Comparison of Family History of Sudden Cardiac Death in Nonischemic and Ischemic Heart Disease

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Background—Recent studies have identified the presence of familial clustering of ischemic sudden cardiac death (SCD) as a clinical expression of coronary artery disease. The purpose of this study was to determine whether nonischemic SCD has a similar familial background, which would be evidence of a genetic predisposition.

Methods and Results—The retrospective case-control study included (1) consecutive victims of nonischemic SCD (n=223), (2) consecutive victims of ischemic SCD (n=596), whose deaths and diagnosis were verified at medicolegal autopsy, and (3) control subjects without heart disease (n=475). In each study group, the family history of SCD among the first-degree relatives was determined and verified from death certificates. The prevalence of SCD in ≥1 first-degree relative was significantly higher in victims of ischemic (34.2%) than nonischemic SCD (13.4%; P<0.001) or controls (17.6%; P<0.001). The history of SCD in first-degree relatives did not differ from controls in nonischemic SCD victims (P=0.155). In a subgroup analysis of victims of ischemic SCD, the prevalence of family history of SCD in first-degree relatives did not differ between those with or without a prior infarct scar at autopsy (33.1% versus 29.9%, respectively; P=0.222).

Conclusions—Ischemic SCD has a strong familial background both in cases with and without a prior myocardial infarction. The family history of SCD is not significantly increased in victims of nonischemic SCD, suggesting a larger role of sporadic occurrence than inherited traits as the cause of nonischemic SCD. (Circ Arrhythm Electrophysiol. 2012;5:757-761.)

Key Words: cardiomyopathy • death, sudden • ischemic heart disease

Results from previous studies have identified the presence of familial clustering of sudden cardiac death (SCD) as a clinical expression of coronary artery disease.1–4 In the study by Jouven et al,2 multivariate analysis indicated that the occurrence of SCD in a parent or first-degree relative (FDR) led to a 1.6- to 1.8-fold increase in SCD susceptibility after controlling for traditional risk factors of coronary artery disease. The risk of SCD seemed to be high if ≥2 FDRs had experienced SCD.3 The case-control study by Friedlander et al4 showed that a family history of acute myocardial infarction (AMI) or sudden death was more common among victims of SCD than among controls. A Dutch study also showed that a family history of SCD was common among those who experienced ventricular fibrillation during AMI.4 In our previous study, a family history of SCD was more common among the victims of autopsy-verified SCD because of an acute coronary event compared with survivors of AMI.5 All these previous studies have focused on family history of SCD in victims of ischemic SCD.

Clinical Perspective on p 761

A nonischemic cause of SCD, mostly because of various cardiomyopathies (CMPs), accounts for ≥20% of all SCDs, but there is no information about the familial background of SCD caused by CMPs at the community level. Therefore, we compared the familial clustering of SCD in victims of nonischemic and ischemic SCD collected from the Finnish Study of Genotype and Phenotype Profile of SCD (FinGesture). A random population sample without any documented heart disease served as the control group. Furthermore, we wanted to examine whether the family history of SCD differs in ischemic SCD between those with and without a prior AMI because the mechanism of cardiac arrhythmia causing cardiac arrest may differ between these subgroups.

Material and Methods

Study Populations

The FinGesture study population was derived from 2661 consecutive victims of SCD in the province of Oulu, Northern Finland, among whom postmortem examinations were performed at the Department of Forensic Medicine of the University of Oulu between 1998 and 2007. The FinGesture database contains 6557 instances of noncardiac causes of sudden death. Victims with noncardiac causes of sudden death, as well as those with normal autopsy (n=9), were excluded from the present study. SCD victims with a witnessed sudden death within 6 hours of the onset of symptoms or within 24 hours of the time the victim was last seen alive in a normal state of health were included in the study.

Because postmortem studies are mandatory in Finland when SCD cannot be attributed to a known disease, when the deceased has not been treated by a physician during his/her last illness, or when death has been otherwise unexpected (Act on the Inquest into the Cause of Death, 459/1973, 7th paragraph: Finnish Law),6 selection...
bias of forensic studies of victims with unexpected SCD is minimal. The definition of the cause of death and information about the SCD victims were based on a combination of medical records, autopsy data, and result of a standardized questionnaire answered by the closest family members of the victims of SCD and were reported according to International Classification of Diseases, Tenth Revision, code classes. Furthermore, the classification, described elsewhere, was used for more detailed descriptions of the underlying cardiac disease based on postmortem findings, in conjunction with data obtained from medical records and specific questionnaires of 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 suspicion of a toxic exposure or cause. The investigation system for sudden death and the means by which a history was obtained are described in the Figure. After exclusion of cases in whom reliable information about SCD of FDRs was not available from questionnaires or death certificates, 223 (38.5%) of 579 SCD victims with a nonischemic CMP and 596 (28.6%) of 2082 victims of ischemic SCD were included in the study.

