

Atrial Fibrillation Inducibility in the Absence of Structural Heart Disease or Clinical Atrial Fibrillation

Critical Dependence on Induction Protocol, Inducibility Definition, and Number of Inductions

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Background—Inducibility of atrial fibrillation (AF) after pulmonary vein isolation has been used to guide additional left atrial ablation in paroxysmal AF. The sensitivity and specificity of AF induction in this setting remains uncertain. We examined the incidence and characteristics of inducible AF in patients without structural heart disease or clinical AF and the effect of different induction protocols on AF inducibility.

Methods and Results—In 44 patients with supraventricular tachycardia with no history of AF or risk factors for AF, atrial refractoriness and conduction were measured, followed by AF induction attempts (10/patient). Each induction was performed after a waiting time that exceeded twice the duration of induced AF from the preceding induction. AF ≥ 1 minute was considered inducible, and ≥ 5 minutes as sustained. Burst pacing (at 200 ms for 10 seconds) was compared to decremental pacing (from 200 ms to shortest cycle length, resulting in 1:1 atrial capture for 10 seconds). After 10 inductions, AF was inducible in 49.5%, and sustained in 29.5% of patients. The incidence of both inducible and sustained AF increased with each induction. Apart from male gender, no clinical or electrophysiological features were associated with sustained AF. Decremental pacing was associated with a higher incidence of sustained AF (41.2% versus 14.8%, $P=0.049$), longer duration of AF ($P=0.006$), and shorter mean AF cycle length ($P<0.001$) compared with burst pacing.

Conclusions—Inducible and sustained AF is common in patients in the absence of structural heart disease or clinical AF, and its incidence varies according to gender, method of induction, and number of inductions. There is a direct relationship between AF persistence and number of inductions, which has not reached a plateau after 10 inductions. (*Circ Arrhythm Electrophysiol.* 2012;5:531-536.)

Key Words: atrial fibrillation ■ supraventricular tachycardia ■ inducibility

Pulmonary vein isolation with catheter ablation is a class I indication for the treatment of symptomatic, drug refractory paroxysmal atrial fibrillation (AF).¹ Lack of AF inducibility with rapid atrial pacing has been associated with a lower risk of recurrence following AF ablation.²⁻⁷ Inducible AF has been used to guide further left atrial substrate modification in paroxysmal AF.^{5,6,8} However, there is considerable heterogeneity between studies in the sites of stimulation, method of stimulation, number of AF inductions, use of pharmacological provocation, and in the definition of inducibility based on AF duration.^{3,5-9} In the first instance, there is very little reference information on the inducibility of AF in a normal heart with rapid atrial pacing.¹⁰⁻¹² Thus the sensitivity and specificity of the AF inducibility test is difficult to estimate. The aim of this study was to examine the incidence and characteristics of inducible AF in the absence of structural heart disease or

clinical AF, and the effect of different AF induction protocols on AF inducibility.

Clinical Perspective on p 536

Methods

Patients aged 18 to 65 years with documented or suspected supraventricular tachycardia (SVT) presenting for catheter ablation were recruited. No patient had a history of structural heart disease as detected by echocardiography, and there was no clinical, ECG, or Holter evidence of AF or atrial flutter. Patients with any comorbid condition predisposing to AF (eg, hypertension, diabetes, thyroid, coronary disease, obstructive sleep apnea), sinus node disease, or amiodarone use were excluded. All patients with palpitations without documented tachycardia had AF or atrial flutter excluded by undergoing 7-day Holter monitoring. All antiarrhythmic drugs were ceased >5 half-lives prior to the scheduled procedure. The

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Melbourne Health Human Research Ethics Committee approved the study protocol.

Electrophysiology Study and Ablation

Intracardiac catheters were positioned as follows: (1) 10-pole coronary sinus (CS) catheter (2–5.2 mm interelectrode spacing), with the proximal bipole positioned at the CS ostium, (2) a quadripolar catheter with 5-mm interelectrode distance in the His-bundle region, and (3) mapping and ablation catheter. Bipolar intracardiac electrograms and 12-lead surface ECG were recorded simultaneously on a computerized digital amplifier system (EPMed Systems). Intracardiac electrograms were filtered between 30 and 500 Hz; 2 authors using on-screen digital calipers at 200 mm/s sweep speed performed the analysis. After the clinically indicated 'electrophysiology (EP) study, ablation, and isoprenaline washout, the research protocol was commenced.

