Temporal Trends in the Clinical and Pathological Characteristics of Victims of Sudden Cardiac Death in the Absence of Previously Identified Heart Disease

M. Juhani Junttila, MD; Eeva Hookana, PhD; Kari S. Kaikkonen, MD; Marja-Leena Kortelainen, MD; Robert J. Myerburg, MD; Heikki V. Huikuri, MD

Background—Coronary artery disease is identified in ≈80% of victims of sudden cardiac death (SCD). Because the prevention strategies and public awareness have changed during the past decades, we studied the temporal trends in the pathogenesis of SCD.

Methods and Results—FinGesture (n=4031) is a prospective study designed to classify the phenotype and genotype profiles of SCD in a consecutive series of victims of SCD in Northern Finland. On the basis of Finnish law, all subjects who die suddenly undergo autopsy. We analyzed the characteristics of SCD victims and autopsy findings in 1998 to 2002, 2003 to 2007, and 2008 to 2012. Among victims of SCD as a first cardiac event (n=2697), the proportion with coronary artery disease decreased during the 2008 to 2012 time period, compared with the 2 preceding 5-year periods: 74.0% in 1998 to 2002, 73.1% in 2003 to 2007, and 66.4% in 2008 to 2012 (P<0.001). Proportion of SCDs associated with hypertensive heart disease with left ventricular hypertrophy in the absence of coronary artery disease increased from 1.7% in 1998 to 2002 to 5.8% in 2003 to 2007 and 8.9% in 2008 to 2012 (P<0.001). Similarly, myocardial fibrosis in the absence of myocarditis or left ventricular hypertrophy, or other known pathogeneses, was 6.7% in the past 5-year period compared with 2 previous 5-year periods (3.7% and 4.0%; P<0.001 between 1998–2002 and 2008–2012 and between 2003–2007 and 2008–2012).

Conclusions—The proportion of SCDs attributable to coronary artery disease, in the absence of a history of heart disease, has decreased, whereas the proportion associated with hypertensive heart disease and idiopathic fibrosis has increased during the past 15 years. (Circ Arrhythm Electrophysiol. 2016;9:e003723. DOI: 10.1161/CIRCEP.115.003723.)

Key Words: coronary artery disease ■ fibrosis ■ heart disease ■ hypertrophy ■ sudden cardiac death
WHAT IS KNOWN?
• Sudden cardiac death (SCD) is one of the most common modes of death in the Western society.
• Coronary artery disease has been identified in ≈80% of sudden death victims from previous population-based studies followed by cardiomyopathies (10–15%) and inherited arrhythmia syndromes (5%).
• Coronary artery disease therapy and SCD prevention have significantly changed in the past 2 decades. Their impact on the incidence and pathogenesis of SCD is unknown.

WHAT THE STUDY ADDS?
• The incidence of SCD has not significantly changed during the past 15 years in the population from Northern Finland.
• The proportion of coronary artery disease as the underlying pathogenesis for SCD has decreased.
• The proportion of hypertension-related cardiomyopathy and idiopathic myocardial fibrosis has increased in SCD victims.

3 consecutive 5-year periods, from 1998 to 2012, using data from the Finnish Study of Genotype and Phenotype characteristics (FinGesture) of SCD victims without a history of cardiac disease.

Material and Methods

Study Populations
FinGesture study is a prospective study including a consecutive series of autopsy-verified out-of-hospital victims of SCD in a specific geographical area in Northern Finland. The study started in 1998, and the design has been previously reported in detail. The study population consists of prospective accumulation of (n=4031; without previous heart disease n=2697) consecutive white victims of SCD in the Province of Oulu, Northern Finland, on whom postmortem examinations were performed at the Department of Forensic Medicine of the University of Oulu between 1998 and 2012. The sudden death autopsy rate in Finland is the highest in Western societies. Postmortem studies are mandatory in Finland whenever sudden death cannot be attributed to a known disease, the deceased has not been treated by a physician during his/her last illness, or when death has otherwise been unexpected (Act on the Inquest into the Cause of Death, 459/1973, 7th paragraph: Finnish Law). The determination of the cause of death and information about the medical history including drug therapy of the victims of SCD was based on a combination of death certificates, medical records, autopsy data, and the result of a standardized questionnaire completed by the closest family members of the victims of sudden death. The data were collected prospectively and stored at the coordinating center of the Medical Research Center Oulu, University of Oulu. A previously described method for classification of causes of SCD was used for detailed descriptions of the underlying cardiac disease based on postmortem findings, in conjunction with data obtained from medical records and specific questionnaires completed by relatives. Histological examination was performed in all cases of SCD. A toxicology investigation was performed when autopsy findings were insufficient to define a cause of death, or if there was any suspicion of a toxic exposure or cause.

