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Noninvasive estimation of organization in atrial fibrillation as a predictor of sinus rhythm maintenance

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Abstract

Previous studies indicate that the predictive value of atrial fibrillatory rate in patients undergoing cardioversion of atrial fibrillation (AF) of long duration is limited. The present study investigates signal entropy in this setting. Standard 12-lead electrocardiograms (ECGs) were recorded from 66 consecutive patients with AF undergoing cardioversion and sample entropy estimated. Patients were followed for 4 weeks. At follow-up, 59% of the patients had relapsed to AF. The AF signal entropy of these patients before cardioversion was 0.099 ± 0.015, whereas it was 0.093 ± 0.012 among the 41% maintaining sinus rhythm ($P = .02$). As hypothesized, signal entropy was lower in patients who maintained sinus rhythm 4 weeks after cardioversion than in those who did not. However, the overlap was large, making its clinical value limited.

Introduction

In animal models, atrial fibrillation (AF) has been shown to cause electrical remodeling of the atria, with a progressive shortening of the refractory period starting immediately following arrhythmia initiation. For the AF episodes to become longer and non-self-terminating, the refractory period had to be shortened to a critical value. The authors coined the expression that "atrial fibrillation begets atrial fibrillation."[1] The term *AF organization* is generally defined as how repetitive the AF signal pattern is,[2] and it has been proposed that there is an association between the number of coexisting atrial wavelets and AF organization, with fewer wavelets correlating with a higher degree of organization.[3]

Means to noninvasively assess atrial electrical remodeling have been presented. One is by measuring the AF rate (AFR), which correlates to the atrial refractory period[4] and thus, theoretically, to the degree of atrial electrical remodeling. A high AFR is a risk factor of AF relapse following electrical cardioversion, but foremost reliable in patients with a short history of AF.[5] In a preliminary report, AF signal entropy (AFSE), that is, the degree of atrial signal irregularity, was shown to discriminate paroxysmal from persistent AF. Persistent AF was associated with higher entropy values than paroxysmal, suggesting a more disorganized atrial activity among patients with persistent AF.[6] Moreover, in another report, primarily validating the method, the same group found that AFSE was able to predict sinus rhythm (SR) maintenance in patients with longstanding AF who underwent cardioversion.[7]

The present study investigated AFSE, before cardioversion, as a predictor of SR maintenance following cardioversion. Our hypothesis was that the AFSE would be lower among the patients who maintained SR after cardioversion.

Methods

Study population

Consecutive patients with persistent AF who had been referred to the cardiology department at Lund University Hospital for cardioversion were included in this study. Exclusion criteria were changes in medication (during the study period or less than 2 weeks before inclusion in the study) or an implanted pacemaker that was active at the time of inclusion in the study. All patients were offered the possibility of not participating in the study. The study was approved by the local committee of ethics and complied with the Declaration of Helsinki.

Data collection

Standard 12-lead electrocardiograms (ECGs) of 5-minute duration were recorded before cardioversion. The data were stored digitally. Lead V1 was used for analyses in this study because it has previously been shown to have a prominent atrial activity and is believed to be best suitable for QRST cancellation. Each ECG recording was divided into sequences of 10 seconds. These short sequences were processed and analyzed individually. The atrial signal was obtained by removing the QRST signal, using spatiotemporal QRST cancellation.[8] The frequency with the highest peak in the frequency spectrum, which is equivalent to AFR, was then determined using Hidden Markov Model (HMM)-based frequency tracking.[9] To reduce residual noise in the atrial activity, the main atrial wave, which constitutes the fundamental waveform of the atrial activity, was obtained from the atrial activity by applying a selective bandpass filter, based on the AFR. Then, AFSE was computed for every 10-second interval. All analyses were entirely automatic by computer, and the operator was

blinded to the result of the cardioversion. Greater AFSE values correspond to more data irregularity. For further details, please refer to Alcaraz et al.[6] A mean AFSE value and mean AFR for the whole recording for each patient were finally calculated. The method used is described in detail elsewhere.[6] and [9]

A standard transthoracic echocardiography was performed in connection with the cardioversion.

Study protocol

The patients were classified as asymptomatic if AF had been diagnosed on routine ECG without simultaneous symptoms. *Atrial fibrillation duration* was defined as the time from the debut of symptoms, or from the latest ECG-confirmed SR among the asymptomatic patients, to cardioversion. *Left ventricular ejection fraction* (LVEF) was defined as either normal (LVEF ≥ 55%) or subnormal (LVEF < 55%).