To clarify the prevalence of family history of SCD in the general population, a control group without a history of coronary heart disease, AMI, aborted cardiac arrest, or echocardiographic evidence of heart disease was included in the study. The controls were subjects from the Oulu Project Elucidating Risk of Atherosclerosis (OPERA) study of randomly selected subjects from the social insurance register covering the entire population of the city of Oulu. The mean age of subjects at the beginning of the study was 51 years. The survey of family history was performed 12 years later, and the follow-up of this group has been extended up to 17 years so that the mean age of controls did not differ from that of ischemic SCD victims. Subjects who died of any cardiac cause during follow-up were excluded from the present study. A total of 475 controls were included.

Familial background of SCD in FDRs (each biological parent, siblings, or a child) was ascertained by telephone call to the controls and by using a previously described questionnaire forwarded to the closest relatives of the victims of SCD. The reported SCD cases in FDRs were verified from death certificates from the Central Statistics Office in Finland and the Causes of Death Register. 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 SPSS version 13.0 (SPSS Inc, Chicago, IL). P<0.05 was considered statistically significant. One-way ANOVA and logistic regression analyses were used for comparisons between study groups. Bonferroni correction was used as the post hoc test for 1-way ANOVA. Logistic regression analysis was used to assess the significance of family history of SCD between groups after adjustment for age, sex, smoking, body mass index, history of diabetes mellitus, hypertension or angina pectoris, number of FDRs, and rate of adequate information about the mode of death of the family members in each group. The generalized estimating equation analysis, which adjusts for the correlation among family members, was also performed. χ² analysis was used for comparison of SCD among FDRs between the victims of ischemic SCD with or without an infarct scar at autopsy.

Results
Characteristics
Table 1 presents the demographic data and some clinical features of victims of SCD and controls. Age and body mass index differed between the groups; nonischemic victims were younger and had higher body mass index than ischemic SCD victims or controls. Smoking status also differed.

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Figure. Investigation system for sudden death and the means by which a history was obtained. SCD indicates sudden cardiac death.
Table 1. Characteristics of Study Subjects

| Characteristic | Victims of Nonischemic SCD (n=223) | Victims of Ischemic SCD (n=596) | Controls (n=459) |
|----------------|----------------------------------|---------------------------------|-----------------
| Age, y         | 53.4 (11.3)*†                    | 64.9 (11.2)                     | 62.5 (5.8)      |
| Sex (male)     | 176/223 (78.9)†                   | 483/596 (81.0)‡                  | 252/459 (54.9)  |
| BMI, kg/m²     | 30.0 (7.9)*†                      | 26.7 (4.9)                      | 27.2 (4.3)      |
| Smoking status | Never                            | 204/596 (34.2)                  | 202/406 (49.8)  |
|                | Ex-smoker                        | 26/223 (11.7)                   | 99/406 (24.3)   |
|                | Current                          | 266/596 (44.6)                  | 105/406 (25.9)  |
| Type I or II diabetes mellitus | 50/223 (22.4)†                    | 153/596 (25.6)‡                 | 6/424 (1.4)     |

SCD indicates sudden cardiac death; BMI, body mass index.

Values are expressed as mean (SD) or number of subjects (%). Probability values refer to 1-way ANOVA and logistic regression analyses between groups.

*P<0.001 nonischemic SCD vs ischemic SCD.
†P<0.001 nonischemic SCD vs control.
‡P<0.001 ischemic SCD vs control.

between the groups, with the number of current smokers being significantly higher among the victims of nonischemic and ischemic SCD compared with controls. The prevalences of hypertension and diabetes mellitus were more common in nonischemic SCD victims compared with controls. The same was true when comparing ischemic SCD victims with controls. Only about one third of the nonischemic SCD victims had a cardiac history, thus in ≈70% of the victims death was the first manifestation of cardiac disease. In ischemic SCDs, a cardiac history existed in 40% of the victims.

