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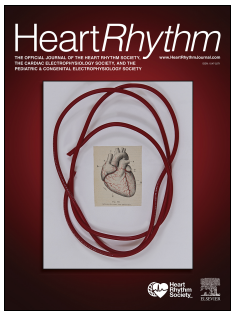

Heart rate variability and stroke or systemic embolism in patients with atrial fibrillation

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Heart rate variability and stroke or systemic embolism in patients with atrial fibrillation

Running title: HRVI and stroke in AF

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Conflict of interest

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Abstract

Background: Stroke remains one of the most serious complications in atrial fibrillation (AF) patients and has been linked to disturbances of the autonomic nervous system.

Objective: We hypothesized that impaired cardiac autonomic function might be associated with an enhanced stroke risk in AF patients.

Methods: We enrolled 1922 AF patients who were either in sinus rhythm (SR-group, n=1121) or AF (AF-group, n=801) on a 5-minute resting ECG recording. HRV triangular index (HRVI), standard deviation of normal-to-normal intervals, root mean square root of successive differences of normal-to-normal intervals, mean heart rate, 5-min total power and power in the high frequency, low frequency and very low frequency range were calculated. We constructed Cox regression models to examine the association of HRV parameters with the composite endpoint of stroke or systemic embolism.

Results: Mean age was 71±8 years in the SR group and 75±8 in the AF group. 37 patients in the SR group (3.4%) and 60 patients in the AF group (8.0%) experienced a stroke or systemic embolism during a follow-up time of 5 years. In patients with SR, HRVI <15 was the strongest HRV parameter to be associated with stroke or systemic embolism (hazard ratio 3.04; 95% confidence interval 1.3-7.0; p=0.009) after adjustment for multiple confounders. In the AF group, we found no HRV parameter to be associated with the composite endpoint.

Conclusion: HRVI measured during SR on a single 5-minute ECG recording is independently associated with stroke or systemic embolism in AF patients. HRV analysis in SR may help to improve risk stratification in AF patients.

Keywords: atrial fibrillation, stroke, cardiac autonomic function, heart rate variability, ECG

Abbreviations

HF	power in the high frequency range (0.15–0.4 Hz)
HRVI	heart rate variability triangular index
LF	power in the low frequency range (0.04–0.15 Hz)
MHR	mean heart rate
RMSSD	root mean square of successive differences
SDNN	standard deviation of the normal-to-normal intervals
VLF	power in the very low frequency range (≤0.04 Hz)

Introduction

Stroke is one of the most important complications in patients with atrial fibrillation (AF) and can be effectively reduced by oral anticoagulation. However, despite the evident benefits of oral anticoagulation, patients with AF have an appreciable residual risk for stroke[1-4]. Numbers of strokes are expected to rise in the near future[5]. Therefore, further stroke risk stratification tools beyond the CHA_2DS_2-VASc score are of high clinical value for patients with AF.

Dysfunction of the cardiac autonomic nervous system, characterized by an increase in sympathetic activity and vagal withdrawal, plays a major role in the pathogenesis of various cardio- and cerebrovascular diseases and is associated with a poor outcome[6]. Cardiac autonomic parameters are strong risk predictors in patients after myocardial infarction, diabetes and heart failure[7]. Cardiac autonomic dysfunction and stroke share common cardiovascular risk factors, such as diabetes and hypertension. Therefore, cardiac autonomic dysfunction may precede stroke and indicate an enhanced stroke risk[8-10]. Thus, cardiac autonomic parameters might be suitable tools for risk stratification in AF patients.

In this analysis of a large prospective multicenter cohort of AF patients, we aim to investigate whether cardiac autonomic function (CAF), assessed via short-term heart rate variability (HRV), is associated with stroke or systemic embolism.

Methods

Patient population

The Swiss Atrial Fibrillation (Swiss-AF) cohort is an ongoing, prospective cohort study at 14 sites across Switzerland. Detailed information about study design and methodology have been described previously[11]. In short, patients qualified for Swiss-AF when they had a documented history of AF and an age ≥ 65 years. A small subset of participants aged 45-65 years was also recruited to analyze the economic burden of AF in younger patients still active in the working life. Exclusion criteria were the inability to provide informed consent, secondary reversible forms of AF, and any acute illness within 4 weeks prior to enrolment.

