ischemic heart disease as the cause of death has been steadily declining from 1998 to 2002, and at the same time, the proportion of especially hypertension-related cardiomyopathy and PMF as a nonischemic cause for SCD has been increasing.\textsuperscript{19} In the current study, subjects with prior diagnosis of heart disease were also included. Therefore, the prevalence of causes of death is not completely compatible to the previous study. Nevertheless, the results seem similar to the previous study, but interesting details can be detected in the sex differences. The proportion of ischemic SCD was lower in the latest 5-year segment in men and also in women, compared to preceding segments (Figure 3). The overall trend toward lower proportion was similar in the subgroup of men (Figure 3). In women, the proportion of ischemic cause of SCD was significantly lower from the first 5-year period, 1998 to 2002, to the following years, but during the last 5-year period, the proportion of ischemic cause of SCD seemed to stabilize to \textasciitilde 70\%. (Figure 3). Altogether, the changes during the last 20 years in causes of SCD seemed to follow the same route in men and women, but in women, the lower proportion of ischemic SCD was even more dramatic than in men. This might be partly caused by development in acute treatment of myocardial infarction, but also attributable to increased awareness of ambient symptoms and preventive measures of coronary artery disease among women. However, these estimations are made from proportions in this study, and distinct conclusions on differences in incidence of ischemic and nonischemic SCD during last 20 years cannot be drawn.

In the present study, a substantial number of females with SCD had a normal or near-normal ECGs prior to death. This suggests that ECG risk markers might not perform as well in women as in men. If traditional prognostic markers for ischemic cardiac disease are thought to poorly predict SCD in women,\textsuperscript{7} traditional prognostic ECG markers do not seem to perform better based on our results. There were no prior ECG abnormalities in 22.2\% of all and in 27.8\% of nonischemic females with SCD, whereas in men, the absence of ECG abnormalities was found among 15.3\% to 16.2\% subjects with SCD.

Prolonged QTc \textasciitilde440/460 ms and QTc \textasciitilde450/470 ms were associated with SCD in both sexes, which is a finding similar to earlier studies,\textsuperscript{20,22–24} but the prevalence of these ECG findings was considerably higher among men than in women. The same applies to prolonged QRS duration and total fragmentation. However, the prevalence of marked QTc prolongation (QTc\textasciitilde490 ms) was similar between men and women. The only exception was LVH which, based on our study, might be used to detect women at risk of SCD, considering the much higher prevalence of this particular ECG abnormality among women than in men and its association with cardiovascular risk. The value of LVH as an ECG marker in women is highlighted in ischemic SCDs, since 22.8\% of the female subjects had LVH-associated findings on prior ECGs, whereas only 10.2\% of males had these findings. In addition, when observed with repolarization abnormalities, LVH was more common in nonischemic SCDs among women than in men (10.2\% versus 4.6\% in women and in men, respectively).

Limitations

In addition, we did not have a specific time of symptom occurrence prior to sudden death, but we used a somewhat lenient 6-hour symptom cut off point in this study. Many subjects with SCD were found dead, and in most, the accurate moment of symptom occurrence is impossible to evaluate. Therefore, we did not want to exclude information on subjects with SCD and prospectively chose to include more subjects in the study. Nevertheless, Finland has the highest autopsy rate of subjects with sudden death in Western societies\textsuperscript{13} because the statute of the Act on the Inquest Into the Cause of Death in Finnish law (459/1973. 7th paragraph). As a result, the Fingesture population contains nearly all subjects with SCD from Northern Finland from 1998 to the present. This decreases the risk of selection bias, even though it might result in some biases, as mentioned in the Discussion section. Unfortunately, in regard to the ECG studies, there were prior ECGs in the medical records of women in approximately one-quarter of subjects with SCD, which may cause a potential bias in this study. Additionally, the timeframe of the ECG recording from the time of death varies significantly. Nevertheless, to our knowledge, the proportion of subjects with prior ECGs in this study is larger than that described in prior studies. We have used standard QT limits for men and women in this study, but there are no uniformly accepted limits for QRS duration, even though there is a subtle difference between men and women. Therefore, we used only QRS 110 ms or over as a cut-off point in this study.

CONCLUSIONS

The present study is the first of its kind to examine the sex differences between autopsy findings, causes of death, and possible ECG findings associated with SCD. We demonstrated that women were more likely to experience nonischemic SCD than men, with PMF a remarkably more common cause of death among women than in men.
Women were considerably older when SCD occurred, and ECGs of female subjects were more likely to be normal than male subjects. This makes the prediction of SCD more demanding in women than in men. The only statistically significant ECG finding that was more common in women than in men was LVH. Based on these results, there are differences in pathogenesis and ECG risk markers of SCD between men and women.

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Disclosures
None.

REFERENCES