Atrial fibrillatory rate and risk of stroke in atrial fibrillation

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Aims

In atrial fibrillation (AF), a relation between electrocardiogram (ECG) parameters such as fibrillatory wave amplitude and stroke has been sought with conflicting results. In this study, we tested the hypothesis that the atrial fibrillatory rate of surface ECG lead V1 is related to stroke risk and may consequently be helpful for identifying high-risk patients.

Methods and results

Atrial fibrillatory rate of 79 consecutive patients with AF and embolic stroke (age 83 ± 7 years, 41% male) was compared with those of a matched AF population without stroke (n = 79). Atrial fibrillatory rate was determined from the surface ECG using spatiotemporal QRST cancellation and time–frequency analysis of lead V1. There was no significant difference in any clinical or echocardiographic variable in patients with stroke compared with AF controls without stroke. Atrial fibrillatory rate measured 373 ± 55 fibrillations per minute (fpm; range 235–505 fpm) in the entire population. There was no fibrillatory rate difference between stroke patients (369 ± 54 fpm, range 256–505 fpm) and AF controls without stroke (378 ± 56 fpm, range 235–488 fpm). There was an inverse correlation between fibrillatory rate and age (R = −0.219, P = 0.006). Individuals aged ≥85 years had a significantly lower fibrillatory rate (356 ± 44 fpm) than individuals aged 65–74 years (384 ± 56 fpm, P = 0.033) and individuals aged 75–84 years (384 ± 60 fpm, P = 0.016). In those subgroups, fibrillatory rates were, however, also similar in stroke patients and AF controls.

Conclusion

Atrial fibrillatory rate obtained from surface ECG lead V1 is not a risk marker for stroke in AF.

Keywords

Atrial fibrillation • Electrocardiography • Stroke

Introduction

Atrial fibrillation (AF) is associated with an increased risk of stroke. Clinical factors commonly used to identify high risk of stroke in patients with AF include congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, and prior stroke (CHADS2 criteria). In addition, reduced left atrial appendage (LAA) flow velocity and the occurrence of spontaneous echocardiographic contrast (SEC) visualized by transoesophageal echocardiography are risk factors for left atrial thrombus formation and stroke. Moreover, electrocardiogram (ECG)-derived factors for an individualized risk-stratification strategy are also under investigation. For instance, previous studies have analysed the relation between reduced LAA flow velocity, SEC, thrombus formation, and embolism with the amplitude of fibrillatory waves on standard ECGs but have found conflicting results. Consequently, fibrillatory wave amplitude has not been established as a clinically useful indicator for LAA dysfunction, thrombus development, and thromboembolic risk. Thus, other ECG parameters such as fibrillatory rate have become the focus of recent research interest. Several studies have shown that fibrillatory rate can reliably be obtained from the ECG during AF. This measurement of atrial refractoriness shows large inter-individual variability but is reproducible under stable conditions. Important for the context of this study, a moderate negative correlation between fibrillatory rate and LAA flow velocity has been reported before.

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As reduced LAA flow velocity is associated with thrombus formation and stroke, and fibrillatory rate is a marker for the degree of LAA dysfunction, we tested the hypothesis that the fibrillatory rate of surface ECG lead V1 is related to stroke and may be helpful for identifying high-risk patients. For this purpose, we compared fibrillatory rates of 79 consecutive stroke patients with AF to those of 79 matched individuals with AF but without stroke.

Methods

Study population

The study group was recruited from the Lund Stroke Register. It comprised 79 consecutive patients aged ≥65 years with persistent, non-valvular AF who were admitted to our institution between March 2001 and November 2004 due to embolic stroke defined according to standard diagnostic criteria. The duration of AF was calculated from the onset of symptoms or first electrocardiographic documentation to the performance of the index ECG (see below). A detailed patient history was taken to identify cardioactive medications and anticoagulants at the time of admission as well as associated cardiovascular morbidity. At the time of the study, none of the patients was taking any class I or III antiarrhythmic drugs known to modify stroke risk.

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ients was taking any class I or III antiarrhythmic drugs known to in-
fluence fibrillatory rate. During the hospital stay, two-dimensional and Doppler transthoracic echocardiography was performed with a 2.5 or 3.5 MHz imaging transducer (Hewlett-Packard Sonos 5500 imaging system, Palo Alto, CA, USA) and transthoracic measurements were obtained according to standard criteria.

Controls without a history of stroke or embolism were identified by queries of the hospital management databases of our institutions and matched with respect to age, gender, AF duration (short- vs. long-lasting AF with a cut-off of 3 months), as well as the remaining CHADS2 criteria (heart failure, hypertension, and diabetes mellitus) and oral anticoagulation use. While the former variables were selected because of their known effect on atrial fibrillatory rate, the latter are known to modify stroke risk.