Of the 2415 patients originally included in Swiss-AF (Figure 1) we excluded 14 patients in whom no resting ECG was performed at baseline and 38 patients with low quality ECGs. After rhythm analysis of baseline ECGs, we excluded a total of 407 patients due to other rhythms than sinus rhythm (SR) or AF (in detail: 360 patients with paced rhythms, 34 with atrial flutter, 6 with atrial tachycardia, 5 with junctional rhythm, 1 with alternating rhythms, 1 with multiple ventricular bigeminy). We excluded 34 patients due to missing follow-up information or withdrawal of informed consent. Thus, 1922 patients (79.5%) were available for the present analysis, of whom 1121 patients were in SR during baseline ECG ("SR group") and 801 patients in prevalent AF ("AF group"). Accordingly, the SR group consists of patients with paroxysmal or persistent AF. The AF group includes patients with paroxysmal, persistent or permanent AF (AF types were defined according to current ESC guidelines[12]). All analyses were performed separately between the SR group and the AF group, because markers of HRV are predominantly established when calculated during SR[13]. Therefore, the SR group was our primary study group. The study was performed in accordance with the declaration of Helsinki, the study protocol has been approved by the local ethics committees and all study participants gave informed consent.

Clinical parameters

We used standardized case report forms to obtain information on patient characteristics, medical history, comorbidities, medical and interventional treatment, and risk factors. Each participant was interviewed on an annual basis with in-person visits. If not possible, each study center offered a telephone call or home visit to obtain follow-up information. As this was an observational study, decisions regarding oral anticoagulation and therapies aiming at rhythm control at baseline or during follow-up were made by the treating physician.

Resting ECG recordings

At baseline, all ECGs comprised 16 leads and were recorded for a total duration of 5 minutes under standardized resting conditions (69% between 6 a.m. and 12 a.m. and 31% between 12 a.m. and 6.30 p.m.). All recordings were saved digitally on a central server with a sampling frequency of 1 kHz (signal bandwidth 0.04-387 Hz) and a resolution of 1µV/bit. We derived

short-term HRV[14] from these ECG recordings and calculated the following time and frequency domain measures of HRV according to previously published algorithms[13]: heart rate variability triangular index (HRVI), mean heart rate (MHR), root mean square of successive differences (RMSSD), standard deviation of the normal-to-normal intervals (SDNN), 5-min total power, power in the very low frequency range (VLF, ≤0.04 Hz), in the low frequency range (LF, 0.04–0.15 Hz) and in the high frequency range (HF, 0.15–0.4 Hz). We a priori decided to use the same cut-off for each HRV parameter as published previously[15].

Clinical outcome measures

The primary endpoint was a composite of stroke (ischemic and haemorrhagic) or systemic embolism in the SR group occurring within a follow-up time of 5 years. All clinical events were reviewed and adjudicated by two investigators. In the case of disagreement, a third investigator revised the event. Stroke was defined as an acute focal neurological deficit of vascular origin with evidence of infarction validated by imaging or autopsy[11]. Systemic embolism was defined as an acute vascular occlusion of the extremities, or any organ (kidneys, mesenteric arteries, spleen, retina or grafts) confirmed by imaging studies or autopsy[11].

Statistical analysis

Patient's baseline characteristics were classified by baseline rhythm (SR versus AF). Means (± standard deviation) are presented for normally distributed continuous variables, whereas medians are used for not normally distributed continuous variables. Counts (percentage) represent numbers for categorical variables. Frequency domain measures of HRV were log-transformed. We constructed an age-sex adjusted Cox regression model and a multivariable Cox regression model (additionally adjusted for AF type, history of stroke or transient ischemic attack (TIA), intake of oral anticoagulation, performance of pulmonary vein isolation (PVI) or electrocardioversion (ECV) to test the association of each HRV parameter with the primary endpoint. The variables "intake of oral anticoagulation, performance of PVI or ECV" were time updated on a yearly basis according to the information obtained at each follow-up visit. We used the same predefined cut-offs for each HRV parameter as published previously[15]. Survival curves were estimated using the Kaplan-Meier method. Results of the Cox regression models are presented as hazard ratios (HRs) with the corresponding 95% confidence intervals (CIs).

