ORIGINAL ARTICLE

Acceleration of sinus rhythm following ablation for atrial fibrillation: a simple parameter predicting ablation efficacy

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KEY WORDS
atrial fibrillation, autonomic regulation, catheter ablation, sinus rate

ABSTRACT

BACKGROUND Pulmonary vein isolation (PVI) is a well-established treatment method in patients with paroxysmal atrial fibrillation (AF). However, the predictors of a successful outcome are less well known. It has been suggested that PVI-induced changes in autonomic control of sinus rate (SR) may correspond to ablation efficacy.

AIMS We aimed to assess whether PVI-induced changes in SR may help identify responders to PVI.

METHODS The study group consisted of 111 consecutive patients (mean [SD] age, 55 [10] years; 81 men) who underwent the first ablation of paroxysmal AF (radiofrequency [RF] ablation, 56 patients; cryoballoon [CB] ablation, 55 patients). The SR was calculated from a standard 12-lead electrocardiogram recorded a day before and 2 days after ablation. Patients were followed for 1 year on an outpatient basis and underwent serial 4- to 7-day Holter electrocardiogram recordings at 3, 6, and 12 months after ablation.

RESULTS Ablation was effective in 74 patients (67%). Univariate and multivariate analyses showed that younger age, faster SR, and a greater increase in SR (ΔSR) after ablation were significantly associated with successful outcome. The results were similar between patients who underwent RF and CB ablation. The sensitivity, specificity, negative predictive value, and positive predictive value of ΔSR higher than 15 bpm for the identification of responders were 53%, 73%, 80%, and 44%, respectively.

CONCLUSIONS Acceleration of SR following ablation for paroxysmal AF may serve as an additional simple clinical parameter that may improve the prediction of outcome after PVI.

INTRODUCTION Pulmonary vein isolation (PVI) has become a widely accepted treatment method for paroxysmal atrial fibrillation (AF).[1,2] The predictors of an unsuccessful procedure include enlarged left atrium (LA), advanced age, reduced left ventricular ejection fraction, long history of AF, LA fibrosis, obstructive sleep apnea, obesity, hypertension, and diabetes.[1] However, their accuracy is limited and thus other prognostic parameters are needed.

Some authors postulated that changes in the autonomic tone, frequently seen after PVI, can be helpful in predicting procedural efficacy[3-13]; however, these findings were not corroborated by other studies.[14,15] A reduction in the parasympathetic activity of the ganglionated plexi may be a particularly valuable marker, because enhanced parasympathetic tone has been long recognized as one of the most important factors promoting AF in patients with paroxysmal AF and no significant cardiac disease.[1]

Ablation-induced changes in the autonomic tone can be assessed noninvasively by analyzing various electrocardiographic (ECG) parameters, such as heart rate variability (HRV), heart rate turbulence, or baroreflex sensitivity. However, these methods are rather complex, time consuming, and often affected by artefacts, medication use, and environmental factors. The simplest and easily accessible ECG parameter that

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WHAT'S NEW?

Catheter ablation for atrial fibrillation is a well-established treatment method; however, the predictors of a successful outcome are less well known. Apart from pulmonary vein isolation, ablation causes significant changes in the autonomic control of the heart, which may be associated with procedural success. The present study shows that a simple parameter, namely, an ablation-induced increase in heart rate, may help identify patients with favorable outcome irrespective of the type of ablation (radiofrequency or cryoballoon).

reflects changes in the parasympathetic drive is the sinus rate (SR).

Numerous studies assessing ablation-induced changes in the autonomic tone used a noninvasive HRV analysis, but only a few studies directly addressed the potential role of ablation-induced changes in SR as a predictor of procedure efficacy.[12,15] Thus, the aim of the present study was to examine whether ablation-induced changes in SR predict the procedure outcome. We hypothesized that the acceleration of SR after ablation may identify responders to treatment. In addition, we aimed to examine whether SR changes depend on the type of procedure (radiofrequency [RF] versus cryoballoon [CB] ablation) or preablation (baseline) SR.