This study was approved by the local Ethical Board and was per-
formed according to the Helsinki Declaration II.

Electrocardiogram selection and analysis

The ECG database was then searched for digital ECGs for the ident-
ified patients and controls. Standard 10 s, 12-lead surface ECG record-
ings (500 Hz sampling rate) made during the index hospital stay were retrieved for further signal processing.

After high-pass filtering to remove baseline wander, atrial fibrillatory activity was extracted in lead V1 using spatiotemporal QRST cancella-
tion. Since the dominant frequency component of interest is within the 4–9 Hz range, the resulting fibrillatory baseline signal was down-
sampled to 50 Hz and subjected to spectral analysis. The time–frequency distribution of the atrial signal (obtained by short-term Fourier transform) was decomposed such that each spectrum can be modelled as a frequency-shifted and amplitude-scaled version of the spectral profile. This procedure is based on a spectral profile, dynami-
cally updated from previous spectra, which was matched to each new spectrum using weighted least squares estimation. The frequency shift needed to achieve optimal matching then yields a measure of instan-
taneous fibrillatory rate of a 2.5 s ECG segment (overlapping with one segment each second) and was trended as a function of time.

It should be noted that the time–frequency analysis includes techniques for rejecting segments with poor signal quality. Thus, frequencies were computed from segments with reliable estimates only, as opposed to conventional power spectral analysis where all segments are included.

Frequencies were converted to fibrillatory rates with its unit fpm as advocated previously (rate = frequency x 60). Mean fibrillatory rate (in fpm) defined as an average of instantaneous fibrillatory rates over the 10 s ECG segment was determined (Figure 1).

Statistical analysis

Continuous variables are expressed as mean ± one standard deviation. Bivariate correlation between fibrillatory rate and clinical as well as echocardiographic variables was performed using Pearson’s corre-
lation coefficients or linear regression. Clinical and echocardiographic parameters, as well as fibrillatory rates, were compared between stroke patients and AF controls without stroke using Student’s t-test for unpaired data for continuous and χ² test for categoric variables. Fibrillatory rate differences among age groups (i.e. 65–74, 75–84, and ≥85 years) were evaluated with analysis of variance (ANOVA) and a post hoc analysis (Bonferroni’s test) was performed.

With a sample size of 79 patients and 79 controls and a predicted within group standard deviation of fibrillatory rate of 60 fpm, fibrilla-
tory rate differences between groups of ± 27 fpm would have been detectable with a power of 80%. This difference is above the spon-
taneous fibrillatory rate variability and would have been considered clinically relevant for risk stratification.

A value of P < 0.05 was considered statistically significant.

Results

Patient characteristics are summarized in Table 1. There was no sig-
nificant difference in any clinical or echocardiographic variable in patients with stroke compared with the matched AF controls without stroke.

Atrial fibrillatory rate measured 373 ± 55 fpm (range 235–505 fpm) in the entire population. There was no fibrillatory rate difference between stroke patients (369 ± 54 fpm, range 256–505 fpm) and AF controls without stroke (378 ± 56 fpm, range 235–488 fpm).

When analysing patients and controls together, there was an inverse correlation between fibrillatory rate and age (R = –0.219, P = 0.006). Individuals aged ≥85 years had a signifi-
cantly lower fibrillatory rate (356 ± 44 fpm) than individuals aged 65–74 years (384 ± 56 fpm, P = 0.033) and individuals aged 75–84 years (384 ± 60 fpm, P = 0.016). In those subgroups, fibrilla-
tory rates were, however, also similar in patients and controls (Figure 2).

Male individuals tended to have higher fibrillatory rates than females (386 ± 59 vs. 368 ± 52 fpm, P = 0.058). There was no relation between any other clinical variable and fibrillatory rate.

Discussion

Main findings

To the best of our knowledge, this study is the first to analyse the possible relationship of fibrillatory rate of the surface ECG and stroke. Fibrillatory rates were, however, similar in AF patients with embolic stroke when compared with matched AF controls without stroke. Also of note, the current study included the
oldest AF population in which fibrillatory rate has been analysed. In comparison with previous studies, we found surprisingly low fibrillatory rates in octogenarians.

**Electrocardiogram variables and thromboembolic risk**

The current study was motivated by two previous observations, i.e. (i) the ongoing debate about ECG parameters such as fibrillatory wave amplitude for predicting thromboembolic risk, and (ii) the possible relation between fibrillatory rate and reduced LAA flow velocity, a known risk factor for thrombus formation, and stroke.