All patients underwent external DC cardioversion. The cardioversion was considered successful if the AF ceased and was followed by at least 2 SR beats. Before hospital discharge, all successfully cardioverted patients were evaluated by ECG.

The patients were followed for 4 weeks. They were offered ECG if they experienced AF symptoms. At follow-up, 4 weeks postcardioversion, new ECG recordings were acquired for rhythm analysis. All drugs with effect on the heart were left unchanged for the duration of the study.

Statistics

Normally distributed data are presented as mean ± SD. Median (and range) is used when normal distribution could not be assumed. Mann-Whitney *U* test was used for continuous variables, and Fisher exact test was used for discrete variables. All tests

were 2 sided, and a *P* value of less than .05 was considered statistically significant. All statistical analyses were carried out using PASW Statistics 18.0.1 (SPSS Inc, Chicago, IL).

Results

Data availability

A total of 73 patients fit the inclusion criteria and were included in the study. The analyses failed on 7 occasions. Echocardiography was not performed in 3 cases, where data concerning left atrial diameter and LVEF are missing. The AF duration was unknown in one case and the possible presence of symptoms in another. These patients contributed to the study in all respects, with the exception of the data that were missing.

Study population

In total, 66 patients (46 men; median [range] age, 69 [34-82] years) were included in this study. Roughly one third, 36%, of the patients had AF alone, whereas the rest had some other concomitant heart disease. Most patients (91%) were on cardioactive medication (Table 1). Symptoms of AF were reported by 71% of the patients. One third of the patients had a history of AF. The median (range) AF duration was 133 (2-983) days. Echocardiography found a mean (SD) left atrial diameter of 49 (7) mm measured in parasternal view. The LVEF was normal in 52% of the patients and subnormal in 44%. At the 4-week follow-up, 59% of the patients had relapsed to AF.

Observed parameters in relation to rhythm at follow-up

Notable is the higher prevalence of congestive heart failure (28% vs 4%, $P = .02$) among the patients who relapsed to AF, compared with the ones who maintained SR. The use of digitalis was also higher among the patients relapsing to AF (49% vs 22%, $P = .04$). The median (range) AF duration turned out to be significantly different in the 2 groups at follow-up: 163 (2-983) days in the AF group and 90 (2-240) days in the SR group, $P < .05$. As for the other patient characteristics (i.e. age, sex, symptoms, AF history, other heart diseases except congestive heart failure, left atrial diameter, LVEF, cardioactive drugs except digitalis), none were found to be significantly different in the 2 groups. Please refer to Table 1 for a complete description of all characteristics.

The mean AFR was higher among the patients who relapsed to AF (372 ± 48 fibrillations per minute) compared with the ones maintaining SR (350 ± 40 fibrillations per minute), $P = .02$. Also, the mean AFSE before cardioversion turned out to be significantly higher among patients relapsing to AF: 0.099 ± 0.015 vs. 0.093 ± 0.012 among patients remaining in SR ($P = .02$) (Fig. 1).

Further investigation of the properties of AFSE

Patients with valvular disease had a significantly lower AFSE (0.066 [0.058-0.084]) than did other patients (0.099 [0.075-0.135]), $P < .0001$. β-Blocker usage was associated with a slightly higher AFSE (0.100 [0.062-0.135]) compared with other patients (0.092 [0.058-0.110]), $P = .04$. Patients on renin-angiotensin-aldosterone system (RAAS) inhibitors demonstrated a higher AFSE (0.103 [0.075-0.126]) than did those not on medication (0.096 [0.058-0.135]), $P = .03$. On the other hand, patients on Ca^{2+}-channel blockers had a significantly lower AFSE (0.087 [0.066-0.103]) than did other patients (0.100 [0.058-0.135]), $P = .004$. Please refer to Table 2

for more details. The correlation between AFR and AFSE turned out to be very high: a Pearson correlation coefficient, r, of 0.996 ($r^2 = 0.992$) (Table 3).

The distribution of AFSE was the same among patients with an AF duration of less than 30 days (0.099 [0.075-0.103]; n = 5) and patients with a duration of 30 days or more (0.099 [0.058-0.135]; n = 60), $P = .40$. The same was true when patients with AF for less than 60 days (0.099 [0.062-0.110]; n = 17) were compared with patients with AF for 60 days or more (0.098 [0.058-0.135]; n = 48), $P = .91$.

Discussion

The AFSE was significantly lower among patients remaining in SR 4 weeks after cardioversion than among those who relapsed to AF. However, there was a great overlap between the 2 groups. No clinically applicable cutoff values for predicting if a patient is likely to maintain SR or relapse to AF could hence be established.