Statistical analyses were performed using SPSS IBM SPSS Statistics for Windows, Version 25 (IBM Corp., Armonk, NY) and R version 4.2.1 (2022-06-23, R Core Team).

Results

Detailed baseline characteristics of the SR and AF group are shown in Table 1. In the primary study group (SR group, n=1121), mean age was 71±8 years and 31% of the participants were females. Diabetes mellitus was present in 13% of patients, hypertension in 65%, chronic kidney disease in 14%, heart failure in 16 %, prior stroke/ TIA in 17% and prior myocardial infarction in 12%. The mean CHA_2DS_2-VASc score was 3.0±1.7. 857 of 1121 patients had at a least a CHA_2DS_2-VASc score of $\geq$ 2 (male) or 3 (female). Hereof, a total of 766 patients (89.4%) were on oral anticoagulation. 66% of the patients had paroxysmal and 34% had persistent AF. Antiarrhythmic drugs (class Ic and III) were prescribed in 31% of patients, betablockers were used in 65%. At baseline, 38% had undergone a previous ECV and 34% a PVI.

During a mean follow-up time of 5 years, 37 patients in the SR group experienced the primary endpoint. 17 of the 37 patients (46%) were in AF at the day of stroke or systemic embolism, and 20 patients (54%) were in AF. In detail, there were 29 ischemic strokes, 7 hemorrhagic strokes and 4 systemic embolisms. Three of the 37 patients had two events (ischemic stroke and systemic embolism). The cumulative incidence of stroke or systemic embolism was 3.30%. Median HRVI was 14.3 (IQR 11.8 - 17.8), SDNN was 88.8 ms (IQR 47.3 - 146.0), rMSSD was 35.9 ms (IQR 21.3 - 46.7), MHR was 86 bpm (IQR 64 – 144), log 5 minute total power was 3.4±0.8, log LF was 3.2±0.8, log HF was 2.8±0.8 and log VLF was 3.1±0.9. The 37 patients who experienced a stroke or systemic embolism had a lower baseline mean HRVI of 12.9 (11.3-14.5), compared to patients without an event during follow-up (14.4 (11.9-17.9), p=0.042). An example of a patient with an impaired HRVI and stroke during follow up and a patient with a preserved HRVI and no event is displayed in Figure 2. In a univariable Cox proportional hazards model, HRVI <15 (HR 3.44; 95% CI 1.52- 7.82; p=0.003) and MHR≥80 bpm (HR 2.18; 95% CI 1.08-4.39; p=0.030) were associated with the composite of stroke or systemic embolism. After adjustment for age and sex, HRVI <15 was the strongest parameter to be independently associated with the primary endpoint (HR 3.05; 95% CI 1.34-6.97; p=0.008). The association of

HRVI <15 remained of a similar magnitude after multivariable adjustment (HR 3.04; 95%CI 1.32-6.96; p=0.009; Table 2, Figure 3 left panel). Mean HRVI was lower in patients suffering from stroke or systemic embolism (mean 14.0±4.51 vs 15.6±5.55, p=0.040) in comparison to patients without stroke or systemic embolism. Compared to the clinical covariables, HRVI <15 was most strongly associated with stroke or systemic embolism (HR 3.04; 95% CI 1.32-6.96, p=0.009, Supplemental Table 1). MHR≥80bpm was also independently associated with stroke or systemic embolism when adjusted for age and sex (HR 2.10; 95% CI 1.01-4.35; p=0.046) and after multivariable adjustment (HR 2.14; 95% CI 1.03-4.45; p=0.042).

