Comparison of Family History of Sudden Cardiac Death in Non-ischemic and Ischemic Heart Disease

Running title: Hookana et al.; Family history of sudden cardiac death

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Abstract:

**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 non-ischemic SCD has a similar familial background, which would be evidence for a genetic predisposition.

**Methods and Results** - The retrospective case-control study included 1) consecutive victims of non-ischemic SCD (N=223), 2) consecutive victims of ischemic SCD (N=596), whose deaths and diagnosis were verified at medico-legal autopsy, and 3) control subjects without heart disease (N=475). In each study group, the family history of SCD among the first-degree relatives (FDR) was determined and verified from death certificates. The prevalence of SCD in one or more FDRs was significantly higher in the victims of ischemic (34.2%) than non-ischemic SCD (13.4%, P<0.001) or controls (17.6%, P<0.001). The history of SCD in FDRs did not differ in non-ischemic SCD victims from controls (P=0.155). In a subgroup analysis of victims of ischemic SCD, the prevalence of family history of SCD in FDRs did not differ between those with or without a prior infarct scar at autopsy (33.1 % vs. 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 non-ischemic SCD, suggesting to a larger role of sporadic occurrence than inherited traits as the cause of non-ischemic SCD.

**Key words:** cardiomyopathy; death, sudden; ischemic heart disease
Results from previous studies have identified the presence of familial clustering of SCD as a clinical expression of coronary artery disease (CAD) 1-4. In the study of Jouven et al. (1999), multivariate analysis indicated that the occurrence of SCD in a parent or first-degree relative led to a 1.6- to 1.8-fold increase in SCD susceptibility after controlling for traditional risk factors for CAD 2. The risk of SCD appeared to be high if 2 or more first-degree relatives (FDRs) had experienced SCD 3. The case-control study of Friedlander et al. showed that a family history of acute myocardial infarction or sudden death was more common among victims of SCD than among control subjects 1. A Dutch study also showed that a family history of SCD was common among those who experienced ventricular fibrillation during acute myocardial infarction (AMI) 4.

In our previous study, a family history of SCD was more common among the victims of autopsy verified SCD due to an acute coronary event as compared to survivors of AMI 3. All these previous studies have focused on family history of SCD in victims of ischemic SCD.

A non-ischemic etiology of SCD, mostly due to various cardiomyopathies (CMP), accounts for about 20% of all SCDs, but there is no information on the familial background of SCD caused by CMP at the community level. Therefore, we compared the familial clustering of SCD in victims of non-ischemic 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 2,661 consecutive victims of SCD in the Province of Oulu, Northern Finland, among whom post-mortem examinations were performed at the Department of Forensic Medicine of the University of Oulu between 1998 and 2007. The number of non-cardiac causes of sudden death is 6,557 in the FinGesture database. Victims with non-cardiac 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 that the victim was last seen alive in a normal state of health were included in the study.

Since post-mortem studies are mandatory in Finland whenever SCD 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 been otherwise unexpected (Act on the Inquest into the Cause of Death, 459/1973, 7th paragraph: Finnish Law)\(^5\), selection bias of forensic studies in victims with unexpected SCD is minimal. The definition of the cause of death and information about the SCD victims were based on combination of medical records, autopsy data, and the result of a standardized questionnaire answered by the closest family members of the victims of SCD\(^3\), and was reported according to ICD-10 code classes. Furthermore, the classification, described elsewhere\(^6\), was used for more detailed descriptions of the underlying cardiac disease based on post-mortem 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. Investigation system for sudden death and the means by which a history was obtained is described in Figure 1. After exclusion of those cases in whom reliable information on the SCD of FDRs was not available
from questionnaires or death certificates, 223 (38.5%) of 579 SCD victims with a non-ischemic 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 OPERA (Oulu Project Elucidating Risk of Atherosclerosis) study on randomly selected subjects from the social insurance register covering the entire population of the city of Oulu\textsuperscript{7}. The mean age of subjects at the beginning of the study was 51 years. The survey on 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 those of the ischemic SCD victims. Subjects who died for any cardiac cause during the follow-up were excluded from the present study. A total of 475 controls were included.