The study complies with the Declaration of Helsinki and the Ethics Committee of the University of Oulu approved the study. The National Supervisory Authority for Welfare and Health (Valvira) approved the review of postmortem data by the investigators.

Statistical Analysis
All analyses were performed with the Statistical Package for Social Studies version 13.0 (SPSS Inc, Chicago, IL). P<0.05 was considered statistically significant. Two-sided t test and χ² analyses were used for comparisons between the study groups. When comparisons were made between the 3 age groups, ANOVA with Bonferroni post hoc analysis was used for multiple comparisons. The reference population used for incidence calculation were the mean population of Oulu Province (1998–2012) and Lapland Province (2010–2012) for each 5-year period.

Results

The demographic data and major clinical characteristics of victims of SCD in 3 consecutive 5-year time periods are presented in Table 1. The mean age at which SCD occurred increased between the first (59.7 years) and last (64.4 years) 5-year period. The prevalence of hypertension, diabetes mellitus, and dyslipidemia also increased between 1998 and 2012. In contrast, the proportion of SCDs in which the event was attributed to an acute coronary syndrome decreased significantly in the course of 15 years from 74.0% to 66.4% (Figure 1).

Table 1. Demographic Features of SCD Victims With No Cardiac History

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>SCD Victims Between Years 1998–2002 (n=768)</th>
<th>SCD Victims Between Years 2003–2007 (n=965)</th>
<th>SCD Victims Between Years 2008–2012 (n=964)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>59.7 (±12.4)*</td>
<td>61.3 (±12.2)†</td>
<td>64.4 (±12.6)‡</td>
</tr>
<tr>
<td>Sex, male</td>
<td>615/768 (80.1)§</td>
<td>763/965 (79.1)†</td>
<td>755/964 (78.3)†</td>
</tr>
<tr>
<td>BMI</td>
<td>27.0 (5.6)</td>
<td>27.6 (6.5)</td>
<td>27.2 (6.3)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>221/764 (28.9)§</td>
<td>355/959 (37.0)†</td>
<td>382/963 (39.7)†</td>
</tr>
<tr>
<td>Diabetes mellitus type I or II</td>
<td>99/766 (12.9)§</td>
<td>172/963 (17.9)§</td>
<td>160/963 (16.6)§</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>34/766 (4.4)§</td>
<td>96/964 (10.0)§</td>
<td>112/963 (11.6)§</td>
</tr>
</tbody>
</table>

Values are expressed as mean (SD) or number of subjects (%). Probability values refer to 1-way ANOVA and χ² analyses between groups. BMI indicates body mass index; and SCD, sudden cardiac death.

*P<0.001 SCD victims between years 1998–2002 vs SCD victims between years 2008–2012.
†P<0.001 SCD victims between years 2003–2007 vs SCD victims between years 2008–2012.
‡P<0.001 SCD victims between years 1998–2002 vs SCD victims between years 2003–2007.
Temporal Trends in Causes of SCD

The overall incidence of SCD as first cardiac event remained relatively stable during the 15-year period. During years 1998 to 2002, the SCD incidence was 1.7/1000, during 2003 to 2007 2.1/1000, and during 2008 to 2012 1.7/1000. The causes of SCD are presented in Table 2. Among victims of SCD as a first cardiac event, the proportion with CAD at autopsy decreased during the time period 2008 to 2012 compared with the 2 preceding 5-year periods: 74.0% in 1998 to 2002, 73.1% in 2003 to 2007, and 66.4% in 2008 to 2012 (P<0.001 between 1998–2002 and 2008–2012 and between 2003–2007 and 2008–2012; Figure 1). At the same time, the proportion with hypertensive heart disease without an autopsy evidence of CAD increased from 1.7% in 1998 to 2002 to 5.8% in 2003 to 2007 and 8.9% in 2008 to 2012 (P<0.001 for all). Similarly, myocardial fibrosis without any known pathogenesis was 6.7% in the past 5-year period compared with 2 previous 5-year periods (3.7% and 4.0%; P<0.001 between 1998–2002 and 2008–2012, and similarly between 2003–2007 and 2008–2012; Figure 2). The use of cardiovascular and diabetes mellitus medication has increased significantly since 1998 to 2002 (Table 3).