Family History of SCD

The prevalence of a positive family history of SCD was more common in ischemic (34.2%) versus nonischemic (13.4%) SCD cases (odds ratio [OR], 4.3; 95% CI, 2.1–8.7; P<0.001; adjusted OR, 5.3; 95% CI 2.0–14.4; P=0.001) (Table 2). However, a history of SCD in ≥2 FDRs was also higher in ischemic (14.7%) than nonischemic SCD (4.0%) victims (OR, 4.3; 95% CI, 1.8–21.5; P<0.001; adjusted OR, 6.2; 95% CI, 1.8–21.5; P=0.004). Similarly, victims of ischemic SCD had a higher prevalence of SCD in FDRs compared with controls (17.6%) compared with controls (14.7%) of ischemic SCD compared with controls (1.3%) (OR, 2.9; 95% CI, 1.1–8.5; P=0.040; adjusted OR, 19.0; 95% CI, 1.2–308.6; P=0.039).

The total number of SCD cases among the total number of FDRs of the victims of nonischemic SCD (3.2%) did not differ from controls (2.4%) (Table 3). However, the number of SCDs among FDRs was significantly higher in victims of ischemic (5.8%) than nonischemic SCD (3.2%) (OR, 2.9; 95% CI, 1.9–4.5; P<0.001; adjusted OR, 2.1; 95% CI, 1.2–3.7; P=0.011). Furthermore, the number of SCD cases among the FDRs of the ischemic SCD victims (5.8%) was higher than in controls (2.4%) (OR, 2.1; 95% CI, 1.6–2.8; P<0.001; adjusted OR, 1.6; 95% CI, 1.1–2.5; P=0.027).

Dependence of correlation among family members on the presence of family history was taken into account with generalized estimating equation analysis; the family members of victims of ischemic SCD were more likely to have another SCD in their family compared with family members of victims of nonischemic SCD (OR, 1.8; 95% CI, 1.1–2.9; P=0.011). The difference was not significant between the family members of the victims of nonischemic SCD and the family members of control cases (OR, 1.3; 95% CI, 0.8–2.2; P=0.234), whereas the prevalence was statistically significant between the family members of the victims of ischemic SCD.

Table 2. Family History of SCD

<table>
<thead>
<tr>
<th>Family History of SCD</th>
<th>Victims of Nonischemic SCD (n=223)</th>
<th>Victims of Ischemic SCD (n=596)</th>
<th>Controls (n=459)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>30/223 (13.4)*†</td>
<td>204/596 (34.2)‡</td>
<td>81/459 (17.6)</td>
</tr>
<tr>
<td>Yes, &gt;1 SCD among FDR</td>
<td>9/223 (4.0)*†</td>
<td>88/596 (14.7)‡</td>
<td>6/459 (1.3)</td>
</tr>
</tbody>
</table>

SCD indicates sudden cardiac death; FDR, first-degree relative.

Values are number of subjects (%). Probability values refer to logistic regression analysis between groups.

*P<0.001 nonischemic SCD vs ischemic SCD.
†P<0.05 nonischemic SCD vs control.
‡P<0.001 ischemic SCD vs control.

Table 3. Total Number of SCDs Among the Total Number of First-Degree Relatives

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Victims of Nonischemic SCD (n=223)</th>
<th>Victims of Ischemic SCD (n=596)</th>
<th>Controls (n=459)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertensive CMP (n=31)</td>
<td>3/31 (9.7)</td>
<td>1/1 (100.0)</td>
<td>0/0 (0.0)</td>
</tr>
<tr>
<td>Inflammatory cardiac disease (n=1)</td>
<td>1/1 (100.0)</td>
<td>1/1 (100.0)</td>
<td>0/0 (0.0)</td>
</tr>
<tr>
<td>DCM (n=9)</td>
<td>0/9 (0.0)</td>
<td>0/9 (0.0)</td>
<td>0/0 (0.0)</td>
</tr>
<tr>
<td>Alcoholic CMP (n=21)</td>
<td>3/21 (14.3)</td>
<td>3/21 (14.3)</td>
<td>0/0 (0.0)</td>
</tr>
<tr>
<td>HCM (n=9)</td>
<td>3/9 (33.3)</td>
<td>3/9 (33.3)</td>
<td>0/0 (0.0)</td>
</tr>
<tr>
<td>CMP related to obesity (n=103)</td>
<td>13/103 (12.6)</td>
<td>13/103 (12.6)</td>
<td>0/0 (0.0)</td>
</tr>
<tr>
<td>ARVD (n=4)</td>
<td>0/4 (0.0)</td>
<td>0/4 (0.0)</td>
<td>0/0 (0.0)</td>
</tr>
<tr>
<td>Fibrotic CMP (n=45)</td>
<td>7/45 (15.6)</td>
<td>7/45 (15.6)</td>
<td>0/0 (0.0)</td>
</tr>
</tbody>
</table>

SCD indicates sudden cardiac death; CMP, cardiomyopathy; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; ARVD, arrhythmogenic right ventricular dysplasia.

Values are number of subjects (%).