Effective Refractory Periods

Atrial effective refractory periods (ERPs) were evaluated at twice diastolic threshold at 3 pacing cycle lengths (600, 500, and 400 ms), with an 8-beat drive followed by an extrastimulus, starting with an extrastimulus coupling interval of 150 ms and increasing in 10-ms increments.¹³ Catheters were repositioned if a diastolic threshold <5 mA could not be obtained. ERP was defined as the longest coupling interval that failed to propagate to the atrium. At each site, the ERP was measured 3 times at each cycle length. If maximum and minimum measurements differed by >10 ms, 2 more measurements were taken and the total was averaged. ERPs were measured at the proximal coronary sinus (PCS), distal coronary sinus (DCS), and right atrial appendage (RAA).¹³

Conduction Times

The following conduction times were recorded: (1) conduction time along the CS by pacing the distal bipole of the CS catheter and measuring activation time to the proximal bipole, (2) intra-atrial conduction time by pacing the distal bipole of the ablation catheter in the RAA and measuring activation time to the atrial electrogram in the PCS, and (3) interatrial conduction time by pacing the distal bipole of the ablation catheter in the RAA and measuring activation to the atrial electrogram in the DCS. Conduction was measured at cycle lengths of 600, 500, and 400 ms after stable capture for at least 10 seconds.¹³ Conduction time was determined 5 times at each cycle length and averaged. P-wave duration in sinus rhythm, measured on lead II of the surface ECG and averaged over 10 beats, was analyzed as a surrogate marker of interatrial conduction time.

Sinus Node Function

Sinus node function was evaluated as follows: (1) baseline sinus cycle length was determined over 10 consecutive sinus cycles, and (2) corrected sinus node recovery time was determined after a 30-second pacing drive train at cycle lengths of 600 and 400 ms, correcting for the baseline cycle length. At each cycle length, corrected sinus node recovery time was determined 3 times and averaged.¹³

Atrial Fibrillation Inducibility

Atrial fibrillation was induced with pacing from a single site being the PCS at 20 mA and 2 ms pulse width. If induction resulted in AF of ≥ 5 minutes, no further AF inductions were performed because of the known effects of AF on atrial refractoriness.¹² If AF <5 minutes resulted, the next induction was delayed for a period of time greater than twice the duration of last induced AF (eg, 9 minutes waiting prior to the next induction if AF was induced for 4.5 minutes).¹² The waiting period was employed to ensure recovery of AF-induced shortening in atrial ERP to baseline values. Reversal of AF-induced electric remodeling is expected to occur over ~5 to 8 minutes in patients with induced AF >5 minutes in the absence of structural heart disease or clinical AF. Up to 10 inductions per patient were allowed (Figure 1).

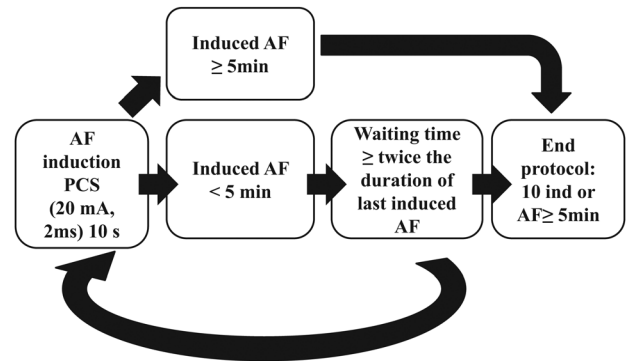


Figure 1. Atrial fibrillation (AF) induction protocol. AF was induced from the proximal coronary sinus in all patients at 20 mA pacing output and 2 ms pulse width, with pacing at either a fixed cycle length or the shortest cycle length, with 1:1 atrial capture for a period of 10 seconds. If sustained AF ≥ 5 minutes was induced, no further inductions were performed. If AF <5 minutes was induced, repeat induction was performed after waiting for a period of time that exceeded twice the duration of the induced AF from the preceding induction. The protocol was completed if sustained AF was induced or 10 inductions were performed.