Methodological issues

The method described and used in the present study has been validated in previous studies.[2], [6] and [9] Alcaraz et al[2] and [6] demonstrated that persistent AF is associated with higher AFSE, that is, a more irregular atrial signal, than paroxysmal AF. This is consistent with invasive findings in humans[10] and dogs,[3] which also demonstrated a greater disorganization in the atrial activity in persistent AF than in paroxysmal AF. The definite biological correlate to AFSE is still lacking.

Because lead V1 is most often analyzed, it is mainly the activity of the right atrium that is estimated, which may limit the ability to obtain a more global atrial

organization measure. The most obvious advantage of the present method is its noninvasive nature, making it suitable for analyzing large patient cohorts.

Study population and traditional factors predicting SR maintenance

More than twice as many men as women were included in this study. It is known that the overall prevalence of AF is about equal among men and women; men predominate among younger patients and women among older (60% of the AF patients older than 75 years are women).[11] The median age in the present study was 69 years; hence, a more equal sex distribution would have been expected. The male predominance in this study may very well be by chance but could possibly also reflect a generally lower likelihood to refer women to cardioversion. The observed AF relapse rate of 59%, 4 weeks after cardioversion, is consistent with previously published data.[12] and [13] In summary, the study population is likely to be representative of the clinical reality.

The median duration of AF was marginally shorter among the patients who maintained SR than among those who did not. Some investigators have made similar findings,[14] whereas others report no association.[15] It has been demonstrated that AF duration of more than 3 weeks has little or no effect on electrical remodeling, and it is therefore likely that the electrical remodeling process is primarily active during the first few weeks of arrhythmia.[16] Congestive heart failure was found to be more common in the group of patients relapsing to AF. Although the clinical association between congestive heart failure and AF is well established,[17] findings in a study similar to the present did not observe this relation.[18] However, that study is different in ways that may be of importance. Foremost, the median AF duration in the present

study was 4 months, whereas the mean AF duration was 15 months in the study by Biffi et al.[18]

Digitalis medication was associated with relapse to AF. There are at least 2 plausible explanations to this. First, digitalis is more often used in patients with congestive heart failure, which, in itself, was found to be a predictor of AF relapse in this study. Second, electrical remodeling is believed to be mediated by a reduction of Ca^{2+} currents through L-type Ca^{2+} channels.[19] Digitalis is known to increase intracellular $[Ca^{2+}]$[20] and could hence, hypothetically, contribute to the electrical remodeling of the atria, rendering the patient prone to AF relapse.

The present study did not confirm left atrial size to be a predictor of SR maintenance. Others have reported a large left atrium to be associated with AF relapse.[15] and [21] However, the power of the present study is not sufficient to reject the widespread notion that a greater left atrial diameter is associated with AF relapse. Patients with valvular disease were found to have a significantly lower AFSE than other patients. It should, however, be noted that only 5 patients had valvular disease; hence, these results should be interpreted with caution. Further studies are needed to confirm or reject this finding.

Patients on β-blockers and RAAS inhibitors had a slightly higher AFSE. Patients on Ca^{2+}-channel blockers turned out to have a significantly lower AFSE. The responses of AFSE to these drugs have not been studied, and hence, the reasons for these findings are unknown.

Indices of electrical remodeling and SR maintenance

The finding of a lower AFSE and a lower AFR in patients maintaining SR following cardioversion is in keeping with the experimental studies on electrical remodeling and

on the clinical studies using noninvasive indices thereof.[1], [5], [6] and [22] However, as in earlier observations from our group studying AFR as an index of atrial remodeling, the overlap between patients maintaining SR and those not maintaining SR is extended.[5] In the present study, the performance of AFSE and AFR was virtually identical. Previous studies have shown slightly better performance of AFSE when discriminating paroxysmal from persistent AF[2] and [6] and predicting SR maintenance following cardioversion.[7] Direct comparison with the cardioversion study by Alcaraz and Rieta[7] is hampered by differences in patient selection and, to some extent, in methodology. The study by Alcaraz and Rieta included patients with very long AF duration (mean, about 10 months; range, 1 to 54 months), a fact that may influence the properties of AFSE, although the primary time "window" of electrical remodeling is most probably closed, as discussed earlier. Moreover, all patients were on amiodarone treatment as opposed to only a single patient in the present study. The impact of amiodarone on AFSE has, to the best of our knowledge, not been described, but antiarrhythmic treatment has in a previous study been shown to alter the predictive properties of AFR in a similar patient population.[5] Finally, the AFSE was estimated using the 10-second ECG recording in the study by Alcaraz and Rieta, whereas in the present study, recordings of 5-minute lengths were used. The possible impact of this, if any, is not known. A very high correlation between AFR and AFSE was found. This is, to some extent, expected because AFSE depends on the AFR, from a methodological standpoint. The earlier studies have shown similar results in this respect, although with slightly lower correlation coefficients.[6] This raises the question of the necessity of analyzing AFSE in addition to the, so far, better-characterized AFR.