In the AF group, 60 patients experienced the primary endpoint. Ischemic strokes occurred in 45 patients, hemorrhagic strokes in 12 patients and systemic embolisms in 5 patients. Two of the 60 patients had two events (ischemic stroke and systemic embolism). The cumulative incidence of stroke or systemic embolism was 7.49%. Median HRVI was 15.3 (IQR 12.7 – 18.6), SDNN was 101.9 ms (IQR 77.9 – 133.8), rMSSD was 54.0 ms (40.9 – 74.1), MHR was 127 bpm (IQR 87 – 152), log 5 minute total power was 3.7±0.3, log LF was 3.5±0.3, log HF was 3.1±0.3 and log VLF was 3.3±0.6. No single HRV parameter was associated with stroke or systemic embolism (Supplemental Table 2, Figure 3 right panel). HRVI was similar in patients with and without stroke or systemic embolism (mean 15.3±4.25 vs 16.1±4.51, p=0.364).

Discussion

We assessed whether cardiac autonomic dysfunction by means of HRV is associated with an increased risk of stroke or systemic embolism in a large AF cohort. The main findings of our analysis are: (1) HRV triangular index assessed from 5-minute SR ECGs is independently associated with stroke or systemic embolism during a mean follow-up of 5 years in patients with AF. (2) Mean heart rate ≥80bpm is also independently associated with stroke or systemic embolism when assessed during SR, but to weaker extent(3) HRV parameters calculated from AF ECGs do not carry prognostic information regarding stroke or systemic embolism.

In this analysis, we were able to show that an impaired HRVI calculated from baseline 5-minute resting ECGs was independently associated with stroke or systemic embolism during follow-up in predominantly anticoagulated AF patients (89.8 % on oral anticoagulation), as long as

HRVI was assessed during SR. Patients with a CHA_2DS_2-VASc scores of ≥ 2 (male) or 3 (female) were even more frequently treated with oral anticoagulants (91.8%). Elevated mean heart rate, which is a known predictor of adverse cardiovascular outcome, was also significantly associated with stroke or systemic embolism in the SR cohort, but to a smaller extent than HRVI. HRV analyses are well established during SR[13], whereas the calculation of HRV during AF is not that well understood[16]. However, we also performed separate analyses to test the value of HRV in the AF group, where (as expected) we did not find any HRV parameter to be associated with the combined endpoint of stroke or systemic embolism. This finding is in line with previous investigations showing that standard measures of HRV during AF may not provide prognostic information[17]. Therefore, most studies assessing the predictive value of HRV so far excluded patients in AF. However, other autonomic measures not used in this study might also provide important clinical information in AF-ECGs. Furthermore, the SR and AF group differ substantially in their baseline characteristics. This may also attenuate the prognostic meaning of HRVI.

Patients with AF are at an enhanced risk for thromboembolic events, such as stroke or systemic embolism. A meta-analysis of 5 randomized controlled trials revealed an annual stroke risk of 4.5% in non-anticoagulated patients vs 1.4% in patients treated with warfarin[18]. Clinical risk scores, such as CHA_2DS_2-VASc score, have been developed in order to predict an individual`s stroke risk. However, its predictive power is only moderate (C-statistic approximately 0.6)[19]. Most other available stroke risk scores including biomarkers have a C-statistic of approximately 0.6-0.67. Therefore, risk markers complementary to the established methods are warranted. HRV parameters offer the advantage of being inexpensive, easily, and quickly obtainable from routine ECG recordings.

Only three studies investigated the prognostic value of autonomic variables and stroke occurrence in AF patients so far. These studies reported that entropy and other complex markers are associated with the occurrence of incident ischemic stroke[17, 20, 21]. However, they excluded patients in SR (e.g., paroxysmal AF) and used long-term ECG recordings (24-hour Holter ECG recording). There are also only few studies investigating the predictive power of HRV for incident ischemic stroke in general populations without AF. A study including more than 12.000 middle-aged adults showed a higher stroke risk to be associated with the lowest

HRV quintiles[10]. In 139 patients with stable ischemic heart disease, patients who reported positive for stroke during follow-up demonstrated baseline reductions in HRV parameters[22]. In 653 healthy elderly individuals, stroke risk was significantly associated with nighttime SDNN derived from 48-hour Holter ECG recordings[23]. Finally, it was shown that HRV parameters were significantly associated with incident stroke in 884 middle-aged patients when added to a validated clinical risk score[24].

