Reduced heart rate response after premature ventricular contraction depending on severity of atrial fibrillation symptoms – Analysis on heart rate turbulence in atrial fibrillation patients☆,☆☆

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ARTICLE INFO

ABSTRACT

Background: The severity of symptoms during atrial fibrillation (AF) may be influenced by heart rate and blood pressure variation, due to irregular beats and the related adaptations in baroreflex sensitivity. This study investigated whether heart rate turbulence (HRT) as a reflection of baroreflex sensitivity is related to symptom severity during AF.

Method: Ninety-seven patients (pts) who underwent electrophysiological study were enrolled. Consecutive 56 pts had paroxysmal AF (21 with milder symptoms [EHRA I or II; Group-M], 35 with severe symptoms [EHRA III or IV; Group-S]), and 41 age-matched controls without AF were included. After delivering a single ventricular extrastimulus during sinus rhythm and repeating the process 10 times, the quantification of HRT was performed by measuring turbulence onset (TO: heart rate acceleration) and turbulence slope (TS: rate of heart rate deceleration).

Results: Group-M pts showed significantly diminished TO as compared to controls and Group-S pts (P = 0.012). There was no significant difference of the TS between the 3 groups. Given that a TO ≥ 0% or TS ≤ 2.5 ms/RR was considered abnormal, Group-M pts showed significantly higher incidences of abnormal HRT as compared to controls and Group-S pts (71% vs 40% vs 21%, respectively, P = 0.0012). Regression analysis demonstrated an independent and significant association between a diminished TO and milder AF symptoms (P < 0.05).

Conclusions: The usual heart rate acceleration after premature ventricular contraction is significantly diminished in pts with milder AF symptoms as compared to pts with severe AF symptoms. The mechanism of association between this diminished response and symptoms should be further investigated.

1. Introduction

Atrial fibrillation (AF) is currently the most common sustained arrhythmia worldwide, and its prevalence increases with age [1,2]. The symptoms associated with AF can be non-specific and include palpitations, shortness of breath, and generalized weakness. These symptoms can significantly affect the daily activities of patients and lead to worsening of quality of life. The symptoms of AF can be objectively classified by the current EHRA classification [3].

On the other hand, asymptomatic AF is associated with worse outcomes and a higher mortality risk, as this group of patients is often under-diagnosed and under-treated, particularly with anticoagulation

to reduce the risk of thromboembolic stroke [4,5]. This has led to the use of implantable cardiac monitors (ICM) to detect subclinical AF in patients with cryptogenic stroke [6]. However, the mechanisms of asymptomatic AF, which can also include patients with rapid AF, have yet to be clarified.

AF is characterized by an irregular heart rate, resulting in beat-to-beat variation of blood pressure. This hemodynamic fluctuation may be affected by baroreflex sensitivity and contribute to the development of AF symptoms. Baroreflex sensitivity can be assessed by heart rate turbulence (HRT). HRT is defined as the heart rate acceleration/deceleration after isolated premature ventricular complexes [7].

We hypothesized that the severity of AF symptoms may be associated with the fluctuation of heart rate and blood pressure in AF, which reflects baroreflex sensitivity. This study assessed the association between HRT and the severity of symptoms during AF.

2. Methods

2.1. Patient population

Participation in this study was voluntary and all patients provided written informed consent. This study was approved by the local institutional review board.

The study population consisted of 97 consecutive patients (pts) admitted to the University Hospital Duesseldorf in Duesseldorf, Germany, between 2014 and 2015 (46 males, mean age 61 ± 11 years) and who underwent electrophysiological study (EPS). This included 56/97 pts with paroxysmal AF (21 with milder symptoms [EHRA class I or II; Group-M], 35 with severe symptoms [EHRA class III or IV; Group-S]), and 41/97 age-matched controls without a history of AF. The patients' characteristics are shown in Table 1.

Exclusion criteria were 1) patients with persistent AF, 2) patients with frequent premature atrial complexes (PAC) or premature ventricular complexes (PVC), defined as 2 or more PAC/PVCs per minute at the beginning of the EPS, 3) patients without VA conduction during ventricular stimulus, 4) patients with an impaired left ventricular ejection fraction < 50% on transthoracic echocardiography.

2.2. Electrophysiological study

EPS was performed in all 97 patients. The indications for pts undergoing EPS are shown in Table 1.