Previous studies have analysed the relation between reduced LAA flow velocity, SEC, thrombus formation or embolism, and the amplitude of fibrillatory waves on ECG. Results of these studies are conflicting. Patients with coarse AF defined as fibrillatory wave amplitudes ≥1 mm have been reported to have a lower LAA flow velocity and subsequently higher rates of SEC, and thrombus formation. This finding could, however, not be confirmed in the SPAF-III trial which showed no correlation between fibrillatory wave size and LAA flow velocity and subsequent thromboembolic risk. In contrast, thromboembolic events were even lower in patients with coarse AF in a recent longitudinal study. As with previous studies in new-onset and persistent/permanent AF, we found, however, an inverse correlation between fibrillatory rate and patients’ age. The correlation coefficient was, however, somewhat lower, since our study only included individuals ≥65 years. The mean fibrillatory rate in previous studies that included substantially younger populations measured 380–400 fpm which is in close agreement with our findings in patients <85 years. Surprisingly low fibrillatory rates with a mean of 356 fpm were, in contrast, observed in individuals ≥85 years in our study. This finding can be explained by longer refractory periods and slower conduction—
both resulting in slower fibrillatory rates—which are present in ageing atria.24 In addition, anatomically determined conduction delay and areas of low voltage have been observed in ageing atria.25 Structural atrial abnormalities such as increased infiltration of fatty tissue, and increased collagen and amyloid deposition are frequently observed in the eighth decade26,27 and may form the atrial substrate for these electrophysiological changes. Finally, ageing is associated with changes in hormonal28 and autonomic states29 that also influence atrial electrophysiology.

Taken together, the ageing-associated increase in stroke risk and the parallel progress of structural and electrical remodelling including the decrease in fibrillatory rate suggest that these processes may be linked. Although fibrillatory rate seems not of value for risk stratification, the observed fibrillatory rate decrease with ageing may reflect a further deterioration of atrial function.

**Limitations**

This study was designed as cross-sectional case–control study with all inherent limitations. Stroke patients and AF controls were, however, well matched for known factors that may influence fibrillatory rate and also for known clinical risk factors for stroke. Nevertheless, the presence of subclinical stroke in the control group cannot be ruled out with certainty.

Although other variables with controversial or unknown influence on fibrillatory rate such as left atrial size, beta-blockers, calcium channel blockers, or digoxin were not included in the matching procedure, they were distributed evenly among the two groups and, in addition, were not associated with fibrillatory rate.

Although there was literally no fibrillatory rate difference between patients with or without stroke, but a lower fibrillatory rate in patients aged ≥85 years.

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<th>Table 1: Patient characteristics</th>
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<tr>
<td>Clinical characteristics</td>
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<td>Age, years 65–74, n (%)</td>
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<td>75–84, n (%)</td>
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<td>≥85, n (%)</td>
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<td>Male sex, n (%)</td>
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<td>AF duration (months)</td>
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<td>Hypertension, n (%)</td>
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<td>Congestive heart failure, n (%)</td>
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<td>Coronary artery disease, n (%)</td>
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<td>CHADS2 score</td>
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<td>1, n (%)</td>
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<td>≥2, n (%)</td>
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<tr>
<td>Medication on admission</td>
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<td>Beta-blocker, n (%)</td>
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<td>Calcium channel blocker, n (%)</td>
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<td>Digitalis, n (%)</td>
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<td>ACE inhibitor/angiotensin</td>
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<td>receptor blocker, n (%)</td>
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<td>Coumadin, n (%)</td>
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<td>Aspirin, n (%)</td>
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<td>LAD (mm)</td>
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<td>LVEF (%)</td>
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<td>Atrial fibrillatory rate (fpm)</td>
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*aCases (N = 28) and controls (N = 65).*

Figure 2: Fibrillatory rates in patients without (closed circle) or with (open circle) stroke stratified by age. Please note that there was no fibrillatory rate difference between patients with or without stroke, but a lower fibrillatory rate in patients aged ≥85 years.

Echocardiography data were not available for all patients and controls, but left atrial diameter and left ventricular ejection...
fraction were similar in both groups and are representative of those found in the older AF population.

Finally, findings and discussion on the relation between age and fibrillatory rate must also be interpreted with caution and should be explored in a longitudinal study that may also detect other, so far unknown modulating factors of fibrillatory rate. Among those, acute effects of stroke itself on the fibrillatory rate cannot be ruled out, although especially in long-lasting AF, as in our population, there is only minor (autonomic tone mediated) fibrillatory rate variation.

Conclusions
Atrial fibrillatory rate obtained from surface ECG lead V1 is not a risk marker for stroke in subjects with AF. Ageing is associated with a fibrillatory rate decrease that may be a sign for advanced atrial remodelling.

Conflict of interest: none declared.

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