Atrial fibrillation induction was performed with either burst atrial pacing at a fixed cycle length of 200 ms, or by decremental pacing (Figure 2) starting at 200 ms and decrementing by 10 ms to the shortest cycle length that resulted in 1:1 atrial capture along with CS fractionation. At this cycle length, 10 seconds of pacing was performed. The first 27 patients underwent stable pacing and the next 17 underwent decremental pacing.

A short atrial pacing run was performed (5 s) prior to each induction to measure the shortest cycle length resulting in 1:1 atrial capture. Sinus cycle length immediately prior to each induction also was recorded to examine if change in autonomic tone was a contributor to AF vulnerability.

Analysis of Induced Atrial Fibrillation

Atrial fibrillation was defined by the beat-to-beat variability in cycle length and morphology.⁴ Total duration and the mean cycle length of induced AF were measured. The AF cycle length was measured in the DCS at a sweep speed of 100 mm/second by averaging 30 consecutive cycles. The shortest and longest AF cycle length was measured within a random 10-second window of induced AF of ≥ 1 minute duration. Interelectrogram intervals of ≤ 100 ms and continuous electric activity were counted as a single interval.⁴

Definitions of Inducibility

Patients were classified according to the longest duration of AF induced in any of their inductions. We reported the incidence of inducible AF of >10 seconds,³ ≥ 1 minute,^{2,6–8,14–16} ≥ 5 minutes,¹⁷ and >10 minutes,^{4,5,18,19} as per previously used definitions. We considered AF ≥ 1 minute as *inducible* and ≥ 5 minutes as *sustained*.¹¹ AF <1 minute was considered noninducible and AF 1 to <5 minutes was considered nonsustained.

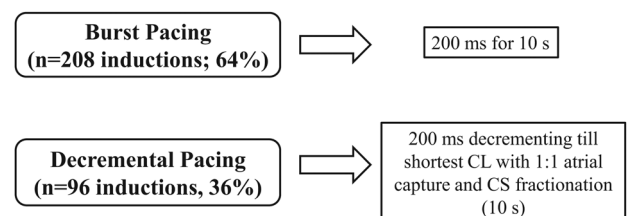


Figure 2. Burst versus decremental pacing protocol. Two protocols were compared in the study.

Table 1. Baseline Characteristics

Variable	N = 44
Age, mean±SD, y	39±13
Female gender, %	68.2
Body mass index	28±5
Body surface area, m ²	1.9±0.3
Symptom duration, mean±SD, y	5.5±5
Arrhythmia, %	
AVNRT	61.9
AVRT	21.4
Non-inducible	16.7
Echocardiographic parameters	
Left atrial size, mm	34±6
Left atrial area, cm ²	18±4
Left ventricular ejection fraction, %	66±4

SD indicates standard deviation; AVNRT, atrioventricular nodal re-entrant tachycardia; AVRT, atrioventricular reentrant tachycardia.

Statistical Analysis

The Statistical Package for the Social Sciences for Windows (SPSS, release 15.0) and the statistical package “R” (R Foundation) were used for analysis. Graphs were constructed using Prism version 5.0d (GraphPad Software, La Jolla, CA). To test for associations between categorical variables, χ^2 tests or Fisher exact test were used. Mean values were compared using the Student *t* test. Mann-Whitney U- or Kruskal-Wallis tests were used for continuous variables where normal distribution was not present.

The incidence of inducible (≥ 1 minute) and sustained AF (≥ 5 minutes) was estimated by use of the Kaplan-Meier method. The Kaplan-Meier method was used first as the protocol specifying that no further inductions were to be performed if ≥ 5 minutes of AF were induced, and second to account for patients with an incomplete set of inductions resulting from a lengthy duration of the primary procedure prohibiting full completion of the research protocol due to patient discomfort. Patients thus were censored if, and only if, they underwent <10 inductions and did not experience sustained AF in any of their inductions.