Study limitations

Seven ECGs could not be analyzed because of high noise level. However, they were few and unlikely to have influenced the overall results. The patient characteristics of these 7 patients did not differ when compared with the 66 patients included in the study. All omitted data, for example, echocardiography results, were random and unintentional. There is no reason to believe that any biased selection has occurred.

Conclusion

We demonstrated that the AFSE was lower among patients who maintained SR 4 weeks after cardioversion than among those who did not. Unfortunately, no clinically applicable cutoff value for predicting what patients are prone to remain in SR could be established, because the overlap in AFSE values between patients remaining in SR and those who relapsed to AF was great.

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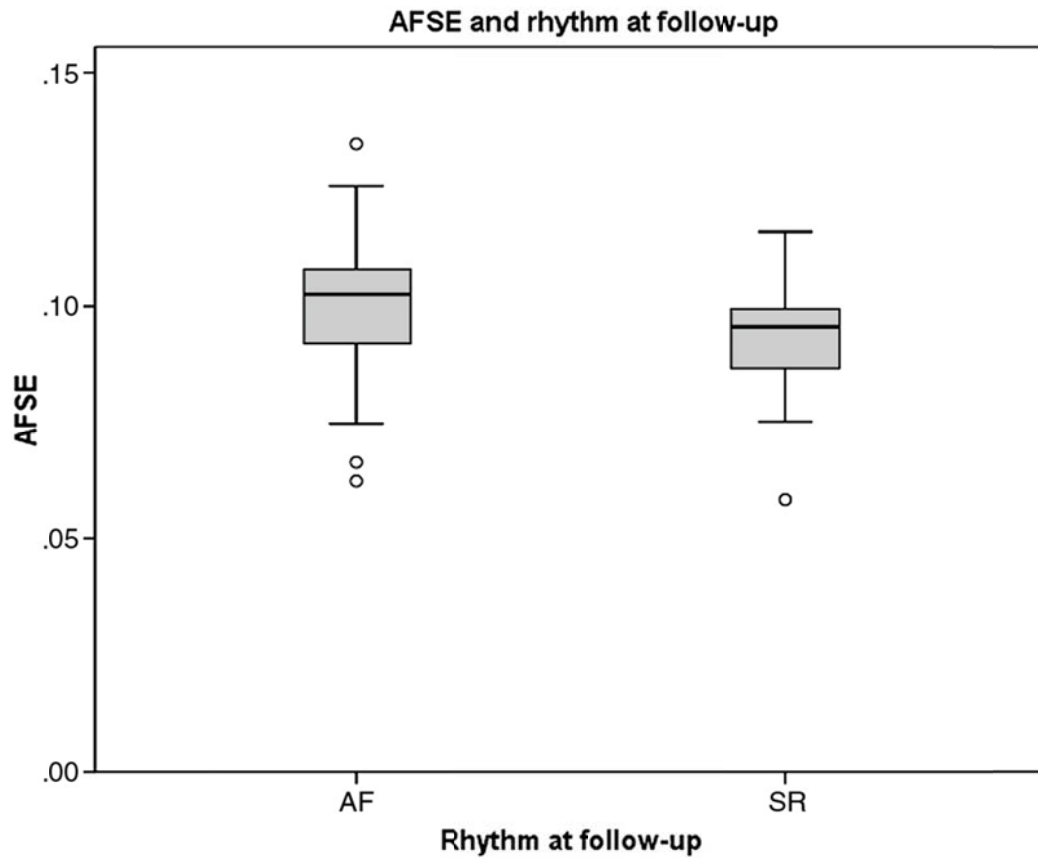
Fig. 1. The difference in AFSE between patients maintaining SR (mean ± SD, 0.093 ± 0.012) and patients relapsing to AF (mean ± SD, 0.099 ± 0.015), $P = .02$. The dark line represents the median, the bottom of the box is the 25th percentile, and the top of the box is the 75th percentile. The whiskers extend 1.5 times the height of the box at most. The circles represent outliers (i.e. values extending more than 1.5 times the height of the box).