The procedure was performed under sedation using a 5 mg bolus of midazolam and a continuous infusion of propofol (0.25 mg/kg/h). A 5 French catheter was positioned at the right ventricular apex (RVA) via the right femoral vein. Measurement of HRT was performed at the beginning of the EPS in all patients, and before transseptal punctures in patients undergoing pulmonary vein isolation.

The method of measuring turbulence onset (TO: heart rate acceleration) and turbulence slope (TS: rate of heart rate deceleration) has been described in detail previously [7]. In brief, after delivering a single ventricular extrastimulus, quantification of HRT was performed by measuring the TO and TS. This process was repeated 10 times during sinus rhythm and averaged. The ventricular extrastimuli were delivered at a coupling interval of 60% of the baseline sinus rhythm cycle length. An abnormal HRT was defined as TO ≥ 0% or TS ≤ 2.5 ms/RR [7].

2.3. Follow-up

In those patients without a previous history of AF, routine follow-up was performed at the outpatient clinics of our hospital or an affiliated clinic. All patients underwent 24-hour-Holter monitoring at 3, 6, and 12 months after the EPS to screen for new incidences of AF.

2.4. Statistical analysis

Study data was analyzed with the JMP 10.0 software package (SAS Institute Inc., Cary, NC, USA). Continuous data were shown as mean ± SD for normally distributed data, and otherwise as median values [first quartile, third quartile]. The chi-square test, Student t-test, or 1-way analysis of variance (ANOVA) was performed when appropriate to test for statistical differences. A P-value < 0.05 was considered statistically significant. For the comparison among three patients' groups the Turkey's HSD post hoc test or Steel-Dwass test was performed when the one-way ANOVA or Kruskal-Wallis test demonstrated a statistical significance.

Table 1
Patients characteristics.

	AF (EHRA I/II)	AF (EHRA III/IV)	No AF	P value
	Group-M (N = 21)	Group-S (N = 35)	(N = 41)	
Male	12 (57%)	18 (51%)	16 (39%)	0.34
Age	62.9 ± 9.8	60.3 ± 10.3	59.9 ± 11.4	0.57
BMI	28.0 ± 4.5	27.5 ± 4.4	26.0 ± 4.5	0.18
Hypertension	11 (52%)	21 (60%)	24 (59%)	0.85
Diabetes mellitus	3 (14%)	4 (11%)	4 (10%)	0.87
History of stroke	2 (6%)	0 (0%)	2 (5%)	0.55
Coronary artery disease	7 (33%)	9 (26%)	7 (17%)	0.34
Serum creatinine (mg/dL)	1.0 ± 0.2	1.0 ± 0.2	1.1 ± 1.2	0.88
Medications				
β-blocker	12 (57%)	30 (86%)	18 (44%)	<0.001
Ca antagonist	4 (19%)	8 (23%)	9 (22%)	0.94
ACEi or ARB	10 (48%)	21 (64%)	17 (41%)	0.16
Statin	6 (29%)	13 (37%)	11 (27%)	0.60
Antiarrhythmic drugs (class I/III)	4 (19%)	10 (29%)	1 (2%)	0.0063
Indications of EPS				
Syncope	0 (0%)	1 (3%)	5 (12%)	
Supraventricular tachycardia	1 (5%)	0 (0%)	27 (66%)	
Premature ventricular complex	2 (9.5%)	0 (0%)	4 (10%)	
Typical atrial flutter	2 (9.5%)	0 (0%)	5 (12%)	
Paroxysmal atrial fibrillation	16 (76%)	34 (97%)	0 (0%)	
AF duration (months)	40.4 ± 39.3	31.8 ± 38.0		0.42
Systolic blood pressure before sedation (mm Hg)	114 ± 14	110 ± 16	112 ± 14	0.60
Systolic blood pressure immediately before HRT measurement (mm Hg)	93 ± 11	94 ± 14	99 ± 15	0.19
Diastolic blood pressure before sedation (mm Hg)	66 ± 10	65 ± 10	66 ± 9	0.88
Diastolic blood pressure immediately before HRT measurement (mm Hg)	55 ± 8	60 ± 9	55 ± 10	0.055

Regression analysis was performed to analyze the association between the abnormal HRT measurements and the other possibly related factors. We included the known risk factors for atrial fibrillation and cardiovascular diseases, and related medications, and first performed univariable analyses. For multivariable analyses we included only the indices which showed statistical significance in the univariable analysis.