Cox regression analysis was performed to determine the predictors of sustained AF. Nine explanatory variables (Table 1) were considered in Cox regression analysis, with the number of inductions to sustained AF ≥ 5 minutes. Grambsch and Therneau test²⁰ was carried out for each of the single explanatory variables as a test of the assumption of proportional hazards. Only those explanatory variables with a univariable probability value <0.2 were entered into the

multivariable model in a backward: likelihood ratio fashion. In all analyses and reporting of results we used patients as the unit of analysis, not inductions.

Shortest atrial pacing cycle length resulting in 1:1 atrial capture prior to AF induction was analyzed by ANOVA with repeated measures. Two-tailed $P<0.05$ was considered statistically significant.

Results

A total of 304 inductions were performed in 44 patients. Baseline characteristics are listed in Table 1. AF >10 seconds, ≥ 1 minute, ≥ 5 minutes, and >10 minutes was present in 34 of 44, 20 of 44, 11 of 44, and 10 of 44 patients, respectively. By the end of 10 inductions, the incidence of AF >10 seconds, ≥ 1 minute, ≥ 5 minutes, and >10 minutes was 82.7%, 49.5%, 29.5%, and 27.8%, respectively. In patients with sustained AF, electric cardioversion was performed in 5 patients, pharmacological reversion with flecainide in 3 patients, and spontaneous termination to sinus rhythm occurred after 10 minutes in 3 patients as preparations for electric cardioversion were being made.

The shortest cycle length that resulted in 1:1 atrial capture did not change between inductions ($P=0.55$). Sinus cycle length did not differ between inductions ($P>0.05$ for paired comparisons between inductions). The incidence of inducible AF (≥ 1 minute) within the population studied increased with each induction (1 induction: 9.1%, 2 inductions: 13.9%, 3 inductions: 23.4%; Figure 3A). Similarly, the incidence of sustained AF (≥ 5 minutes) within the population studied increased with each induction (1 induction: 4.5%, 2 inductions: 9.3%, 3 inductions: 11.7%; Figure 3B).

There were no significant differences in atrial ERPs, CS conduction, interatrial or intra-atrial conduction, corrected sinus node recovery time, or P-wave duration between the groups (Figure 4). Baseline characteristics of patients with sustained AF versus noninducible/nonsustained AF are listed in Table 2. There were a significantly higher number of males, higher body surface area, and a trend toward a higher incidence of atrioventricular re-entrant tachycardia in patients with sustained AF.

The Grambsch and Therneau test was carried out for each of the single explanatory variable models considered in the Cox regression analysis, and the results were consistent with the assumption of proportional hazards (all $P>0.2$). Male gender was the only independent predictor of sustained AF in the multivariable analysis (Table 3).

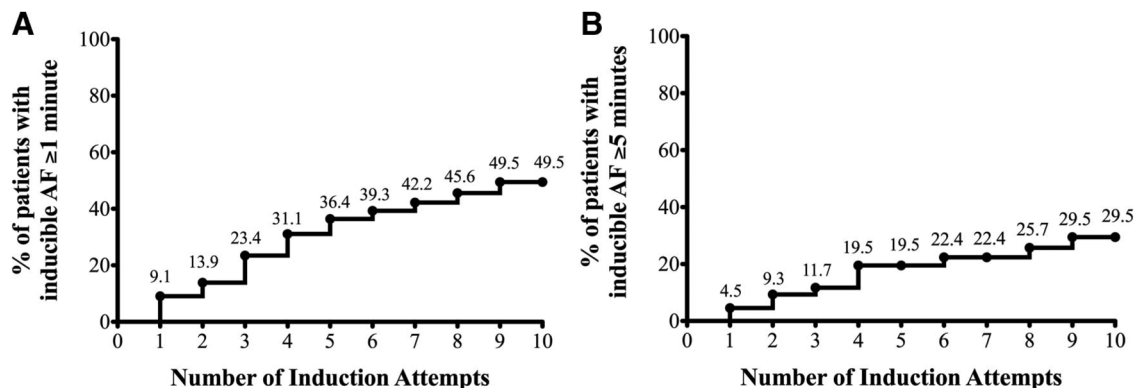


Figure 3. A, Incidence of inducible atrial fibrillation (AF; ≥ 1 minute) and **(B)** sustained AF (≥ 5 minutes). Kaplan-Meier 1-survival plots. Dots represent censored events where <10 inductions were performed and did not experience sustained AF in any of their inductions.