HRV triangular index is a geometrical measure of HRV, derived from standard ECG recordings, and is a robust and reproducible marker of global HRV[13]. The calculation of HRVI was described previously[13, 25]. Prior studies in the Swiss-AF cohort have shown that an impaired HRVI is an independent predictor of cardiovascular mortality[25], is associated with silent brain infarcts on MRI[15] and with a worse cognitive performance in the Montreal-Cognitive-Assessment test[26]. The present analysis is the first to prospectively show that HRVI is associated with future strokes and systemic embolisms, an endpoint that is of high relevance in AF patients.

A large body of evidence supports a pathophysiological link between reduced HRV and incident stroke[10, 17, 20, 22, 27]. Stroke and HRV impairment have similar cardiovascular risk factors. In patients with cardiovascular diseases, HRV impairment could precede the occurrence of a stroke and might therefore be a marker of an enhanced stroke risk, as shown by our data. Furthermore, impairment of HRV can also be a direct stroke complication if cerebral regions responsible for autonomic control get ischemic (especially right insular cortex region)[28]. Consequently, impairment of the cardiac autonomic function has been observed in various stroke cohorts[8, 29, 30]. In addition, stroke is thought to contribute to cardiac autonomic derangement via a catecholaminergic overdrive[8, 9, 29, 31]. Furthermore, HRV reduction is a marker of post-stroke morbidity, disability, and mortality. In the SR group of our cohort, 17% of patients had a history of stroke/TIA at baseline. However, we found similar results when excluding patients with a history of stroke/TIA from our analysis (HRVI<15: HR 3.25, 95% CI 1.16-8.25, p=0.018).

Strengths and limitations

A major strength of our study is the availability of a large number of ECGs from of a well-characterized prospective AF cohort with a low number of lost to follow-up. However, when

interpreting our results various limitations should be taken into consideration. First, we assessed HRV parameters in short-term ECG recordings over a period of 5 minutes, whereas 24-hour Holter ECG recordings still represent the gold standard for HRV assessment. However, short-term HRV is already established in research[14] and can be easily performed under standard resting conditions. Second, the association of an impaired HRVI with stroke or systemic embolism was only present if calculated during SR. Therefore, patients in AF may not benefit from HRVI assessment. Third, given the nature of our observational study, we cannot establish causality. Therefore, we cannot rule out that some unknown confounders might have an impact on our results. Finally, this is a secondary, exploratory analysis of the Swiss-AF cohort and generalizability to other patient populations remains to be determined.

Conclusions

In conclusion, HRVI assessed in SR is the strongest HRV parameter being independently associated with the development of stroke or systemic embolism in patients with AF. HRV analysis may be a promising component to determine individual stroke risk, particularly in patients where AF has not yet progressed to a more sustained form of the arrhythmia. In the future, HRV analysis in SR may help to improve risk stratification in AF patients.

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Table 1 Characteristics of atrial fibrillation patients grouped by baseline ECG rhythm

Characteristic	**SR group (n=1121)**	**AF group (n=801)**
Age, years	71±8	75±8
Female sex, No. (%)	351 (31)	181 (23)
Body mass index, kg/m2	27.3±4.8	28.3±4.9
Blood pressure, mm Hg	136±18/77±11	133±18/79±13
History of hypertension, No. (%)	725 (65)	600 (75)
History of diabetes mellitus, No. (%)	147 (13)	164 (21)
Active and former smokers (%)	626 (56)	454 (57)
History of electrocardioversion, No. (%)	429 (38)	263 (33)
History of pulmonary vein isolation, No. (%)	375 (34)	50 (6)
History of myocardial infarction, No. (%)	135 (12)	136 (17)
History of heart failure, No. (%)	184 (16)	262 (33)
History of chronic kidney disease, No. (%)	160 (14)	189 (24)
History of clinical stroke or TIA, No. (%)	188 (17)	196 (25)
Paroxysmal atrial fibrillation, No. (%)	736 (66)	124 (16)
Persistent atrial fibrillation, No. (%)	385 (34)	233 (29)
Permanent atrial fibrillation, No. (%)	0 (0)	444 (55)
CHA_2DS_2-VASc score	3.0±1.7	3.8±1.7
Antiarrhythmic therapy (class Ic and III), No. (%)	343 (31)	192 (24)
Beta-blockers, No. (%)	724 (65)	570 (71)