Table 4. Family History of SCD in Nonischemic SCDs

<table>
<thead>
<tr>
<th>Cause of Nonischemic SCD (n=223)</th>
<th>Family History of SCD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cause of Nonischemic SCD (n=223)</td>
<td></td>
</tr>
<tr>
<td>Hypertensive CMP (n=31)</td>
<td>3/31 (9.7)</td>
</tr>
<tr>
<td>Inflammatory cardiac disease (n=1)</td>
<td>1/1 (100.0)</td>
</tr>
<tr>
<td>DCM (n=9)</td>
<td>0/9 (0.0)</td>
</tr>
<tr>
<td>Alcoholic CMP (n=21)</td>
<td>3/21 (14.3)</td>
</tr>
<tr>
<td>HCM (n=9)</td>
<td>3/9 (33.3)</td>
</tr>
<tr>
<td>CMP related to obesity (n=103)</td>
<td>13/103 (12.6)</td>
</tr>
<tr>
<td>ARVD (n=4)</td>
<td>0/4 (0.0)</td>
</tr>
<tr>
<td>Fibrotic CMP (n=45)</td>
<td>7/45 (15.6)</td>
</tr>
</tbody>
</table>

SCD indicates sudden cardiac death; CMP, cardiomyopathy; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; ARVD, arrhythmogenic right ventricular dysplasia.

Values are number of subjects (%).
members of victims of ischemic SCD and the family members of controls (OR, 2.4; 95% CI, 1.9–3.1; \(P<0.001\)).

The prevalence of SCD among the FDRs of victims of nonischemic SCD with various underlying causes of cardiac disease is described in Table 4. Only those with a hypertrophic cardiomyopathy (HCM) tended to have a higher prevalence of SCD in FDRs compared with the other groups or controls, the prevalence being in the same range as in those with ischemic SCD.

In a subgroup analysis of victims of ischemic SCD with and without autopsy evidence of an old infarct scar, there was no difference in family history of SCD between those with (33.1%) and without an infarct scar (29.9%) \((P=0.222)\).

Discussion

The results of the present study support the concept that even though nonischemic heart disease may be partly caused by inherited traits, the vast number of cases of nonischemic heart disease has a sporadic occurrence. We also confirm here in a large sample of victims of SCD with autopsy-verified coronary artery disease that ischemic SCD has a strong familial background so that 1 of 3 victims of SCD has had ≥1 SCD among their FDRs, in those both with and without a previous AMI.

Some demographic and clinical variables differed between the groups. Victims of nonischemic SCD were younger and their body mass index was higher than in the victims of ischemic SCD or controls. The number of current smokers was also highest in the nonischemic SCD group. A history of hypertension and diabetes mellitus was more common in the victims of SCD compared with controls. Thus, the risk profile of victims of SCD differed in several aspects from those of controls. When the prevalence of SCD in FDRs was adjusted with these features in the statistical analyses, the main results remained the same, suggesting that the strong family history of SCD in those with ischemic heart disease is not simply the result of inheritance of specific risk factors of SCD, such as smoking, hypertension, or diabetes mellitus, but some other genetic factors are probably involved in ischemic SCD.

Family History of SCD in Nonischemic Heart Disease

In previous studies, it has been claimed that in subjects with well-defined SCD syndromes, having a family history noticeably increases the risk of SCD. For example, a family history of SCD in patients with HCM is associated with a 5-fold risk of SCD. In the analysis of various subtypes of nonischemic SCD in the present study, a family history of SCD was also relatively common (33%) in SCD victims with evidence of HCM at autopsy. However, the number of cases with HCM was relatively low in the present population of victims of SCD. Consequently, the overall prevalence of family history of SCD remained low in the total sample of nonischemic cases. HCM has been reported to be the most frequently occurring CMP and the most common monogenic cardiac disorder in the United States. A previous study also indicated that HCM is the most common cause of SCD in the young. It is evident that the reported causes of nonischemic SCD are variable among different populations and may be because of differences in genetic profiles and features of acquired heart disease between various countries. In addition, autopsy rates and reporting of autopsy results are clearly different between countries.

The causes of nonischemic SCD of the present study differ from those reported previously. In accordance with the present study, we recently reported in a larger sample size that obesity, alcoholic CMP, and idiopathic myocardial fibrosis were more prevalent causes of nonischemic SCD than causes of nonischemic SCD reported previously. This may partly explain the lack of familial clustering of nonischemic SCD in our population. The inheritance of the most prevalent causes of nonischemic SCD does not seem to be as straightforward as that of specific arrhythmia syndromes, such as arrhythmogenic right ventricular dysplasia and HCM, which seem to be more prevalent causes of SCD in other populations. It should also be noted that we excluded subjects with a normal autopsy, which excludes victims of SCD caused by inherited ion channel disorders, such as long-QT or Brugada syndrome.