Discussion

In this study, we found that among victims of SCD as a first cardiac event, the proportion of CAD at autopsy decreased progressively during the three 5-year intervals between 1998 and 2012. These findings, along with the progressive increase in mean age at the time of SCD, are in line with the trends suggesting a decrease in age-adjusted risk in mortality because of CAD in the Western societies.1–4 The overall incidence of SCDs has not decreased in the same geographical area during this period, but there has been a trend toward an increase in the nonischemic SCD rate during the past 10 years. The decrease in the SCD caused by CAD probably reflects the decreasing trend of ischemic heart disease because of improved primary prevention, such as statin use and lifestyle changes, and improved invasive treatment of acute coronary events. Risk reduction estimates based on published literature have estimated that more than half of the decline in CHD mortality between 1968 and 1976 was attributable to lifestyle changes.22 The risk factor profile data in the Framingham study demonstrated decline in mean systolic blood pressure, cholesterol, and smoking over time.23 In this study, some demographic and clinical variables

Table 2. Underlying Cardiac Disease of Victims of SCD With No Cardiac History

<table>
<thead>
<tr>
<th>Condition</th>
<th>SCD Victims Between Years 1998–2002 (n=768)</th>
<th>SCD Victims Between Years 2003–2007 (n=965)</th>
<th>SCD Victims Between Years 2008–2012 (n=964)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary artery disease</td>
<td>568/768 (74.0)*</td>
<td>705/965 (73.1)†</td>
<td>640/964 (66.4)</td>
</tr>
<tr>
<td>Hypertensive CMP</td>
<td>13/768 (1.7)*</td>
<td>56/965 (5.8)†</td>
<td>86/964 (8.9)†</td>
</tr>
<tr>
<td>Valvular heart disease</td>
<td>9/768 (1.2)</td>
<td>9/965 (0.9)†</td>
<td>11/964 (1.1)†</td>
</tr>
<tr>
<td>Inflammatory cardiac disease</td>
<td>8/768 (1.0)</td>
<td>10/965 (1.3)†</td>
<td>15/964 (1.6)†</td>
</tr>
<tr>
<td>DCM</td>
<td>1/768 (0.1)</td>
<td>5/965 (0.5)†</td>
<td>3/964 (0.3)†</td>
</tr>
<tr>
<td>Alcoholic CMP</td>
<td>42/768 (5.5)</td>
<td>49/965 (5.1)†</td>
<td>82/964 (8.5)†</td>
</tr>
<tr>
<td>HOCM</td>
<td>2/768 (0.2)</td>
<td>1/965 (0.1)</td>
<td>0/964 (0.0)†</td>
</tr>
<tr>
<td>HCM</td>
<td>2/768 (0.2)</td>
<td>6/965 (0.6)</td>
<td>2/964 (0.2)†</td>
</tr>
<tr>
<td>CMP related to obesity</td>
<td>73/768 (9.5)*</td>
<td>77/965 (7.9)†</td>
<td>52/964 (5.4)†</td>
</tr>
<tr>
<td>ARVD</td>
<td>4/768 (0.5)</td>
<td>1/965 (0.1)</td>
<td>1/964 (0.1)†</td>
</tr>
<tr>
<td>Fibrotic CMP</td>
<td>31/768 (4.0)*</td>
<td>36/965 (3.7)†</td>
<td>65/964 (6.7)†</td>
</tr>
<tr>
<td>Structurally normal heart</td>
<td>3/768 (0.4)</td>
<td>6/965 (0.6)</td>
<td>2/964 (0.2)†</td>
</tr>
<tr>
<td>Coronary anomaly</td>
<td>3/768 (0.4)</td>
<td>0/965 (0.0)</td>
<td>0/964 (0.0)†</td>
</tr>
</tbody>
</table>

Values are number of subjects (%). ARVD indicates arrhythmogenic right ventricular dysplasia; CMP indicates cardiomyopathy; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; HOCM, hypertrophic obstructive cardiomyopathy; and SCD, sudden cardiac death.

