Excessive Supraventricular Ectopic Activity and Increased Risk of Atrial Fibrillation and Stroke

Zeynep Binici, MD; Theodoros Intzilakis, MD; Olav Wendelboe Nielsen, MD, PhD, DMSc; Lars Køber, MD, DMSc; Ahmad Sajadieh, MD, DMSc

Background—Prediction of stroke and atrial fibrillation in healthy individuals is challenging. We examined whether excessive supraventricular ectopic activity (ESVEA) correlates with risk of stroke, death, and atrial fibrillation in subjects without previous stroke or heart disease.

Methods and Results—The population-based cohort of the Copenhagen Holter Study, consisting of 678 healthy men and women aged between 55 and 75 years with no history of cardiovascular disease, atrial fibrillation, or stroke, was evaluated. All had fasting laboratory tests and 48-hour ambulatory ECG monitoring. ESVEA was defined as ≥30 supraventricular ectopic complexes (SVEC) per hour or as any episodes with runs of ≥20 SVEC. The primary end point was stroke or death, and the secondary end points were total mortality, stroke, and admissions for atrial fibrillation. Median follow-up was 6.3 years. Seventy subjects had SVEC ≥30/h, and 42 had runs of SVEC with a length of ≥20 SVEC. Together, 99 subjects (14.6%) had ESVEA. The risk of primary end point (death or stroke) was significantly higher in subjects with ESVEA compared with those without ESVEA after adjustment for conventional risk factors (hazard ratio 1.64; 95% confidence interval, 1.03 to 2.60; P=0.036). ESVEA was also associated with admissions for atrial fibrillation (hazard ratio 2.78; 95% confidence interval, 1.08 to 6.99; P=0.033) and stroke (hazard ratio 2.79; 95% confidence interval, 1.23 to 6.30; P=0.014). SVEC, as a continuous variable, was also associated with both the primary end point of stroke or death and admissions for atrial fibrillation.

Conclusions—ESVEA in apparently healthy subjects is associated with development of atrial fibrillation and is associated with a poor prognosis in term of death or stroke. (Circulation. 2010;121:1904-1911.)

Key Words: arrhythmia ■ prognosis ■ risk factors ■ stroke

Stroke is the third leading cause of death worldwide and a major cause of burden and disability in many developed countries. The incidence of stroke, as seen in 2003, is increasing and is expected to double by 2020.1–6 Stroke kills ≈150 000 Americans each year, and almost 1 of 3 stroke victims dies within a year. Three million Americans are currently permanently disabled from stroke. In the United States, stroke costs ≈$30 billion per year in direct costs and loss of productivity.7 Two-thirds of strokes occur in people aged >65 years. These epidemiological facts are similar worldwide and illuminate the significance of preventive measures to avoid stroke and stroke-related mortality and morbidity.7–10

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The ischemic type of stroke is caused by occlusion of a brain artery by either atherosclerotic thrombi or emboli. Cardioembolic stroke comprises ≈15% of all strokes (range, 6% to 23%).11,12 Major risk factors for cardioembolic stroke are atrial fibrillation, myocardial infarction, congestive heart failure, valvular abnormalities including prosthetic valves, and atrial septal defect.11 Other risk factors such as hypertension, hypercholesterolemia, smoking, sedentary lifestyle, obesity, asymptomatic carotid artery stenosis, and alcohol consumption (≥5 drinks per day) dispose people to both cardiac and cerebrovascular diseases.13 Potentially treatable risk factors may be observed from a resting or a continuous ECG recording. For example, the most frequent ECG findings in patients with acute cerebral infarction and transient ischemic attack are atrial ectopic beats in addition to atrial fibrillation, sinus tachycardia, and atrioventricular block.14 These ectopic beats may indicate a tendency to paroxysmal atrial fibrillation, which may not be recognized before either stroke or transient ischemic attack occurs. The extent to which atrial ectopic beats contribute to the incidence of cardioembolic
stroke is not clear. The clinical implications are uncertain, but it is likely that excessive numbers of premature atrial ectopic contractions may trigger bursts of atrial fibrillation and thereby increase the risk of atrial fibrillation. The aim of this study was to evaluate the prevalence and prognostic significance of atrial arrhythmias other than atrial fibrillation in relation to the risk of stroke, atrial fibrillation, and death.