Direct oral anticoagulants, No. (%)	682 (61)	330 (41)
Vitamin K antagonists, No. (%)	289 (26)	425 (53)

Data are means ± SD or counts (percentages). * p value compares patients with SR and AF. P values were obtained from Wilcoxon's rank-sum tests (Mann-Whitney U-test) for continuous variables and chi-square tests for categorical variables. CHA_2DS_2-VASc = congestive heart failure, hypertension, age ≥75 yeas (2 points), diabetes, prior stroke or TIA or thromboembolism (2 points), vascular disease, age 65 to 74 years, female sex; TIA = transient ischemic attack. No. = number.

Table 2 Cox proportional Hazard Models for the association of autonomic markers with stroke or systemic embolism in AF patients (SR at baseline)

Autonomic Parameter	**No. of patients with events**	**Incidence/1000 patient years**	**Age-sex adjusted Model HR (95% CI)**	**p-value**	**Multivariable Model HR (95% CI)**	**p-value**
HRVI						
HRVI≥15 (Ref.)	7	1.25	3.050 (1.34; 6.97)	**0.008**	3.037 (1.32; 6.96)	**0.009**
HRVI<15	30	5.35				
SDNN						
SDNN≥70ms (Ref.)	27	4.821.78	0.61 (0.30 – 1.27)	0.188	0.62 (0.30 – 1.29)	0.201
SDNN<70ms	10					
rMSSD		2.32				
rMSSD≥42ms (Ref.)	13	4.28	1.09 (0.56 – 2.16)	0.797	1.08 (0.55 – 2.13)	0.825
rMSSD<42ms	24					
MHR						
MHR<80bpm (Ref.)	10	1.784.82	2.10 (1.01 – 4.35)	**0.046**	2.14 (1.03– 4.45)	**0.042**
MHR≥80bpm	27					
Log 5 min total power			1.26 (0.78 – 2.01)	0.343	1.25 (0.77 – 2.00)	0.367
Log LF			1.20 (0.77 – 1.84)	0.421	1.19 (0.76 – 1.84)	0.449
Log HF			1.29 (0.79 – 2.11)	0.308	1.28 (0.78– 2.09)	0.325
Log VLF			1.02 (0.69 – 1.52)	0.914	1.00 (0.67 – 1.49)	0.999

Data are hazard ratios (HR) (95% confidence intervals [CI]). P-values were based on Cox regression models. Frequency domain measures of HRV have been log transformed. HF = high frequency (0.15-0.4 Hz). HRVI = HRV index. LF = low frequency (0.04 – 0.15 Hz). MHR = mean heart rate. No.= number. Ref. = reference. rMSSD = square root of the mean squared differences of successive normal-to-normal intervals. SDNN = standard deviation of the normal-to-normal intervals. SR = sinus rhythm. VLF = very low frequency (≤0.04 Hz). Multivariable model was adjusted for the age, sex, AF type, time updated oral anticoagulation, time updated pulmonary vein isolation and time updated electrocardioversion.

Figure legends

Figure 1: Flowchart of patient inclusion

Figure 2: Example of impaired (left panel) and a preserved (right panel) heart rate variability triangular index in patients with and without stroke or systemic embolism during 5-year follow-up

Figure 3: Cumulative rates of stroke or systemic embolism of patients stratified by heart rate variability triangular index (left panel: sinus rhythm ECG at baseline, right panel: atrial fibrillation ECG at baseline)

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