TABLE 1 Demographic and clinical characteristics of the study group

Parameter	Value
Age, y, median (SD)	57 (10)
Male sex, n (%)	81 (27)
CHA_2DS_2-VASc, median (SD)	1 (1.1)
β-Blockers, n (%)	90 (81.1)
Propafenone, n (%)	44 (39.6)
Amiodarone, n (%)	23 (20.7)
No antiarrhythmic drugs, n (%)	44 (39.6)
Hypertension, n (%)	52 (46.8)
Diabetes, n (%)	11 (9.9)
Previous stroke / TIA, n (%)	1 (0.9)
Chronic heart failure, n (%)	1 (0.9)
CAD, n (%)	8 (7.2)
Chronic kidney disease, n (%)	0
RF/CB ablation, n (%)	56 (50) / 55 (50)
LA diameter, mm, median (SD)	39 (5)
LVEF, %, median (SD)	63 (5)
Baseline SR, bpm, median (SD)	57 (8.8)
SR after ablation, bpm, mean (SD)	71.4 (11.1)

Abbreviations: CAD, coronary artery disease; CB, cryoballoon; CHA_2DS_2-VASc, congestive heart failure, hypertension, age >75 years, diabetes mellitus, history of stroke or thromboembolism, vascular disease, age 65 to 74 years, female sex; LA, left atrium; LVEF, left ventricular ejection fraction; RF, radiofrequency; SR, sinus rate; TIA, transient ischemic attack

METHODS

Patients The study group consisted of 111 consecutive patients (mean [SD] age, 55 [10] years; 81 men) who: 1) underwent the first catheter ablation of paroxysmal AF in our center from 2012 to 2016; 2) were included in the FALA study[16] (n = 60) and ongoing ABLANSAF study (Changes in Cardiac Autonomic Nervous System Following Atrial Fibrillation Ablation; ClinicalTrials.gov identifier, NCT03811639) (n = 51); and 3) completed a 1-year follow-up. All patients gave their written informed consent to participate in the study. The study protocol was approved by the local ethics committee (approval no., 65/PB/2015). In order to be included in the present analysis, patients had to be in SR before and after ablation. Demographic and clinical characteristics of the patients are presented in TABLE 1.

Assessment of sinus rate The SR was calculated from a standard 12-lead ECG recorded a day before and 2 days after ablation (ELI 250c, Mortara Instrument, Inc., Milwaukee, Wisconsin, United States). An automatically calculated SR displayed by the ECG machine was taken for analysis. The ablation-induced change in SR was presented as ΔSR (SR after ablation minus SR before ablation). According to our protocol, patients were maintained on the same medication and dosage after ablation as before the procedure.

Ablation procedure Both RF and CB ablations were performed according to widely accepted protocols. Patients were randomly allocated to either RF or CB ablation unless they had a prominent common trunk of the left pulmonary vein assessed by cardiac computed tomography or intracardiac echocardiography. In such a case, patients were treated with RF ablation (n = 3). To exclude the presence of an LA thrombus, patients underwent transesophageal echocardiography within 24 hours before the procedure (n = 108) or intracardiac echocardiography at the beginning of the procedure (n = 3). The point-by-point PVI using RF energy was performed after a double transseptal puncture using irrigated ablation catheters (Thermocool SF or Thermocool SmartTouch ST, Biosense Webster, Diamond Bar, California, United States), LASSO catheter (Biosense Webster), and the CARTO 3 system (Biosense Webster). The usual energy settings were 30 watts for 30 seconds at the anterior LA wall and 20 to 25 watts at the posterior LA wall. The pulmonary veins were isolated at the antral level. The CB ablation for PVI was performed using a single transseptal puncture. A steerable 15F sheath (FlexCath Advance, Medtronic, Minneapolis, Minnesota, United States) was positioned in the LA, and an inner lumen mapping catheter (Achieve, Medtronic) was advanced into each pulmonary vein ostium. A 28-mm cryoballoon (Arctic Front or Arctic Front Advance, Medtronic) and Achieve catheter to confirm PVI were used. Usually, 3-minute freezes per vein were applied without additional applications if PVI was achieved no later than 60 seconds after starting the application.

Both procedures were performed in patients under mild sedation, with uninterrupted anticoagulation, and with the goal to obtain complete PVI. No additional lines in the LA, or specific sites of the ganglionated plexi, or areas of fractionated potentials were targeted. The only additional line was the cavotricuspid isthmus ablation in patients with a concomitant typical atrial flutter. One or two days after the ablation, all patients underwent transthoracic echocardiography to assess pericardial effusion. In all patients, the effusion was classified as none or small.

Follow-up The follow-up lasted 1 year. Patients were seen on an outpatient basis and underwent serial 4- to 7-day Holter ECG recordings (DMS 300-4A, DM Software, Stateline, Nevada, United States) at 3, 6, and 12 months after ablation. Our usual protocol is to maintain the medication regimen up to 3 months after ablation, then to stop antiarrhythmic drugs if they are still used and no AF recurrence is observed, and then to stop anticoagulation 6 months after the procedure if there is no AF recurrence and there are no other indications for anticoagulation.