Methods

Copenhagen Holter Study

The Copenhagen Holter Study is the largest Holter study in appearance.15 In brief, within 2 well-defined postal regions in the city of Copenhagen, all men aged 55 years and all men and women aged 60, 65, 70, and 75 years (n=2969) were contacted with a questionnaire asking about cardiovascular risk factors, use of medication, and medical history. Subjects with current or past cardiac disease, atrial fibrillation, stroke, cancer, or other life-threatening conditions were excluded. The study includes up to 48-hour successful Holter monitoring in 678 subjects.15 Holter recording for up to 48 hours was performed with the use of 2-channel SpaceLabs tape recorders (9025; SpaceLabs Inc, Redwood, Wash), and recordings were evaluated and interpreted by trained personnel. The quality of the analyses has been described in detail previously, and the interobserver variability shows κ values between 0.91 and 0.94.16 The range of technically acceptable recording and analysis time was 17.2 to 49.2 hours. The median value was 44.1 hours, and first and third quartiles (Q1, Q3) were 41.4 to 45.5 hours. More than 98% of the subjects had >24 hours of recording.

Definitions

Two classes of supraventricular arrhythmias were studied: (1) isolated supraventricular ectopic complexes (SVEC) and (2) runs of ≥3 SVEC. The identification of SVEC was based on 3 criteria: prematurity, postcontraction pause, and morphology. The coupling interval to the preceding QRS complex had to be ≤70% of the mean RR interval of basic rhythm before the event. QRS complexes had a duration of <0.11 seconds unless aberration was suspected. The postcontraction pause had to be noncompensatory. Frequency of SVEC and length of runs of SVEC were analyzed as both continuous and dichotomized variables. With the assumption that SVEC had to be excessive to increase the adverse events substantially, we set the cutoff value at the top 10th percentile for both frequency of SVEC and length of runs of SVEC. Thus, excessive supraventricular ectopic activity (ESVEA) was defined as ≥30 SVEC per hour or any episode of runs of ≥20 SVEC.

Further Risk Stratification

A modified Framingham atrial fibrillation risk score was calculated according to the method described by Schnabel et al.17 on the basis of information about age, sex, body mass index, systolic blood pressure, hypertension, cardiac murmurs, PR distance on ECG, and heart failure. The only differences were that none of the participants of this study had congestive heart failure and PR interval was coded according to Minnesota codes.

End Points

Data on stroke, atrial fibrillation, and death were obtained through the national central patient registry, discharge letters from hospital admission, and, if necessary, patient files. All deaths, hospital admissions, and discharges in Denmark are reported to this registry within 2 weeks. The diagnosis of stroke was based on history (ie, neurological deficits and verification by computed tomographic scanning or magnetic resonance imaging scanning of cerebrum); only verified ischemic strokes were accepted for this study. The diagnosis of atrial fibrillation from discharge letters had to be verified with adequate documentation (ECG and in most cases both ECG and telemetry). Discharge summaries were used to identify patients with potential episodes of clinically relevant atrial fibrillation and had to be documented from hospital records. Discharge summaries were used to identify patients with potential episodes of clinically relevant atrial fibrillation, and documentation was available from hospital records. All strokes in our study were of the ischemic type. Hemorrhagic stroke was not included in the statistical analysis. All medications were registered at baseline, and no participants were on warfarin. Combined end points were based on combined all-cause mortality or first event of stroke.

Ethics

All participants provided their written informed consent. The Regional Ethical Committee of Copenhagen and Frederiksborg approved the study. The study complied with the Helsinki Declaration.