3. Results

There were no significant differences in the baseline characteristics except the medication between the patients with mildly symptomatic AF (EHRA I or II; Group-M), highly symptomatic AF (EHRA III or IV; Group-S) and control patients without AF (Table 1).
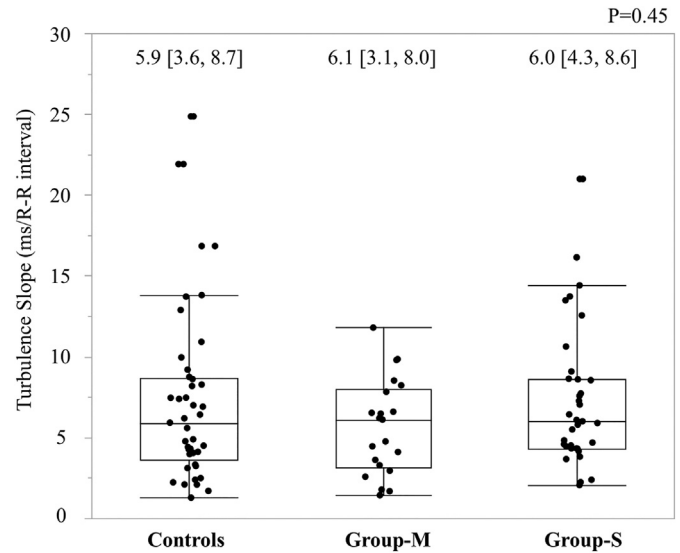
Significantly more patients with AF were treated with β-blockers and antiarrhythmic drugs (AAD). In Group-M 3 patients took class I AAD (flecainide 200 mg/d) and 1 patient took amiodarone 200 mg/d. In Group-S flecainide 200 mg/d was taken in 7 patients, propafenone 900 mg/d in 2 patients, and amiodarone 200 mg/d in 1 patient. In control group, only one patient took amiodarone 200 mg/d. There were no significant differences in the use of other medications including Ca antagonists and renin-angiotensin system inhibitors among the 3 groups.

Baseline blood pressure measurements before sedation and immediately before HRT assessment showed no significant differences between 3 groups.

3.1. Turbulence onset and turbulence slope

Results of the TO measurements are shown in Fig. 1. The patients with milder symptoms (Group-M) had significantly diminished TO as compared to those patients with severe symptoms (Group-S) and those patients without AF (0.08 [−0.38, 0.68] vs −0.47 [−1.19, 0.29] vs −0.29 [−1.16, 0.20], P = 0.0039, P = 0.041, respectively). Group-S patients and control patients without AF had no significant differences in TO (P = 0.82).

The TS results are shown in Fig. 2. There were no significant differences in the TS between the 3 groups, although the mean TS of Group-M patients were the lowest among the 3 groups.

Fig. 1. Turbulence onset of 3 groups. Turbulence onset (TO) in Group-M patients was significantly diminished as compared to that in Group-S or control patients. Group-S patients and controls had no significant difference in TO.

Fig. 2. Turbulence slope of 3 groups. There was no significant difference in the turbulence slope (TS) among the three groups (Kruskal-Wallis, P = 0.45).
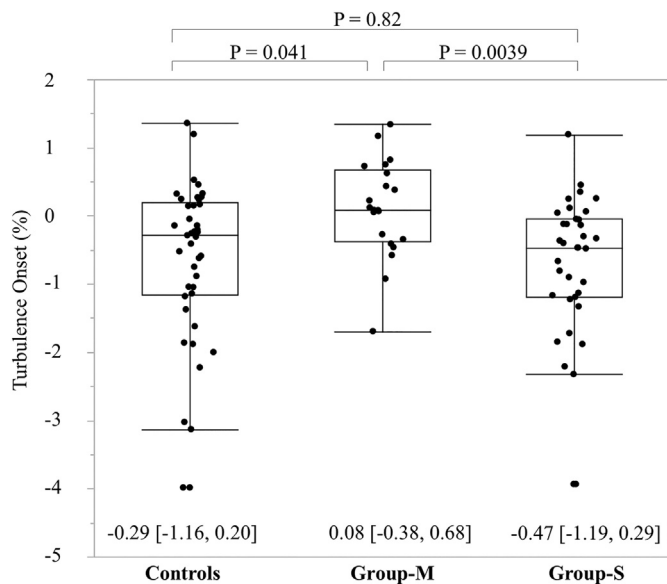
3.2. Basic cycle length

The basic cycle length (BCL) during sinus rhythm of Group-M, Group-S and patients without AF were 921 ± 107 ms, 948 ± 134 ms and 787 ± 130 ms, respectively. The BCL of patients without AF was significantly longer as compared to that of Group-M and Group-S (P = 0.0005, P < 0.0001, respectively).

