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

M. Juhani Junnila, 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

Age-adjusted death rates because of cardiac disease has decreased dramatically in industrialized countries during the past 30 years.1–4 Despite recent progress in prevention and treatment of coronary artery disease (CAD), sudden cardiac death (SCD) remains a major public health challenge, representing close to one fifth of all mortality in developed countries. Up to 50% of SCD victims are not known to have had heart disease or impaired cardiac function (left ventricular ejection fraction <35%) before the fatal event. Our ability to recognize risk among subjects in this general population before the event is severely limited.5

The total population burden of SCD because of CAD remains incompletely defined and debated.6 Estimates of the total number of SCDs annually in the United States are based largely on retrospective death certificate analyses,7 8 the American Heart Association statistical updates based on data from the National Center for Health Statistics,9 and nationwide extrapolations from well-studied community experiences.10–11 The most widely cited estimates have remained in the range of 300000 to 350000 SCDs annually since the early 1980s,12 suggesting an overall incidence between 1 and 2 deaths per 1000 person-years among the general population.13 However, estimates from the same death certificate sources range from 250000 SCDs to 460000 SCDs annually. The current number may be influenced by the impact of therapies intended for the prevention of CAD; interventions during acute coronary syndromes, and therapies for chronic ischemic heart disease. Therefore, although it is possible that previous estimates of SCD incidence and numbers may overestimate current risk, a recent in depth analysis of available data suggests a burden remaining >350000/y in the United States.14 Regardless of changes in the absolute numbers of the SCD burden, it remains generally accepted that the proportion of all SCDs resulting from CAD remains at 80% and that SCD accounts for 50% of all CAD-related deaths, with ≤50% of these deaths being first cardiac events.15

Because the primary prevention strategies, public awareness of early symptoms of CAD, and secondary prophylaxis has changed during the past 2 decades, we studied the temporal trends in the pathogenesis of unexpected SCD during
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.16–19 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.20,21 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).19–21 The determination of the cause of death and information about the medical history including drug therapy of the victims of SCD were 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.16–15 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 SCD19 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.
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 |
|-----------------------------|-----------------------------|-----------------------------|
|                             | SCD Victims Between Years 1998–2002 (n=768) | SCD Victims Between Years 2003–2007 (n=965) | SCD Victims Between Years 2008–2012 (n=964) |
| Coronary artery disease      | 568/768 (74.0)*              | 705/965 (73.1)†              | 640/964 (66.4)                           |
| Hypertensive CMP             | 13/768 (1.7)†‡              | 56/965 (5.8)‡               | 86/964 (8.9)                             |
| Valvular heart disease       | 9/768 (1.2)                 | 9/965 (0.9)                | 11/964 (1.1)                            |
| Inflammatory cardiac disease | 8/768 (1.0)                 | 10/965 (1.3)               | 15/964 (1.6)                            |
| DCM                         | 1/768 (0.1)                 | 5/965 (0.5)                | 3/964 (0.3)                             |
| Alcoholic CMP                | 42/768 (5.5)                | 49/965 (5.1)†              | 82/964 (8.5)                            |
| HOCM                        | 2/768 (0.2)                 | 1/965 (0.1)                | 0/964 (0.0)                             |
| HCM                         | 2/768 (0.2)                 | 6/965 (0.6)                | 2/964 (0.2)                             |
| CMP related to obesity       | 73/768 (9.5)*               | 77/965 (7.9)               | 52/964 (5.4)                            |
| ARVD                        | 4/768 (0.5)                 | 1/965 (0.1)                | 1/964 (0.1)                             |
| Fibrotic CMP                | 31/768 (4.0)*               | 36/965 (3.7)†              | 65/964 (6.7)                            |
| Structurally normal heart    | 3/768 (0.4)                 | 6/965 (0.6)                | 2/964 (0.2)                             |
| Coronary anomaly             | 3/768 (0.4)                 | 0/965 (0.0)                | 0/964 (0.0)                             |

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.
increased recognition of the entity, but the diagnosis requires increased risk factors for CAD had increased. This is most probably because of improved detection 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 15-year time period. Another reason might be the known fact that most subjects with hypertension do not meet the blood pressure goals described in the guidelines.24 In addition, 1 explanation for the increase in idiopathic myocardial fibrosis phenomenon is the increased recognition of the entity, but the diagnosis requires exclusion of other underlying pathogeneses for SCD and thus would not be a surrogate finding rising from other entities. At the same time, the proportion of SCD in structurally normal hearts has remained the same. Obvious reasons for the observation that the incidence of SCD itself has not decreased are that the age of the victims of SCD has increased and at the same time the prevalence of cardiac disease related to obesity/diabetes mellitus and hypertension have increased in victims of SCD. Thus, there seems to be a shift toward a reduced number of ischemic heart diseases in younger SCD victims and at the same time an increased number of hypertensive and obesity/diabetic heart disease as a cause of SCD in older subjects.

Two other significant European SCD autopsy efforts have been described lately: the Veneto study from Italy and the Danish autopsy study.25,26 In addition to our study, the Veneto study is a prospective effort, and the Danish study is retrospective in nature. In the Danish study, the proportion of SCD in structurally normal hearts is significantly larger than in our study and the Veneto study. One reason could be the difference in rigorous histological studies of the myocardium. In our study, histological studies of the myocardium have been a prerogative since the beginning. To our knowledge this was also the case in the Veneto study. Histological studies reveal fine interstitial fibrosis undetectable by gross anatomic examinations. In Veneto study, structurally normal myocardium was detected almost as seldom as in our study, but in their study fibrosis was interpreted as arrhythmogenic ventricular cardiomyopathy, which seems to be endemic in their geographical area. In North Finland, clinical arrhythmogenic right ventricular dysplasia/cardiomyopathy is rare and thus it would be unlikely that the entity would be over-represented among SCD autopsy population. Nevertheless, it remains to be studied whether the population with idiopathic myocardial fibrosis includes subjects with arrhythmogenic right ventricular dysplasia/cardiomyopathy or primary ion channelopathies. We are currently conducting more research to define the reasons for idiopathic fibrosis in our database, including molecular genetics, micro-RNA assays, and detailed phenotyping. It is possible that idiopathic fibrosis, occurring often in young victims with an SCD, is a unique disease entity observed only locally in

<table>
<thead>
<tr>
<th>Table 3. Medications of the SCD Victims</th>
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<tbody>
<tr>
<td>SCD Victims Between Years 1998–2002 (n=768)</td>
</tr>
<tr>
<td>Antihypertensive medication</td>
</tr>
<tr>
<td>Statins</td>
</tr>
<tr>
<td>Antidiabetic medication</td>
</tr>
<tr>
<td>Asthma or COPD medication</td>
</tr>
<tr>
<td>Psychotropic medication</td>
</tr>
<tr>
<td>Antidepressants</td>
</tr>
<tr>
<td>Antipsychotics</td>
</tr>
<tr>
<td>Antiepileptic medication</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 2008–2012.

P<0.001 SCD victims between years 2003–2007 vs SCD victims between years 2008–2012.
our area. Alternatively, it may have been under diagnosed as a cause of SCD in countries where metoliculous 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.

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This study was funded by the Sigrid Juselius Foundation and the Foundation of Cardiac Research, Helsinki, Finland.

Disclosures
None.

References
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