Familial background of SCD in the FDRs (each biological parent, siblings, or a child) was ascertained by telephone call to the control subjects, and by using a previously described questionnaire forwarded to the closest relatives of the victims of SCD\textsuperscript{3}. The reported SCD cases in the 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 post-mortem data by the investigators.

**Statistical analysis**

All analyses were performed with the Statistical Package for Social Studies version 13.0 (SPSS Inc, Chicago, Ill). \( P<0.05 \) was considered statistically significant. One-way analysis of variance
ANOVA and logistic regression analyses were used for comparisons between study groups. Bonferroni correction was used as the post hoc test for one-way ANOVA. Logistic regression analysis was used to assess the significance of family history of SCD between the groups after adjustment for age, gender, smoking, BMI, history of diabetes mellitus, hypertension or angina pectoris, number of first-degree relatives, and rate of adequate information on the mode of death of the family members in each group. The GEE-analysis (Generalized Estimating Equations), which adjusts for the correlation among family members, was also performed. \(\chi^2\) analysis was used for comparison of SCD among FDR 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 SCD and controls. Age and BMI differed between the groups with non-ischemic victims being younger and they had higher BMI than ischemic SCD victims or controls. Smoking status also differed between the groups, the number of current smokers being significantly higher in the non-ischemic and ischemic SCD victims compared to controls. The prevalences of hypertension and diabetes were more common in non-ischemic SCD victims compared to controls. The same was true when compared ischemic SCD victims and controls. Only about one third of the non-ischemic SCD victims had a prior cardiac history, thus in \(~70\%\) of the victims, death was the very first manifestation of cardiac disease. In ischemic SCDS, a prior 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%) vs.
non-ischemic (13.4%) SCD cases (OR 4.3, 95 % CI 2.1 to 8.7, P<0.001; adjusted OR 5.3, 95 % CI 2.0 to 14.4, P=0.001) (Table 2.). The history of SCD in 2 or more FDRs was also higher in ischemic (14.7%) than non-ischemic SCD (4.0%) victims (OR 4.3, 95 % CI 2.1 to 8.7, P<0.001; adjusted OR 6.2, 95 % CI 1.8 to 21.5, P=0.004, respectively). Similarly, ischemic SCD victims had a higher prevalence of SCD in FDRs as compared to controls (17.6%) (OR 12.5, 95 % CI 5.4 to 28.9, P<0.001; adjusted OR 13.5, 95 % CI 4.3 to 42.8, P<0.001).

When non-ischemic SCD victims (14.7%) were compared to controls, positive family history of SCD was observed somewhat more often in controls, but the difference disappeared after adjustments for confounding variables (17.6%) (OR 0.5, 95 % CI 0.3 to 0.9, P=0.020; adjusted OR 0.9, 95 % CI 0.4 to 1.7, P=0.641) (Table 2.). However, a history of SCD in 2 or more FDRs was higher in non-ischemic SCD victims (4.0%) as compared to controls (1.3%) (OR 2.9, 95 % CI 1.1 to 8.5, P=0.040; adjusted OR 19.0, 95 % CI 1.2 to 308.6, P=0.039).

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

Dependence of correlation among family members to the presence of family history were taken into account with GEE analysis; Family members of ischemic SCD victims were more likely to have another SCD in their family, compared to family members of non-ischemic SCD victims (OR 1.8, 95 % CI 1.1 to 2.9, P=0.011). The difference was not significant between the
family members of the non-ischemic SCD victims and the family members of control cases (OR 1.3, 95 % CI 0.8 to 2.2, P=0.234), whereas the prevalence was statistically significant between the family members of ischemic SCD victims and the family members of control cases (OR 2.4, 95 % CI 1.9 to 3.1, P<0.001).

The prevalence of SCD among the first-degree relatives of non-ischemic SCD victims 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 when compared to the other groups or controls, the prevalence being in the same range as in those with ischemic SCD.