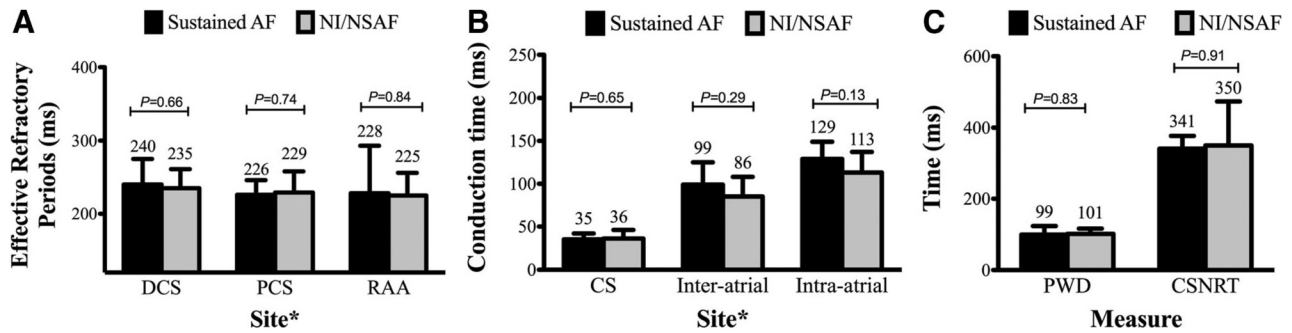


Figure 4. Refractoriness, conduction, sinus node function (CSNRT), and P-wave duration (PWD) in the sustained atrial fibrillation (AF) versus noninducible (NI)/nonsustained AF (NSAF) groups (*representative data for refractory periods, conduction and sinus node function at 600 ms is shown). There were no significant differences in any of the measured parameters.

At a mean follow up of 28 ± 22 months (median, 23 months; interquartile range, 25%–75%; 11–50 months), no patient had episodes of clinical AF or flutter, or recurrence of the index SVT.

Burst Versus Decremental Pacing

Decremental pacing was associated with a significantly higher incidence of inducible AF ≥ 1 minute (75.5% versus 32.2%, log rank $P=0.002$) and sustained AF ≥ 5 minutes (43.5% versus 20.5%, log rank $P=0.026$) compared with burst pacing. Mean AF duration was significantly longer with decremental pacing compared with burst pacing (45 ± 87 s versus 28 ± 63 s, $P=0.006$). Compared with burst pacing, decremental pacing was associated with shorter mean AF cycle length (CL) (176 ± 14 ms versus 197 ± 22 ms, $P<0.001$). Mean of the shortest AF CL was lower with decremental pacing compared with burst pacing (136 ± 23 ms versus 159 ± 24 ms, $P<0.001$), as was the mean of the longest AF CL (207 ± 19 ms versus 217 ± 22 ms, $P<0.001$).

Discussion

The main finding of this study was that inducible (≥ 1 minute) and sustained AF (≥ 5 minutes) is common in patients without structural heart disease or clinical AF. Its incidence is critically dependent on the cut off used for its definition

Table 2. Characteristics of Sustained Atrial Fibrillation Versus Noninducible/Nonsustained Atrial Fibrillation

Variable	Sustained AF (≥ 5 Min)	Noninducible/Nonsustained AF	P Value
Age, mean \pm SD, y	38 \pm 13	40 \pm 13	0.7
Male gender, %	63.6	21.2	0.009
Body mass index	29 \pm 6	27 \pm 5	0.29
Body surface area, m ²	2 \pm 0.3	1.8 \pm 0.3	0.04
Symptom duration, mean \pm SD, y	4 \pm 4	6 \pm 5	0.3
AVRT, %	36.4	15.2	0.19
Left atrial size, mm	33 \pm 6	34 \pm 6	0.71
Left atrial area, cm ²	16 \pm 0.7	19 \pm 4	0.24
Left ventricular ejection fraction, %	65 \pm 2	66 \pm 2	0.79

AF indicates atrial fibrillation; SD, standard deviation; AVRT, atrioventricular reentrant tachycardia.