3.3. Abnormal heart rate turbulence and symptoms of atrial fibrillation

Abnormal HRT, defined as TO ≥ 0% or TS ≤ 2.5 ms/RR, was noted in 40 out of 97 patients (41%). Group-M patients had significantly higher incidences of abnormal HRT as compared to patients of Group-S and patients without AF (15/21 [71%], 9/35 [26%], 16/41 [39%], respectively, P = 0.0032).

Regression analysis was performed assessing other related comorbidities (Table 2), and demonstrated the significant association between abnormal HRT and milder symptoms during AF (Group-M). Multivariable regression analysis demonstrated that milder symptoms during AF were independently associated with abnormal HRT. The indices which are included in the multivariable analysis were not considered that they have any multicollinearity in the present study.

Table 2
Predictivity of abnormal heart rate turbulence.

	Univariable analysis		Multivariable analysis	
	Odds ratio [95% CI]	P value	Odds ratio [95% CI]	P value
Group-M/Group-S	7.22 [2.25–26.0]	<0.001	7.08 [2.15–26.2]	0.001
Age (10 years)	1.62 [1.09–2.45]	0.016	1.60 [1.06–2.51]	0.026
Group-M/controls	3.91 [1.30–13.0]	0.015	3.63 [1.17–12.3]	0.025
Diabetes mellitus	2.81 [0.79–11.4]	0.11		
β-blocker	0.51 [0.22–1.17]	0.11		
Coronary artery disease	1.79 [0.70–4.67]	0.23		
Serum creatinine (1 mg/dL)	0.61 [0.08–1.30]	0.29		
Sleep apnea syndrome	1.95 [0.48–8.36]	0.34		
Male	0.71 [0.31–1.61]	0.42		
Antiarrhythmic drug (class I/III)	1.30 [0.42–3.96]	0.64		
History of stroke	1.42 [0.16–12.3]	0.73		
ACEi or ARB	1.15 [0.51–2.63]	0.74		
BMI (1 kg/m²)	1.01 [0.92–1.10]	0.90		
Hypertension	0.98 [0.43–2.24]	0.97		

3.4. Follow-up of control patients

During a follow-up period of 310 ± 136 days, new incidences of AF were documented in 2 out of 41 patients without AF (4.9%). One patient out of the two showed abnormal HRT during index EPS, and asymptomatic AF was demonstrated by Holter monitoring during follow-up. The second patient had normal HRT during EPS and developed symptomatic AF documented by 12 lead-ECG during follow-up.

4. Discussion

To the best of our knowledge, this is a first detailed analysis of the association between heart rate turbulence and the severity of AF symptoms. The main findings of our study are that; 1) the patients with symptoms of EHRA I or II classification demonstrated a significantly diminished TO response after PVCs as compared to those with symptoms of EHRA III or IV classification, or individuals without AF, and 2) asymptomatic or mildly symptomatic AF was independently associated with a diminished TO after PVCs after adjusting for other relating factors in a subgroup analysis of AF patients.

We additionally performed follow-up of control patients without AF history in order to detect the incidence of AF. As a result, above mentioned results were further confirmed with AF documentation.

4.1. Heart rate turbulence and AF

The mechanism of HRT is considered to be derived from baroreflex sensitivity, which is activated by blood pressure fluctuations that occur during PVCs and the associated subsequent pause that occurs before the next sinus beat ensues [6]. The heart rate acceleration response after a PVC (the turbulence onset) reflects a withdrawal of vagal activity, and the gradual heart rate deceleration in the following phase (the turbulence slope) reflects vagal recruitment after the sympathetically mediated overshoot of arterial pressure [7]. HRT has been reported to be a predictor of mortality in patients with angina pectoris, acute myocardial infarction, and chronic heart failure [8–10].