Statistical Analysis

Statistical analyses were made with the use of the SAS statistical software program (version 9.1; SAS Institute Inc., Cary, NC). For normally distributed variables, mean and SD are presented; otherwise, median value and quartiles (Q1 to Q3) are presented. Univariate associations between ESVEA and other parameters were evaluated by the Wilcoxon rank sum test or χ² test as appropriate. Two-tailed tests of significance are reported, and P values <0.05 are considered statistically significant. Regression analyses (logistic or linear) were performed to evaluate the covariate-adjusted association of the variable of interest. Event-free survival in patients with and without ESVEA was estimated by the Kaplan-Meier method, and statistical differences were evaluated by means of the log-rank test. Cox proportional hazard models were used to evaluate the risk factor-adjusted associations of SVEC with death or stroke. In Cox models with end points involving death and death or stroke, adjustment was made for the conventional risk factors of age, sex, diabetes mellitus, systolic blood pressure, and cholesterol. Additional adjustments for the other variables, which were associated with ESVEA with P≤0.05 at baseline, were also performed. In forward selection models, P≤0.05 was used to enter the model, and P≤0.05 was used to remain in the model. Baseline variables, which were associated with atrial fibrillation in univariate analyses, were used to adjust for the association between SVEC and atrial fibrillation. In Cox models with stroke as the only end point, the association with SVEC was not linear, and for this reason we used a dichotomized variable based on the top 10th percentile, as described in Definitions. To evaluate the possible effect of atrial fibrillation on the primary end point, secondary analyses were performed with the participant censored at the time of atrial fibrillation. The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

In total, 678 subjects participated in this study, and their baseline characteristics are shown in Table 1. Ninety-nine subjects were identified with ESVEA, 70 subjects had SVEC >30/h, and 42 had runs of SVEC with a length of ≥20 SVEC, reflecting that 13 subjects had both abnormalities. Table 1 shows the associations of baseline variables of interest with ESVEA. In a multivariable logistic regression with relevant baseline variables, only age, N-terminal prohormone B-type natriuretic peptide (NT-proBNP), and systolic and diastolic blood pressure were associated with the presence of ESVEA. The median follow-up time was 76 months (Q1 to Q3=74 to 78 months).

Primary End Point

Event frequencies observed in up to 7 years of follow-up (median, 76 months) in all participants are shown in Table 2.
Figure 1 shows Kaplan-Meier survival curves in participants with and without ESVEA. The primary end point of death or stroke occurred in 105 of all participants: 29 in 99 participants with ESVEA and 76 in 579 participants without ESVEA (P<0.0001 in univariate analysis). This remained significant after adjustment for conventional risk factors (smoking, systolic blood pressure, diabetes mellitus, cholesterol, sex, and age) (hazard ratio [HR] = 1.64; 95% confidence interval [CI], 1.03 to 2.60; P=0.036; Table 3). SVEC as a continuous variable was associated with the primary end point in both univariate and multivariable analyses (Table 3). Runs of SVEC as a continuous variable were associated with the primary end point in univariate but not in multivariable analysis (Table 3). Further adjustment for body mass index, level of physical activity, and blood glucose level did not change the results. The use of high-density lipoprotein and low-density lipoprotein cholesterol instead of total cholesterol also did not change the results (data not shown).

After additional adjustments for other variables (plasma glucose, NT-proBNP, use of aspirin, diuretics) that at baseline were associated with ESVEA (P=0.05), in addition to the conventional risk factors, SVEC remained in the model (HR=1.23; 95% CI, 1.02 to 1.50; P=0.029). If use of medication body mass index, and level of physical activity did not change the results significantly (data not shown). If use of medication is not considered in the analyses, the results will remain almost unchanged.

In forward selection models that included all conventional variables together with plasma glucose, NT-proBNP, use of aspirin, diuretics, and ESVEA or SVEC as continuous variables, both ESVEA and SVEC remained in the model and independently correlated with the primary outcome (HR for ESVEA=1.79; 95% CI, 1.14 to 2.81; P=0.012; HR for SVEC=1.23; 95% CI, 1.02 to 1.50; P=0.029). Further adjustments for angiotensin-converting enzyme inhibitors, body mass index, and level of physical activity did not change the results significantly (data not shown). If use of medication is not considered in the analyses, the results will remain almost unchanged.