(highest incidence with short duration of cut off) and the method of stimulation (higher incidence with decremental pacing). Importantly, AF inducibility increased with the number of inductions performed despite allowing sufficient time for reversal of ERP-remodeling and absence of change in autonomic tone between inductions. The marked difference in the incidence of inducible and sustained AF between AF induction protocols and the relatively common finding of AF in normal hearts suggests that the specificity of AF inducibility is low

Prior Studies

A number of studies have described the use of AF inducibility as an electrophysiological end point after pulmonary vein

Table 3. Univariable and Multivariable Predictors of Sustained Atrial Fibrillation by Cox-Regression Analysis for Sustained Atrial Fibrillation (≥ 5 Minutes)

Variable	Univariable Hazard Ratio (95% CI)	P Value	Multivariable Hazard Ratio (95% CI)	P Value
Male gender*	5.4 (1.5–18.5)	0.008	6.9 (1.8–27)	0.006
Body surface area (each m ² increment)*	4.5 (0.9–24.4)	0.08	...	
AVRT (vs others)*	2.5 (0.7–8.7)	0.14	...	
Age	0.99 (0.9–1.1)	0.69		
Symptom duration (each y increment)	0.99 (0.9–1.0)	0.7		
Body mass index	1.1 (0.9–1.2)	0.3		
Left atrial size (each 1 mm increment)	0.96 (0.8–1.2)	0.68		
Left atrial area (each 1 cm ² increment)	0.3 (0.04–2.8)	0.31		
Left ventricular ejection fraction (each % increment)	0.85 (0.5–1.5)	0.57		

*Inserted into multivariable model. Manifest preexcitation was not a predictor of sustained AF (hazard ratio 2.0, 95% CI, 0.5–7.4, $P=0.32$).

AVRT indicates atrioventricular re-entrant tachycardia; AF, atrial fibrillation.

isolation (PVI) to predict long-term outcomes and to determine which patients require additional substrate modification.^{3,4,6–8} Noninducibility predicted greater AF free survival (82%–87%) than for patients who remained inducible over 6 to 12 months of follow-up (42%–62.5%).^{6–8} Furthermore, additional linear ablation in patients who remained inducible after PVI increased AF free survival to match that of patients who were noninducible after PVI alone.^{5,6}

In contrast, Richter et al⁷ showed that AF inducibility after PVI had a poor sensitivity (46.7%), intermediate specificity (75%), and a low positive and negative predictive value for future AF recurrence (53.8% and 69.2%, respectively). One reason for these differing observations is that the studies have used diverse induction protocols and definitions of AF inducibility.^{3,4,6–8}

Following pulmonary vein isolation in patients with paroxysmal AF, rates of AF inducibility varied according to the definition used. Thus it was reported in 43% of patients for a definition of >10 seconds,³ 14% to 56% of patients for a definition of ≥ 1 minute,^{2, 6–8, 14–16} 36% of patients for a definition of ≥ 5 minutes,¹⁷ and 7% to 28% of patients for a definition of >10 minutes.^{4,5,18,19} In the absence of clinical AF or structural heart disease, we found a higher incidence of inducible AF of >10 seconds (82.7%), but similar incidence of AF ≥ 1 minute (49.5%), of AF ≥ 5 minutes (29.5%), and of AF >10 minutes (27.8%). Importantly, patients with sustained AF (≥ 5 minutes) did not exhibit changes in atrial refractoriness and conduction to explain AF inducibility. Although voltage mapping and left atrial measurements were not made, the population in this study was identical to the controls without AF or structural heart disease in previous studies who were found to have no conduction or voltage abnormalities.^{21,22}

The number of AF inductions has varied from 2 to 9 inductions between different studies,^{3–7} and between 3 to 5 inductions within 1 study.² We found that the incidence of inducibility increases by each induction and had not yet reached a plateau after 10 inductions. This occurred despite allowing sufficient time for reversal of acute ERP remodeling,¹² and demonstrates an increased probability of AF induction with increasing attempts unrelated to risk of clinical AF. Importantly, none of this cohort developed AF in long-term follow-up.