The autonomic nervous system has been associated with the occurrence of AF [11,12]. Simantirakis et al. have recently reported that the severity of AF symptom was associated with higher heart rate and lower heart rate variability during AF [13]. Although the hemodynamic effects of heart rate fluctuation during AF can be theoretically influenced by baroreflex sensitivity, there have previously been no reports on the baroreflex sensitivity or HRT in patients with AF, and its association with the severity of AF symptoms.

Previous studies have demonstrated that oxidative stress is increased in patients with AF [14]. As a factor that augments this oxidative stress, angiotensin II has been identified as a possible medical target in AF patients [15]. Angiotensin II acting on angiotensin II type 1 receptors in the solitary tract nucleus depresses the baroreflex activity [16]. Moreover, the inhibition of endothelial nitric oxide synthase enhanced the baroreceptor reflex in rats [17]. In the context of this relationship between atrial fibrillation and oxidative stress involving the renin-angiotensin system, diminished HRT in patients with milder AF symptoms may reflect augmented angiotensin II activity resulting in the suppression of the baroreflex sensitivity. To validate this hypothesis, further studies to evaluate the association between HRT and the renin-angiotensin system should be conducted.

4.2. Heart rate turbulence and symptoms during AF

In the present study, patients with milder AF symptoms (Group-M) showed significantly diminished TO (Fig. 1) as compared to those with severe AF symptoms or controls. On the other hand, there was no significant differences in the TS between the 3 groups (Fig. 2).

The TO is considered to reflect vagal withdrawal due to a reduced and insufficient ventricular contraction caused by a PVC, and the TS derives from the sympathetically mediated vasomotor response and subsequent vagal activation [18]. Our results indicate that Group-M patients had diminished TO, suggesting a diminished vagal withdrawal in these patients.

There may be two explanations for this diminished vagal withdrawal. One explanation is that patients with milder AF symptoms have already reduced vagal activity at baseline. In the present study, only BCL was recorded which may partially reflect baseline vagal activity. Group-M patients showed significantly longer BCLs, however, with not significantly higher rate of oral β-blocker administration. To test this hypothesis, the measurement of heart rate variability during sinus rhythm can be taken into account in the future research.

Another explanation is that patients with milder AF symptoms had diminished vagal withdrawal after PVC due to a ground affecting the baroreflex arch, which could not be clarified in the present study. In spite of the known main mechanisms of HRT, the diminished HRT response in this patient population (normal LVEF, no heart failure) and its mechanism has not yet been fully clarified. The association between having only abnormal TO and the severity of AF symptoms was much stronger in this study and was independent of other indexes (Table 3). Based on our results, we may at least say, that diminished TO is associated with milder AF symptoms.

4.3. Other possible factors affecting HRT

Our data corresponded to previous data that reported a correlation between increasing age and an increasing incidence of abnormal HRT [19].

The measurement of HRT has previously been reported to be dependent on BCLs, and HRT is reduced during higher heart rates [20,21]. In our study, patients with AF showed lower heart rates as compared to control patients, however, the patients with milder AF symptoms had diminished TO. This paradoxical result further underscores the abnormal response in these patients.

In our study, a significantly higher proportion of patients with clinically diagnosed AF were treated with oral β-blocker, likely secondary to the consecutive nature of enrollment, and as a result, the baseline heart rate was significantly lower. The tendency to lower diastolic blood pressure in AF patients before HRT assessments may be attributed to this medication.

Previously Lin et al. demonstrated that β-blocker therapy can improve TS but not TO [22]. This suggests that the non-significance of difference in our data on TS may be well explained by this possible effect of oral β-blocker in AF patients. Although these results should be carefully interpreted due to the difference of patient population and limited patients number, our findings of an abnormal TO was considered not to be affected by the β-blocker therapy. The precise difference with

Table 3
Predictivity of abnormal turbulence onset.