*P<0.001 SCD victims between years 1998–2002 vs SCD victims between years 2008–2012.
†P<0.001 SCD victims between years 2003–2007 vs SCD victims between years 2008–2012.
‡P<0.001 SCD victims between years 1998–2002 vs SCD victims between years 2003–2007.
differed between the three 5-year periods; age was significantly increased between the first (59.7 years) and last (64.4 years) 5-year period. The prevalence of diagnosed hypertension, diabetes mellitus, and dyslipidemia also increased during the follow-up time. Thus, the proportion of CAD as a cause of SCD had declined during the 15-year time period, but the risk factors for CAD had increased. This is most probably because of improved diagnosis of the risk factor profiles, rather than to worsening of the overall risk profiles of atherosclerotic diseases.

Concomitant to the decrease in the proportion of CAD related to SCD, the proportion of nonischemic SCD has increased. Most striking feature within the increased nonischemic SCD population is the significant increase in hypertension-related cardiomyopathy and idiopathic myocardial fibrosis, which both present accumulation of fibrotic tissue in myocardium. The significant proportional increase in hypertension-related cardiomyopathy might be explained by the increase in mean age of the SCD victims during the 15-year time period. Another reason might be the known fact that most subjects with hypertension do not meet the blood pressure goals during the follow-up time. Thus, the proportion of CAD as a cause of SCD had increased. This is most probably because of improved diagnosis of the risk factor profiles, rather than to worsening of the overall risk profiles of atherosclerotic diseases.

Table 3. Medications of the SCD Victims

<table>
<thead>
<tr>
<th>Medication</th>
<th>SCD Victims Between Years 1998–2002 (n=768)</th>
<th>SCD Victims Between Years 2003–2007 (n=965)</th>
<th>SCD Victims Between Years 2008–2012 (n=964)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antihypertensive medication</td>
<td>221/764 (28.9)*†</td>
<td>355/959 (37.0)</td>
<td>382/963 (39.7)</td>
</tr>
<tr>
<td>Statins</td>
<td>17/610 (2.8)*†</td>
<td>75/764 (9.8)</td>
<td>82/794 (10.3)</td>
</tr>
<tr>
<td>Antidiabetic medication</td>
<td>42/615 (6.8)*</td>
<td>94/775 (12.1)</td>
<td>74/796 (9.3)</td>
</tr>
<tr>
<td>Asthma or COPD medication</td>
<td>39/615 (6.3)</td>
<td>76/775 (9.8)</td>
<td>63/796 (7.9)</td>
</tr>
<tr>
<td>Psychotrophic medication</td>
<td>139/615 (22.6)</td>
<td>197/788 (25.0)</td>
<td>163/803 (20.3)</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>55/610 (9.0)</td>
<td>79/775 (10.2)</td>
<td>73/786 (9.3)</td>
</tr>
<tr>
<td>Antipsychotics</td>
<td>78/609 (12.8)</td>
<td>96/775 (12.4)</td>
<td>76/788 (8.6)</td>
</tr>
<tr>
<td>Antiepileptic medication</td>
<td>45/768 (5.9)</td>
<td>39/965 (4.0)*†</td>
<td>68/820 (8.3)</td>
</tr>
</tbody>
</table>

Values are number of subjects (%). COPD indicates chronic obstructive pulmonary disease; and SCD, sudden cardiac death.

†P<0.001 SCD victims between years 1998–2002 vs SCD victims between years 2006–2012.
‡P<0.001 SCD victims between years 2003–2007 vs SCD victims between years 2008–2012.

Figure 2. Proportion of hypertensive cardiomyopathy and idiopathic myocardial fibrosis as a cause of sudden cardiac death during 1998 to 2012. HTA indicates hypertensive heart disease; and IMF, idiopathic myocardial fibrosis.
our area. Alternatively, it may have been under diagnosed as a cause of SCD in countries where meticulous autopsies, including histological examinations, are not routinely performed.

Limitations

The present research included only white subjects from Finland. There may be racial and geographical differences in the epidemiology of SCD. Therefore, the present results cannot be completely generalized to other societies. The autopsies were performed by different forensic pathologists. Although all of them were experienced pathologists, there may be some interobserver differences in the definitions of autopsy findings between the pathologists.

Conclusions

In conclusion, the proportion of SCDs attributable to CAD, in the absence of a history of heart disease, has been decreasing, whereas the proportion associated with hypertensive heart disease and idiopathic fibrosis has been increasing between 1998 and 2012.

Sources of Funding

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Disclosures

None.

References


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