In secondary analyses of the primary end point, with exclusion of the participant at the time of atrial fibrillation, the effect of atrial fibrillation on development of further events was assessed. These analyses showed that ESVEA was associated with the primary end point in both univariate
SVEC as a continuous variable and runs of SVEC as a continuous variable were also associated with the primary end point at univariate analyses (HR = 1.46; 95% CI, 1.22 to 1.73; P < 0.0001 for SVEC; HR = 1.13; 95% CI, 1.05 to 1.21; P = 0.0007 for runs of SVEC), and the corresponding multivariable analyses showed almost the same results as in primary analyses (HR = 1.27; 95% CI, 1.05 to 1.53; P = 0.013 for SVEC; HR = 1.06; 95% CI, 0.98 to 1.15; P = 0.14 for runs of SVEC, respectively).

Secondary End Point

Total Mortality
Twenty-one of the subjects with ESVEA (21/99) and 66 of the subjects without ESVEA (66/579) died during the follow-up (HR = 2.12; 95% CI, 1.30 to 3.47; P = 0.003 in univariate analysis). After adjustment for conventional risk factors, ESVEA became statistically nonsignificant (HR = 1.40; 95% CI, 0.83 to 2.37; P = 0.207; Table 3). Although SVEC as a continuous variable was associated with total mortality in univariate as well as in multivariable
analyses, runs of SVEC were associated with total mortality only in univariate analysis (Table 3).

**Stroke**
During the follow-up period, 27 subjects experienced a stroke. Ten events of stroke occurred in subjects with ESVEA and 17 in subjects without (HR = 3.88; 95% CI, 1.78 to 8.48; P = 0.0007). This remained significant after adjustment for age and sex (HR = 2.79; 95% CI, 1.23 to 6.30; P = 0.014). This also remained significant after further adjustment for other major risk factors for stroke (smoking, diabetes mellitus, systolic blood pressure, and body mass index) (HR = 2.37; 95% CI, 1.02 to 5.50; P = 0.044). SVEC as a continuous variable and runs of SVEC as a continuous variable did not correlate with stroke (HR = 1.12; 95% CI, 0.97 to 1.29; P = 0.13 for runs of SVEC; HR = 0.83; 95% CI, 0.58 to 1.98; P = 0.83 for SVEC, respectively).

**Atrial Fibrillation**
Table 2 shows the up to 7-year rate of atrial fibrillation in all participants with and without ESVEA. Figure 1 shows event-free (atrial fibrillation) survival in participants with and without ESVEA. Subjects who developed atrial fibrillation during the follow-up period had significantly higher systolic blood pressure at baseline (169.5 versus 155.9 mm Hg; P = 0.02) and were older (67.5 versus 64.4 years; P = 0.03). Other baseline variables and risk factors (sex, cholesterol, smoking, diabetes mellitus, alcohol, plasma glucose, and NT-proBNP) were not significantly different between the groups. In Cox regression models, ESVEA was associated with an increased risk of atrial fibrillation in both univariate and adjusted models (Table 4). SVEC as a continuous variable and runs of SVEC as a continuous variable were also significantly associated with occurrence of atrial fibrillation in both univariate and age- and sex-adjusted models (Table 4). Further adjustments for systolic blood pressure and body mass index did not change the results. In Cox regression models with entrance of both SVEC and Framingham risk score for atrial fibrillation (both as continuous variables), SVEC remained significantly associated with atrial fibrillation (HR = 1.50; 95% CI, 1.05 to 2.14; P = 0.02).

In contrast to stroke, which was more prevalent in patients with higher frequency of SVEC, a linear association between the frequency of SVEC or length of runs of SVEC and incidence of atrial fibrillation was present (Figure 2). In this regard, there was a 10-fold difference in the incidence of atrial fibrillation in subjects with highest frequency of SVEC versus those in the lowest groups (P = 0.0006).