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

**Discussion**

The results of the present study support the concept that even though a part of non-ischemic heart disease may be due to inherited traits, the vast number of non-ischemic heart diseases has a sporadic occurrence. We also confirm here in a large sample of victims of SCD with autopsy verified CAD that ischemic SCD has a strong familial background, that one out of three SCD victims have had one or more SCDs in their FDRs both in those with and without a previous AMI.

Some demographic and clinical variables differed between the groups. Victims of non-ischemic SCD were younger and their BMI was higher than in the ischemic SCDs or controls. The number of current smokers was also highest in the non-ischemic SCD group. A history of hypertension and diabetes were more common in the SCD victims compared to controls. Thus,
the risk profile of SCD victims differed in several aspects from those of control subjects. 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 ischemic heart disease is not simply the result of inheritance of specific risk factors of SCD, such as smoking, hypertension or diabetes, but some other genetic factors are probably involved in ischemic SCD.

**Family history of SCD in non-ischemic 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 non-ischemic SCD in the present study, a family history of SCD was also relatively common (33 %) in those SCD victims with the evidence of HCM 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 non-ischemic 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 non-ischemic SCD are variable among different populations and may be due to differences in genetic profiles and features of acquired heart disease between the various countries. In addition, the autopsy rates and reporting of autopsy results are clearly quite different between countries.

The causes of non-ischemic SCD of the present study differ from those reported previously. In accordance with the present study, we reported recently in a larger sample size
that obesity, alcoholic CMP, and idiopathic myocardial fibrosis were more prevalent causes of non-ischemic SCD than the causes of non-ischemic SCD reported previously. This may partly explain the lack of familial clustering of non-ischemic SCD in our population. The inheritance of the most prevalent causes of non-ischemic 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 be also noted that we excluded here those subjects with a normal autopsy, which excludes those SCD victims 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 non-ischemic SCD and controls (table 3), the number of more than one SCD in the FDRs was somewhat higher in the non-ischemic group than controls (table 2). This may be due to inherited monogenic mutations with a high penetrance of disease in some families with non-ischemic SCD. However, the number of these cases was also relatively small, resulting in a low overall prevalence of family history of SCD in non-ischemic 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 due to an acute coronary event as compared to survivors of such an event. The present data confirm and extend these results with 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 two 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 two 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 prior cardiac disease.

**Study limitations**

Resuscitated cardiac arrest victims 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 of 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 non-ischemic SCD victims, the possibility of vasospasm and ischemic ventricular fibrillation cannot be entirely left out. However, all major coronary branches have been dissected and analysed for coronary plaques followed by a histological analysis, if there is any suspicion of even minor coronary plaque complication, minimizing the possibility for 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 non-ischemic 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 sub-groups of the non-ischemic SCD victims were being compared, the number of cases in each group was small which hindered reliable statistical comparisons. Another difficulty was the gaining of accurate data from phone calls and questionnaires to family members of deceased individuals. However, as far as we are aware, this the first study examining the family history of SCD in non-ischemic SCD. We also acknowledge
that the reported causes of non-ischemic SCD are variable among different populations, and these features of the Finnish population in regard to the family history of non-ischemic 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 an emphasis placed on ischemic SCD so that ideally non-ischemic SCD cases can be excluded from these types of studies.

Conclusions

Ischemic SCD has a strong familial background both in those individuals with and those 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 non-ischemic SCD without HCM or inherited ion channel disorders. The prevention of obesity and heavy alcohol consumption may be key factors in reducing non-ischemic SCD at the community level.

Conflict of Interest Disclosures: None.

References:


sudden death is an important risk factor for primary ventricular fibrillation: a case-control study in acute myocardial infarction patients. *Circulation.* 2006;114:1140-1145.