Despite the lack of differences in SCD between the total number of FDRs of the victims of nonischemic SCD and controls (Table 3), the number of >1 SCD in the FDRs was somewhat higher in the nonischemic group than controls (Table 2). This may be because of inherited monogenic mutations with a high penetrance of disease in some families with nonischemic SCD. However, the number of these cases was also relatively small, resulting in a low overall prevalence of family history of SCD in nonischemic cases.

Family History of SCD in Ischemic Heart Disease

We have previously reported an increased family history of SCD in a series of 138 victims of SCD because of an acute coronary event compared with survivors of such an event. The present data confirm and extend these results to a larger sample size. We also performed here a subgroup analysis of family history of SCD in those with and without an old infarct scar at autopsy because the pathophysiological mechanism of SCD of these 2 entities may differ. Ventricular tachycardia related to the presence of an infarct scar has been proposed to be the primary initiating arrhythmia leading to cardiac arrest in those with an old infarct scar, whereas primary ventricular fibrillation has been considered to be the major mechanism of cardiac arrest in individuals without an infarct scar. However, no differences were observed in the family history of SCD between these 2 groups, suggesting that genetic factors may play a similar role in SCD in those who have cardiac arrest as the first manifestation of their cardiac disease and in those with a history of a cardiac disease.

Study Limitations

Resuscitated victims of cardiac arrest were not a part of the FinGesture study. Distances in Northern Finland are long, and, therefore, certain rural effect may cause a bias in cardiac arrest survival. Nevertheless, most victims were found dead at home, and the resuscitation attempts were mostly useless. Also, coronary spasm cannot be excluded by autopsy. Especially in some of the obese and smoking victims of nonischemic SCD, the possibility of vasospasm and ischemic ventricular fibrillation cannot be entirely left out. However, all major coronary branches have been dissected and analyzed for coronary plaques followed by a histological analysis, if there is any suspicion of
even minor coronary plaque complication, minimizing the possibility of false-negative result of ischemic SCD.

Despite the collection a consecutive victims of SCD over a long time period in the FinGesture study, we were able to obtain a relatively small sample number of victims of nonischemic SCD. Lack of reliable family history from the closest relatives of the victims of SCD, including the review of death certificates, was the main obstacle preventing the collection of a larger sample. Especially when various subgroups of the victims of nonischemic SCD were being compared, the number of cases in each group was small, which hindered reliable statistical comparisons. Another difficulty was gaining accurate data through phone calls and questionnaires to family members of deceased individuals. However, as far as we are aware, this is the first study examining the family history of SCD in nonischemic SCD. We also acknowledge that the reported causes of nonischemic SCD are variable among different populations, and these features of the Finnish population in regard to the family history of nonischemic SCDs may not be generalizable to other parts of the world. Despite these limitations, we feel that these results may have some relevance in future studies of SCD, such as in defining the cases for genotype-phenotype association studies. There should be emphasis placed on ischemic SCD so that, ideally, nonischemic SCD cases can be excluded from these types of studies.

Conclusions
Ischemic SCD has a strong familial background in individuals with and without evidence of a previous myocardial infarction. Future research should focus on clarifying the reasons for familial clustering of SCD in ischemic heart disease. SCD is not over-represented in families of victims of nonischemic SCD without HCM or inherited ion channel disorders. The prevention of obesity and heavy alcohol consumption may be key factors in reducing nonischemic SCD at the community level.

Disclosures
None.

References

CLINICAL PERSPECTIVE
Recent studies have identified the presence of familial clustering of ischemic sudden cardiac death (SCD) as a clinical expression of coronary artery disease. The purpose of this study was to determine whether nonischemic SCD has a similar familial background, which would give evidence for a genetic predisposition. The results of the present study support the concept that even though a part of nonischemic heart disease may be because inherited traits, the vast number of cases of nonischemic heart disease has a sporadic occurrence. We also confirm here in a large sample of victims of SCD with autopsy-verified coronary artery disease that ischemic SCD has a strong familial background, so that 1 of 3 SCD victims have had ≥1 SCDs in their first-degree relatives among those with and without a previous myocardial infarction. Future research should focus on clarifying the reasons for familial clustering of SCD in ischemic heart disease. SCD does not seem to be over-represented in families of victims of nonischemic SCD without hypertrophic cardiomyopathy or inherited ion channel disorders. The prevention of obesity and heavy alcohol consumption may be key factors in reducing nonischemic SCD at the community level.
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