	Univariable analysis		Multivariable analysis	
	Odds ratio [95% CI]	P value	Odds ratio [95% CI]	P value
Group-M/Group-S	6.75 [2.11–23.9]	0.0011	6.55 [2.01–23.6]	0.0016
Group-M/controls	4.31 [1.45–13.9]	0.0083	4.06 [1.33–13.3]	0.014
Age (10 years)	1.54 [1.04–2.33]	0.033	1.51 [0.99–2.35]	0.055
Diabetes mellitus	2.36 [0.66–8.81]	0.18		
Sleep apnea syndrome	2.50 [0.62–10.8]	0.20		
β-blocker	0.61 [0.26–1.42]	0.25		
Antiarrhythmic drug (class I/III)	1.67 [0.54–5.18]	0.36		
Coronary artery disease	1.51 [0.57–3.92]	0.40		
Serum creatinine (1 mg/dL)	0.81 [0.18–1.45]	0.53		
History of stroke	1.79 [0.21–15.5]	0.57		
BMI (1 kg/m²)	1.02 [0.93–1.12]	0.63		
ACEi or ARB	1.16 [0.50–2.71]	0.73		
Hypertension	1.16 [0.50–2.72]	0.73		
Male	0.90 [0.39–2.06]	0.80		

and without oral β-blocker should be further confirmed in the future research with 24-hour Holter ECG.

The regression analysis revealed no association of AAD with the abnormal heart rate turbulence. However, theoretically, some AAD may affect heart rate variability which reflects cardiac autonomic function [23]. In the present study, only a part of patients took AAD, hence, detailed evaluation of the AAD effect on heart rate turbulence should be performed in the future studies.

4.4. Clinical implications and future perspectives

Our data suggests that the unknown mechanism affecting the increased heart rate response after premature ventricular contractions (TO) may be associated with more severe AF symptoms. As previously reported, patients with diminished HRT response frequently harbor multiple risk factors for the development of AF. Asymptomatic AF can lead to strokes before appropriate anticoagulation therapy can be commenced and result in higher mortality [4]. The implication of identifying a diminished TO suggests that further trials are required to assess the benefit of implantable cardiac monitors in this patient population to detect subclinical AF.

Furthermore, Salam et al. have reported that the lack of symptoms in patients with AF is associated with worse outcomes based on registry data of 3850 patients [5]. This worse prognosis in patients with a lack of AF symptoms may be ascribed to an abnormal HRT, as in patients with heart failure or ischemic heart disease. Further studies to assess this association should be performed.

Conversely, if diminished baroreceptor sensitivity is a reason for milder AF symptoms, there may be pharmaceutical interventions on baroreceptor sensitivity in highly symptomatic AF patients. For example, cyclosporine A has been reported to diminish baroreceptor sensitivity [24]. An evaluation of AF symptoms in patients taking cyclosporine A may also help clarify the relationship between diminished baroreceptor sensitivity and AF symptoms. Although pulmonary vein isolation (PVI) is currently a cornerstone therapy for highly symptomatic AF, there remains patients with highly symptomatic AF even after PVI or without an appropriate indication for PVI (e.g. highly enlarged left atrium), who need certain interventions. For these patient populations our data may serve as a basis of further investigation.

4.5. Study limitations

There are several limitations in the present study. This study was conducted in a single center with a small number of patients. The medications such as beta-blockers and antiarrhythmic drugs may affect the baroreflex sensitivity, and the evaluation of effects by these medications was not an aim of the present study. Hence, our findings should be further confirmed in larger studies. Secondly, the AF symptoms are subjective and may be reduced by rate-control therapy with β-blockers or Ca channel antagonist. The highly symptomatic patients (Group-S) in our study remained symptomatic despite attempts at rate-control. To objectively assess symptoms, we divided patients into 2 groups according to the EHRA classification. As Simantirakis et al. reported recently, AF symptoms depend on the heart rate during AF. In the present study we could not assess the heart rate during AF as the aim of this study was to evaluate the baseline cardiac autonomic activity in patients with PAF. The diastolic LV function was not assessed in the present study, which may also affect AF symptoms. Finally, we have included the patients with paroxysmal AF in the present study. The HRT characteristics of persistent AF patients should be further investigated.

5. Conclusion

The increase in heart rate response after PVC (turbulence onset) was significantly diminished in mildly symptomatic AF pts as compared to severely symptomatic AF pts or patients without AF. Our data

suggests that in patients with impaired HRT, subclinical AF may be underdiagnosed. The mechanism of the association between diminished heart rate response and AF symptoms should be further investigated. This may lead to symptom targeted therapy for AF patients in the future.

Potential conflicts of interest

The authors report no relationships that could be construed as a conflict of interest.

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