There also has been considerable heterogeneity in the methods of pacing used for AF induction in prior studies. Some studies have used burst pacing at a fixed cycle length,³ while others have paced at the shortest cycle length resulting in loss of 1:1 capture.^{5–8} In the current study we observed that the incidence of inducible or sustained AF was significantly higher with decremental pacing compared with burst pacing, as was the total duration of induced AF. Thus, variations in the definition of inducibility, aggressiveness of AF induction protocol, and the number of AF inductions critically influence the use of AF inducibility as a valid electrophysiological end point.

Our rate of sustained AF (≥ 5 minutes) of 29.5% was higher than that recently reported by Huang et al (18.6%),¹¹ who also studied an SVT population for AF inducibility after 3 induction attempts. The population in the present study was

homogenous with no structural heart disease or risk factors for AF in contrast to Huang et al,¹¹ in which 16% had hypertension. Detailed electrophysiological evaluation of atrial refractoriness (3 sites), conduction, and sinus node function were performed in our study, while only single ERP measurements from the PCS were reported in that study. Last, we performed a larger number of AF inductions to elucidate the incremental relationship between number of induction attempts and inducibility, and to demonstrate no plateau effect in AF inducibility even after 10 attempted inductions.

Study Limitations

We did not test the effect of pacing from different sites such as the mid or distal CS or RAA on AF inducibility, nor did we use pharmacological provocation. However, this is unlikely to have changed the conclusions drawn from the study. We did not test AF inducibility prior to catheter ablation. Thus, the possibility of interaction between substrate for SVT and AF cannot be excluded. We did not compare burst versus decremental pacing within the same patient; thus, paired comparison was not possible. Due to the long duration of the research protocol, we did not repeat ERP measurements between AF inductions, which would be the most sensitive way to exclude AF induced electric remodeling. However, a waiting time that exceeded twice the duration of induced AF (eg, 9 minutes waiting between induction for 4.5 minutes of induced AF) would have been sufficient for ERP reversal, consistent with findings of Daoud et al,¹² in which AF-induced shortening in ERP recovered to baseline in ~5 to 8 minutes, even if AF >5 minutes was induced.

Conclusions

Inducible and sustained AF is common in the absence of structural heart disease or clinical AF. Its incidence is dependent on both the definition and type of induction protocol used. Critically, we demonstrated a linear relationship between number of induction attempts and inducibility without observing a plateau effect. These findings suggest that AF inducibility as an electrophysiological end point in the setting of catheter ablation is of limited value.

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Disclosures

None.

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CLINICAL PERSPECTIVE

Apart from pulmonary vein isolation, catheter ablation of atrial fibrillation (AF) lacks reliable electrophysiological end points. AF inducibility has been used to predict long-term outcomes and to determine the need for additional substrate modification. There is considerable heterogeneity between studies in the definition of inducible AF, pacing protocols, number of inductions, and in the use of pharmacological provocation. Inducible AF has been defined as AF >10 seconds, ≥ 1 minute, ≥ 5 minutes, or even >10 minutes. Burst or decremental pacing protocols have been used and the number of inductions has varied from 2 to 9 inductions. This variety of definitions and methods is confounded by the fact that there is very little reference information on AF inducibility in a normal heart. This study assessed the incidence of inducible AF in 44 patients with no structural heart disease or clinical AF, and examined the effect of varying AF inducibility definitions, methods of induction, and number of inductions on AF incidence. We found that the incidence of inducible AF in this population was similar to that reported in patients with a history of AF. There were no abnormalities in cardiac structure, atrial refractoriness, conduction, or sinus node function to explain these findings. AF inducibility was higher with decremental than burst pacing. There was increased probability of AF induction with increasing attempts, which had not yet reached a plateau after 10 inductions. None of this cohort developed AF in long-term follow-up. These findings suggest that AF inducibility as an electrophysiological end point in the setting of catheter ablation is of limited value.