Definition of a successful procedure Effective ablation was defined as no symptoms attributed to AF or atrial tachycardia (AT) and no AF or AT (episodes of arrhythmia lasting longer than 30 seconds) during 4- to 7-day Holter monitoring at 3, 6, and 12 months after ablation.

Statistical analysis The results were presented as mean (SD) as well as numbers and percentages for normally distributed variables, and as median (SD) for nonnormally distributed variables. Data were tested for normal distribution using the Shapiro–Wilk test. The *t* test or the Mann–Whitney test was used to compare variables, respectively. The χ^2 test or Fisher test was used to compare qualitative variables.

A logistic multivariate analysis was performed to identify independent parameters associated with the outcome. The sensitivity, specificity, positive and negative predictive values, and total accuracy for the identification of patients without AF recurrence were calculated according to standard definitions. A *P* value of 0.05 or lower was considered significant.

RESULTS In all patients, ablation procedures were completed without major cardiac or neurologic complications. Complete PVI was achieved in 88.3% of the patients. There were no differences in the rate of complete PVI between patients with successful and unsuccessful ablation (91.8% [68/74] vs 81% [30/37]). Minor complications (access-site problems) occurred in 5 patients (4.5%): groin hematoma not requiring blood transfusion in 1 patient, arteriovenous fistula in 3 patients, and femoral artery pseudoaneurysm in 1 patient. No patient had a significant amount of pericardial effusion on echocardiography performed 1 to 2 days after the procedure. All patients were discharged home 2 to 7 days after the procedure.

All patients completed the 1-year follow-up and attended outpatient visits to undergo serial Holter monitoring according to the study protocol. There were no deaths or severe ablation-related complications during follow-up. Ablation was effective in 74 patients (67%). Among patients with unsuccessful ablation, 3 had AT and 3 had both AT and AF. The predictors of successful ablation in the univariate analysis are shown in TABLE 2. Younger age and faster SR after ablation were significantly associated with successful outcome. Responders to ablation had also a higher ablation-induced increase

TABLE 2 Predictors of successful ablation in the univariate analysis

Parameter	Responders to ablation (n = 74)	Nonresponders to ablation (n = 37)	*P* value
Baseline SR, bpm, median (SD)	58.5 (8.9)	56 (8.2)	NS
SR after ablation, bpm, mean (SD)	73.8 (11.5)	66.5 (8.4)	<0.0003
ΔSR[a], bpm, mean (SD)	15.1 (10.4)	10.7 (9)	<0.02
Age, y, median (SD)	55 (11)	59 (8)	<0.01
LA diameter, mm, median (SD)	38 (5)	40 (5)	NS
LVEF, %, median (SD)	62 (7)	64 (7)	NS
CHA_2DS_2-VASc, median (SD)	1 (0.94)	0 (1.37)	NS
Complete PVI, n (%)	68 (91.8)	30 (81)	NS

a Difference between SR after and before ablation

Abbreviations: NS, not significant; PVI, pulmonary vein isolation; others, see TABLE 1 in SR (ΔSR) than patients with AF recurrence during follow-up.

The results of the multivariate analysis are shown in TABLE 3. Younger age and faster SR after the procedure independently predicted successful ablation.

A comparison between patients treated with RF and CB ablation is shown in TABLE 4. There were no significant differences between groups with respect to baseline SR, SR after ablation, ΔSR, other demographic and clinical parameters, as well as ablation efficacy.

The predictors of effective ablation separately for patients treated with RF and CB ablation are shown in TABLE 5. In both subgroups, faster SR after ablation was significantly associated with good outcome. In the subgroup treated with RF ablation, other predictors included younger age and smaller LA diameter. In the subgroup undergoing CB ablation also faster SR before ablation predicted the favorable outcome.

The sensitivity, specificity, positive and negative predictive values, as well as total accuracy of various cutoff values for ΔSR are shown in TABLE 6.

TABLE 3 Predictors of successful ablation in the multivariate analysis

Covariates	Coefficient	*P* value	OR	95% CI
Age	–0.07	0.04	0.94	0.88–1.00
LVEF	–0.06	NS	0.94	0.87–1.01
LA diameter	–0.02	NS	0.94	0.89–1.09
Baseline SR	–0.02	NS	0.94	0.93–1.05
SR after ablation	0.06	0.04	1.06	1.00–1.12
CHA_2DS_2-VASc	0.29	NS	1.33	0.82–2.17

Abbreviations: OR, odds ratio; others, see TABLES 1 and 2

DISCUSSION The main finding of our study is that the acceleration of SR after ablation is a significant but not very strong predictor of successful outcome.