Table 1. Characteristics of study subjects.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Victims of non-ischemic SCD (N=223)</th>
<th>Victims of ischemic SCD (N=596)</th>
<th>Controls (N=459)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>53.4 (11.3) *†</td>
<td>64.9 (11.2)</td>
<td>62.5 (5.8)</td>
</tr>
<tr>
<td>Sex (male)</td>
<td>176/223 (78.9) †</td>
<td>483/596 (81.0) ‡</td>
<td>252/459 (54.9)</td>
</tr>
<tr>
<td>BMI</td>
<td>30.0 (7.9) *†</td>
<td>26.7 (4.9)</td>
<td>27.2 (4.3)</td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>72/223 (32.3) †</td>
<td>204/596 (34.2) ‡</td>
<td>202/406 (49.8)</td>
</tr>
<tr>
<td>Ex-smoker</td>
<td>26/223 (11.7)</td>
<td>126/596 (21.2)</td>
<td>99/406 (24.3)</td>
</tr>
<tr>
<td>Current</td>
<td>125/223 (56.0)</td>
<td>266/596 (44.6)</td>
<td>105/406 (25.9)</td>
</tr>
<tr>
<td>Diabetes type I or II</td>
<td>50/223 (22.4) †</td>
<td>153/596 (25.6) ‡</td>
<td>6/424 (1.4)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>106/223 (47.5) †</td>
<td>368/596 (61.8) ‡</td>
<td>147/421 (34.9)</td>
</tr>
<tr>
<td>Prior cardiac history</td>
<td>75/223 (32.3) *</td>
<td>246/596 (41.3)</td>
<td>-</td>
</tr>
</tbody>
</table>

BMI indicates body mass index.
Values are expressed as mean (SD) or number of subjects (%). Probability values refer to one-way ANOVA and logistic regression analyses between groups.
*P<0.001 non-ischemic SCD vs ischemic SCD; †P<0.001 non-ischemic SCD vs control; ‡P<0.001 ischemic SCD vs control.

Table 2. Family history of SCD

<table>
<thead>
<tr>
<th>SCD among FDR</th>
<th>Victims of non-ischemic 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>

FDR indicates first-degree relative.
Values are number of subjects (%). Probability values refer to logistic regression analysis between groups.
*P<0.001 non-ischemic SCD vs ischemic SCD; †P<0.05 non-ischemic SCD vs control; ‡P<0.001 ischemic SCD vs control.
Table 3. Total number of SCD among the total number of first-degree relatives

<table>
<thead>
<tr>
<th></th>
<th>FDR of victims of non-ischemic SCD (N=1770)</th>
<th>FDR of victims of ischemic SCD (N=5651)</th>
<th>FDR of controls (N=3671)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCD among FDR</td>
<td>56/1770 (3.2)*</td>
<td>328/5651 (5.8)†</td>
<td>87/3671 (2.4)</td>
</tr>
</tbody>
</table>

FDR indicates first-degree relatives.
Values are number of subjects (%).
*P<0.001 non-ischemic SCD vs ischemic SCD; †P<0.001 ischemic SCD vs control.

Table 4. Family history of SCD in non-ischemic SCDs

<table>
<thead>
<tr>
<th>Cause of non-ischemic SCD (N=223)</th>
<th>Family history of SCD</th>
</tr>
</thead>
<tbody>
<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>

CMP indicates cardiomyopathy; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; ARVD, arrhythmogenic right ventricular dysplasia.
Values are number of subjects (%).

Figure Legend:

Figure 1. Investigation system for sudden death and the means by which a history was obtained.
Act on the Inquest into the Cause of Death, 459/19873, Finnish law

1) Death is due to suspected homicide, suicide, accident, occupational disease or complication of medical care
2) Death is not due to a known disease and the deceased has not been treated by a physician during his/her last illness
3) Death is otherwise unexpected

Police investigation: The police collect all available information on the circumstances of death, previous diseases, medication, alcohol consumption and other significant data relevant to the case. The relatives, medical staff and other persons involved are interviewed by the police.

The police orders to perform a medico-legal autopsy. Case histories are based on the results of police investigation and all available medical records.

Medico-legal autopsy with microscopic and toxicological investigations

Death certificate, autopsy protocol and attached documents

SCD study cases: interview of the family members
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Circ Arrhythm Electrophysiol. published online July 11, 2012;
Circulation: Arrhythmia and Electrophysiology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1941-3149. Online ISSN: 1941-3084

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