**Discussion**
Our study shows that ESVEA was associated with a >60% increase in the rate of death or stroke after adjustment for other risk factors. Furthermore, ESVEA was associated with a 2.7-fold increased rate of atrial fibrillation in the follow-up period. For each increase of 10 SVEC per hour, the risk of the primary end point of death or stroke increased by 27% and the risk of atrial fibrillation by 50%.

Engstrom et al 18 studied the risk of stroke in relation to SVEC in the cohort of “men born in 1914” and demonstrated an increased risk of stroke in men with an increasing number of SVEC, a finding that is in perfect agreement with our study. To our knowledge, there are no other population-based Holter study evaluating the risk of mortality or atrial fibrillation in relation to SVEC. ECG studies in subjects with stroke have shown that increased atrial premature contractions are associated with paroxysmal atrial fibrillation. 19,20 Our data indicate that such premature contrac-

### Table 3. Cox Regression Models Showing the Risk of Death or Stroke or of All-Cause Mortality in Relation to SVEC, Runs of SVEC, and ESVEA

<table>
<thead>
<tr>
<th>Variable</th>
<th>HR (95% CI) for Death or Stroke</th>
<th>P</th>
<th>HR (95% CI) for All-Cause Mortality</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Univariate</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SVEC (for each increment of 10 SVEC/h)</td>
<td>1.44 (1.21–1.71)</td>
<td>&lt;0.0001</td>
<td>1.49 (1.24–1.79)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Runs of SVEC (for lengthening of runs by 4 SVEC)</td>
<td>1.12 (1.05–1.21)</td>
<td>0.001</td>
<td>1.12 (1.03–1.21)</td>
<td>0.006</td>
</tr>
<tr>
<td>ESVEA</td>
<td>2.54 (1.66–3.90)</td>
<td>&lt;0.0001</td>
<td>2.12 (1.30–3.47)</td>
<td>0.003</td>
</tr>
<tr>
<td><strong>Multivariable</strong>*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SVEC (for each increment of 10 SVEC/h)</td>
<td>1.25 (1.04–1.52)</td>
<td>0.021</td>
<td>1.27 (1.04–1.55)</td>
<td>0.019</td>
</tr>
<tr>
<td>Runs of SVEC (for lengthening of runs by 4 SVEC)</td>
<td>1.06 (0.98–1.14)</td>
<td>0.16</td>
<td>1.06 (0.97–1.15)</td>
<td>0.20</td>
</tr>
<tr>
<td>ESVEA</td>
<td>1.64 (1.03–2.60)</td>
<td>0.036</td>
<td>1.40 (0.83–2.36)</td>
<td>0.207</td>
</tr>
</tbody>
</table>

*Adjusted for age, sex, smoking habits, diabetes mellitus, systolic blood pressure, and total cholesterol (full models).
tions may have persisted long before the stroke and may not be caused by the hemodynamic effects of an acute stroke.

SVEC are among the most frequent arrhythmias in the population, and individuals with ESVEA constitute ≈15% of this middle-aged or elderly population. Our data suggest that as SVEC increases, there is an increased risk of atrial fibrillation, as well as death or stroke.

The origin and mechanism of increased SVEC are not clear, but several possibilities exist. Increased SVEC may originate from pulmonary veins and act as forerunners of atrial fibrillation. Second, increased SVEC may be genetically determined or may be an early manifestation of hypertension or another underlying structural heart disease that elevates filling pressures. Longstanding hypertension can lead to diastolic dysfunction and enlargement of the left atrium, which can potentially lead to increased atrial wall stress, increased SVEC, and eventually atrial fibrillation. Our finding of strong associations between increased SVEC and blood pressure, NT-proBNP, stroke, and the primary end point supports this.