Changes in SR following ablation have been studied by numerous other investigators.[3-15] However, most studies examined

TABLE 4 Comparison between patients treated with radiofrequency and cryoballoon ablation

Parameter	RF ablation (n = 56)	CB ablation (n = 55)	*P* value
Age, y, median (SD)	58 (10)	56 (11)	NS
Baseline SR, bpm, median (SD)	60 (8.7)	55 (8.9)	NS
SR after ablation, bpm, mean (SD)	71 (11.8)	71.7 (10.4)	NS
ΔSR[a], bpm, mean (SD)	12.7 (11.4)	14.6 (8.9)	NS
LA diameter, mm, median (SD)	40 (5)	38 (6)	NS
LVEF, %, median (SD)	64 (7)	61 (8)	NS
CHA_2DS_2-VASc, median (SD)	1 (1.1)	1 (1)	NS

a Difference between SR after and before ablation

Abbreviations: see TABLES 1 and 2

TABLE 5 Predictors of successful outcome in patients undergoing radiofrequency and cryoballoon ablation

Parameter	Responders to RF ablation (n = 32)	Nonresponders to RF ablation (n = 24)	*P* value	Responders to CB ablation (n = 42)	Nonresponders to CB ablation (n = 23)	*P* value
Baseline SR, bpm, median (SD)	61 (8.5)	58 (9.1)	–	56 (9.4)	53 (4.7)	<0.02
SR after ablation, bpm, mean (SD)	73.8 (13.3)	67.3 (8.4)	<0.029	73.8 (10.1)	65.1 (8.7)	<0.006
ΔSR, bpm, mean (SD)	15.1 (12.5)	9.5 (9.1)	–	15.2 (8.7)	12.8 (8.2)	NS
Age, y, median (SD)	55.5 (11)	59 (8)	<0.03	55 (11)	60 (7)	NS
LA diameter, mm, median (SD)	37 (4)	41 (5)	<0.026	38 (6)	37.5 (4)	NS
LVEF, %, median (SD)	64 (7)	64 (7)	–	60 (7)	63 (8)	NS
CHA_2DS_2-VASc, median (SD)	1 (0.9)	1 (1.4)	–	1 (1)	1 (1)	NS

Abbreviations: see TABLES 1 and 2

TABLE 6 Sensitivity, specificity, negative predictive value, positive predictive value, and total accuracy of various cutoff values for ΔSR

Total	ΔSR ≥10 bpm	ΔSR ≥15 bpm	ΔSR ≥20 bpm
Sensitivity, %	63.5	52.7	35.1
Specificity, %	43.2	73	81.1
PPV, %	69.1	79.6	78.8
NPV, %	37.2	43.6	38.5
Total accuracy, %	56.8	59.5	50.5

a Difference between SR after and before ablation

Abbreviations: NPV, negative predictive value; PPV, positive predictive value

ablation-induced changes in HRV, usually during a 1-year follow-up. These studies rather uniformly showed that ablation attenuates HRV and predominantly suppresses the parasympathetic part of the autonomic tone. Whether these changes are maintained is a matter of debate. Pappone et al[9] showed that over 1 year alterations in HRV disappeared in most patients. Other investigators reported that ablation-induced HRV changes were more stable after RF ablation with irrigated catheters or CB ablation.[5,15] It is possible that newer techniques produce more transmural lesions and destroy ganglionated plexi more permanently than ablation with non-irrigated catheters.[15]

The above studies also showed that HRV changes corresponded to ablation efficacy in most patients. Individuals in whom the attenuation of HRV was permanent remained in SR, while a return to preablation values was associated with AF recurrence.[4,6,12,13] However, because of a rather complex methodology of HRV analysis and numerous problems with the interpretation of HRV recordings, this parameter has not became widely used in clinical practice to predict ablation efficacy.

Only a few studies examined the value of the simplest parameter of the autonomic tone, namely, changes in SR. Ketels et al[17] failed to find any significant relationship between changes in SR and HRV during ablation and procedure efficacy. In contrast, Yu et al,[12] in a group of 991 patients, found that the acceleration of SR after ablation indicated a successful outcome.