Table 1 Clinical characteristics of the study population as a whole and with respect to rhythm at follow-up

	Study population (n = 66)	SR at follow-up (n = 27)	AF at follow-up (n = 39)	P-value
Age (y), mean (range)	69 (34-82)	69 (52-79)	70 (34-82)	.47
Male/female	46 (70%)/20 (30%)	18 (67%)/9 (33%)	28 (72%)/11 (28%)	.79
AF duration (d) mean (range)	133 (2-983)	90 (2-240)	163 (2-983)	< .05
Symptomatic: yes/no	47 (71%)/18 (27%)	20 (74%)/7 (26%)	27 (69%)/11 (28%)	1.00
History of AF	22 (33%)	11 (41%)	11 (28%)	.30
Other heart disease				
None	24 (36%)	10 (37%)	14 (36%)	1.00
Hypertension	22 (33%)	11 (41%)	11 (28%)	.30
Ischemic heart disease	11 (17%)	5 (19%)	6 (15%)	.75
Congestive heart failure	12 (18%)	1 (4%)	11 (28%)	.02
Valvular disease	5 (8%)	2 (7%)	3 (8%)	1.00
Left atrial diameter (mm), mean ± SD	49 ± 7	48 ± 8	50 ± 7	.39
LVEF: normal/subnormal	34 (52%)/29 (44%)	18 (67%)/9 (33%)	16 (41%)/20 (51%)	.13
Cardioactive drugs				
None	6 (9%)	3 (11%)	3 (8%)	.68
β-Blocker	47 (71%)	20 (74%)	27 (69%)	.79
Sotalol	7 (11%)	4 (15%)	3 (8%)	.43
Class III antiarrhythmic agent	1 (2%)	0 (0%)	1 (3%)	1.00
Digitalis	25 (38%)	6 (22%)	19 (49%)	.04
RAAS inhibitor	25 (38%)	9 (33%)	16 (41%)	.61
Ca^{2+}-channel blocker	10 (15%)	5 (19%)	5 (13%)	.73
AFR (fibrillations/min)	363 ± 46	350 ± 40	372 ± 48	.02
AFSE	0.097 ± 0.014	0.093 ± 0.012	0.099 ± 0.015	.02

Table 2 Clinical characteristics with respect to AFSE

	AFSE	P-value
Male/female	0.100 (0.058-0.126)/0.096 (0.075-0.135)	.23
Symptomatic: yes/no	0.100 (0.058-0.135)/0.094 (0.062-0.111)	.11
History of AF: with/without	0.098 (0.066-0.116)/0.099 (0.058-0.135)	.53
Other heart disease		
None/any heart disease	0.099 (0.075-0.135)/0.098 (0.058-0.126)	.71
Hypertension: yes/no	0.099 (0.058-0.135)/0.096 (0.081-0.110)	.51
Ischemic heart disease: yes/no	0.097 (0.075-0.108)/0.099 (0.058-0.135)	.61
Congestive heart failure: yes/no	0.097 (0.075-0.108)/0.099 (0.058-0.135)	.18
Valvular disease: yes/no	0.066 (0.058-0.084)/0.099 (0.075-0.135)	< .0001
LVEF: normal/subnormal	0.098 (0.058-0.112)/0.100 (0.062-0.135)	.19
Cardioactive drugs		
None/any	0.102 (0.058-0.109)/0.098 (0.062-0.135)	.89
β-Blocker: yes/no	0.100 (0.062-0.135)/0.092 (0.058-0.110)	.04
Sotalol: yes/no	0.099 (0.075-0.102)/0.099 (0.058-0.135)	.54
Class III antiarrhythmic agent: yes/no	0.103 (0.103-0.103)/0.099 (0.058-0.135)[a]	.55
Digitalis: yes/no	0.099 (0.062-0.135)/0.099 (0.058-0.116)	.56
RAAS inhibitor: yes/no	0.103 (0.075-0.126)/0.096 (0.058-0.135)	.03
Ca^{2+}-channel blocker: yes/no	0.087 (0.066-0.103)/0.100 (0.058-0.135)	.004

[a] Only one patient treated with a Class III antiarrhythmic agent.

Table 3 Correlations between continuous variables and AFSE

	r	r^2	*P*-value
Age	-0.140	0.020	.26
AF duration	-0.114	0.013	.37
Left atrial diameter	-0.148	0.022	.25
AFR	0.996	0.992	< .001

r indicates Pearson correlation coefficient; r^2, coefficient of determination.