The mechanisms by which increased SVEC may increase the risk of death or stroke and atrial fibrillation are also not clear. The most likely mechanism is that increased SVEC triggers atrial fibrillation or is a forerunner of atrial fibrillation. However, it cannot be ruled out that increased SVEC and atrial fibrillation are epiphenomena of other heart diseases or conditions that also increase the risk of death and stroke. It is well known that atrial fibrillation is one of the major causes of cardioembolic stroke. Paroxysmal atrial fibrillation may also lead to stroke, but thus far no studies have estimated the extent to which strokes are caused by paroxysmal atrial fibrillation. Our study provides an indirect estimate of this risk because subjects who have excessive supraventricular activity are at increased risk of paroxysmal atrial fibrillation. Wallmann et al reported that in subjects with stroke, 33% of subjects with and 5% of subjects without ESVEA developed atrial fibrillation. In our secondary analysis censoring patients when atrial fibrillation occurred, SVEC still correlate with death or stroke. However, the mechanism by which SVEC may increase events may still be due to development of atrial fibrillation because episodes of atrial fibrillation may be clinically silent.

The manner in which to treat patients with ESVEA to reduce the associated risk of atrial fibrillation, death, or stroke is currently not apparent. Appropriate risk factor modification
may be effective, and, in patients with hypertension, antihypertensive regimens, including blockade of the renin-angiotensin system, may reduce the incidence of atrial fibrillation.22–27 Newer drugs that maintain sinus rhythm in atrial fibrillation can also be tested in patients with ESVEA. Our results may thus have a significant impact on clinical practice.

Limitations

The diagnosis of atrial fibrillation in our study is highly specific but is probably underestimated because it was based on admission for atrial fibrillation, and the number of cases of asymptomatic atrial fibrillation is not known. It is possible that some patients with atrial fibrillation have been treated as outpatients, and therefore hospital admissions were prevented. The small number of events limits both the power to detect associations and the ability to control completely for all potential confounders in the final multivariable models.

There are no clear and accepted cutoff points for the frequency and runs of SVEC to be considered pathological. Our data suggest that the top 10% of incidence may be pathological in this apparently healthy population (SVEC >30/h), but further studies are needed for comparison.

This study was performed in middle-aged and elderly white subjects. Thus, application of these data to other ethnic groups should be done with caution. Because not all eligible subjects were able to or willing to participate, some selection bias cannot be excluded.

Conclusions

Excessive supraventricular ectopic activity is associated with an increased risk of atrial fibrillation, stroke, and death. Subjects with ESVEA may need strict risk factor modification and close follow-up for the early detection of atrial fibrillation. More investigation in this field is needed.

Acknowledgments

The authors wish to thank laboratory technician Kirsten Andersen for her helpfulness and excellent assistance.

Sources of Funding

The Copenhagen Holter Study was supported by grants from the Danish Heart Foundation.

Disclosures

None.

References

Supraventricular ectopic complexes are quite common, and \( \approx 10\% \) to \( 15\% \) of middle-aged and elderly subjects with no apparent heart disease may have excessive supraventricular ectopic activity. This study shows that excessive supraventricular ectopic activity in these subjects increases the risk of death, stroke, and atrial fibrillation beyond conventional risk factors or the Framingham risk score for atrial fibrillation. Physicians frequently see patients with excessive supraventricular ectopic activity during routine examinations or in other contexts. The finding that such supraventricular activity leads to a high risk may urge physicians to intensify risk modification, treat comorbidities more aggressively, and perhaps increase patient compliance. Closer follow-up of these subjects is likely to identify subjects with asymptomatic atrial fibrillation and thus promote appropriate preventive treatment as well as anticoagulant therapy. Interventional studies to prevent atrial fibrillation and later stroke or death in such patients are welcome.

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Circulation. 2010;121:1904-1911; originally published online April 19, 2010;
doi: 10.1161/CIRCULATIONAHA.109.874982
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2010 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/121/17/1904

An erratum has been published regarding this article. Please see the attached page for:
/content/122/13/e474.full.pdf
In the article by Binici et al, “Excessive Supraventricular Ectopic Activity and Increased Risk of Atrial Fibrillation and Stroke,” which appeared in the May 4, 2010 issue of the journal (Circulation, 2010;121:1904–1911), there was an error in Figure 1. In panels A and B, the survival curves representing “ESVEA+” and “ESVEA−” were mislabeled. The corrected Figure appears below:

The correction has been made to the current online version of the manuscript. The authors regret the errors.

DOI: 10.1161/CIR.0b013e3181f33218