In our study, acceleration of SR after ablation was shown to be a significant but weak predictor of procedural success. For example, ΔSR higher than 15 bpm identified responders, with a sensitivity, specificity, positive predictive value, negative predictive value, and total predictive accuracy of 53%, 73%, 80%, 44%, and 59%, respectively. These results suggest that SR acceleration following ablation may have a moderate predictive value and may be useful in postablation management. For example, it may be speculated that the decision on continuation of antiarrhythmic therapy or an earlier decision to perform the second ablation might be influenced by the lack of changes in SR after ablation in some patients.

In our study, we did not find significant differences in baseline SR between responders and nonresponders. Our hypothesis was that slow baseline SR identified patients with vagally mediated paroxysmal AF; therefore, a greater acceleration of SR after ablation would identify responders. However, we did not confirm this hypothesis, which may be possibly explained by the fact that preablation bradycardia is not a particularly sensitive and specific marker of vagally mediated AF. Slow SR may be not only due to increased parasympathetic activity but also due to medication or sinus node disease, especially in older people.[18-20] In this population, the tachycardia–bradycardia syndrome is often observed during paroxysmal AF. It has been well established that slow SR promotes episodes of AF.[19] In line with this, Wu et al[3] showed that in people aged 65 years or older, resting SR of less than 50 bpm was an independent predictor of AF recurrence after ablation for paroxysmal AF. These results again highlight the importance of SR in predicting the efficacy of ablation for AF.

We did not find a significant difference between RF and CB ablation in terms of SR changes. We initially hypothesized that CB ablation may exert more profound effects on SR than RF ablation, because CB-induced lesions around the pulmonary vein and in the posterior wall of the LA are usually extensive and thus more likely to affect the ganglionated plexi. Moreover, it seems that ablation-mediated vagal responses (bradycardia or asystole) during left PVI and SR acceleration (parasympathetic withdrawal) following right PVI are more often seen during CB ablation, which might suggest that CB ablation exerts greater effects on the ganglionated plexi than RF ablation. However, we observed no such differences, so both techniques possibly have a similar impact on autonomic innervation of the heart.

Finally, the question arises why changes in SR were shown to be a rather weak predictor of successful ablation. Firstly, SR changes are only a surrogate of the complex interplay between the ganglionated plexi and may not reflect the numerous other important mechanisms. Secondly, from a pathophysiologic point of view, ablation-induced acceleration of SR should be beneficial mainly in patients with vagally mediated AF and not in all consecutive patients undergoing ablation for paroxysmal AF. Therefore, a better identification of such patients is warranted to document not only a significant but also clinically more useful predictive value of SR changes. Our results suggest that considering only preablation SR does not accurately identify patients with vagally mediated AF. Perhaps other parameters, such as a detailed history and circumstances of AF episodes, would facilitate a better identification of these patients. Clearly, SR changes after ablation are not a prognostic marker in all patients undergoing PVI.

An effective and durable PVI is important for achieving high efficacy of AF ablation. Our success rate of complete PVI is slightly lower than that reported in recent studies[21,22]; however, the 1-year success rate is in line with the FIRE and ICE study.[21] Most patients with incomplete PVI were recruited from the FALA study, which was conducted in the years 2012 to 2014, before the era of the ablation index, contact force catheters, CLOSE protocol,[22] and Arctic Front Advance cryoballoon. Nowadays, complete PVI is achieved in more than 98% of patients in our center. Our participants were rather young and had a low CHA_2DS_2-VASc score, which means that they were probably the most suitable candidates for AF ablation. Patients recruited in the CLOSE study had similar demographic and clinical characteristics.[22]

Our study has several limitations. First, the number of patients was relatively small, but it was large enough to show the potential role of SR changes in predicting the outcome. Second, the majority of patients were on chronic medical treatment, which might have influenced SR. However, the treatment regimen remained unchanged after ablation, thus enabling a reliable comparison between pre- and postablation SR in each patient. Third, we did not collect historical data on the circumstances of AF episodes, which precluded a subgroup analysis on the role of ablation-induced SR changes in patients with vagally mediated versus adrenergic AF. Fourth, the follow-up was relatively short. Fifth, our results are only applicable to relatively young patients with paroxysmal AF and a low CHA_2DS_2-VASc score. Finally, the lack of continuous ECG monitoring, such as with an implantable loop recorder or daily transmissions of ECG, might have resulted in the underdetection of AF recurrence. However, 4- to 7-day Holter recordings at 3, 6, and 12 months after ablation, a standard ECG recorded in case of symptoms, and regular outpatient visits are regarded as the current standard of care.

In conclusion, the acceleration of SR following ablation for paroxysmal AF may serve as a simple additional clinical parameter that may improve outcome prediction.

ARTICLE INFORMATION

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