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CLINICAL RESEARCH
Cardiac electrophysiology

New-onset atrial fibrillation after cavotricuspid isthmus ablation: identification of advanced interatrial block is key

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Aims A significant proportion of patients develop atrial fibrillation (AF) following cavotricuspid isthmus (CTI) ablation for typical atrial flutter (AFl). The objective of this study was to assess whether the presence of advanced interatrial block (aIAB) was associated with an elevated risk of AF after CTI ablation in patients with typical AFl and no prior history of AF.

Methods and Results This study included patients with typical AFl and no prior history of AF that were referred for CTI ablation. Patients were excluded when they had received repeat ablations or did not demonstrate a bidirectional block. In all patients, a post-ablation electrocardiogram (ECG) in sinus rhythm was evaluated for the presence of aIAB, defined as a P-wave duration $\geq$120 ms and biphasic morphology in the inferior leads. New-onset AF was identified from 12-lead ECGs, Holter monitoring, and device interrogations. The cohort comprised 187 patients (age 67 $\pm$ 10.7 years; ejection fraction 55.8 $\pm$ 11.2%). Advanced interatrial block was detected in 18.2% of patients, and left atrium was larger in patients with aIAB compared with those without aIAB (46.2 $\pm$ 5.9 vs. 43.1 $\pm$ 6.0 mm; $P = 0.01$). Over a median follow-up of 24.2 months, 67 patients (35.8%) developed new-onset AF. The incidence of new-onset AF was greater in patients with aIAB compared with those without aIAB (64.7 vs. 29.4%; $P < 0.001$). After a comprehensive multivariate analysis, aIAB emerged as the strongest predictor of new-onset AF [odds ratio (OR) 4.2, 95% confidence interval (CI): 1.9–9.3; $P < 0.001$].

Conclusion Advanced interatrial block is a key predictor for high risk of new-onset AF after a successful CTI ablation in patients with typical AFl.

Keywords Interatrial block • Atrial flutter • Atrial fibrillation • Ablation • Cavotricuspid isthmus ablation

Introduction

Catheter ablation of the cavotricuspid isthmus (CTI) is an established, curative first-line therapy for patients with typical atrial flutter (AFl), with success rates exceeding 90%. However, a significant proportion of patients with successful ablations will develop atrial fibrillation (AF) during follow-up.[1–7] This probably reflects a common underlying substrate for both types of arrhythmia.[8]

Interatrial block (IAB), a delay in conduction over the Bachmann bundle, is manifested in the 12-lead electrocardiogram (ECG) by a P-wave duration >120 ms. In advanced IAB, a biphasic [$\pm$] morphology appears in the inferior leads, a feature that is not present in partial IAB.[9] The appearance of advanced IAB is frequently associated with atrial tachyarrhythmias, and it was found to predict AF in many different clinical scenarios.[9] Delayed conduction between the right and left atria (LA) induces interatrial dyssynchrony, which leads to electrical heterogeneity in the LA. This condition is known to contribute to AF maintenance.

The aim of the present study was to assess whether the presence of advanced IAB was associated with an increased risk of developing

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What's new?

- Many recent series have emphasized a high incidence of new-onset atrial fibrillation (AF) after successful ablation of typical atrial flutter (up to 82%, Natale *et al.*). Therefore, the optimal duration of anticoagulation is unknown, and also it has been proposed that isolation of the pulmonary veins should be considered at the time of cavotricuspid isthmus ablation. In consequence, the identification of these patients with a substrate for AF development is helpful for clinical decisions.
- This multicentre retrospective study showed that the presence of advanced interatrial block on a 12-lead ECG (P-wave duration >120 ms and biphasic P-waves in inferior leads) is a significant predictor of AF occurrence in the univariate and multivariate analysis.

AF after CTI ablation in patients with typical AFl and no prior history of AF.

Methods

Patients

Multinational multicentre cohort was selected from patients who underwent catheter ablations for typical AFl from January 2008 to December 2011. The inclusion criteria were: (i) paroxysmal or persistent typical AFl and no prior history of AF, (ii) available records of a post-ablation, 12-lead ECG, and (iii) successful catheter ablation, defined by the demonstration of a bidirectional conduction block over the isthmus. The exclusion criteria were: (i) repeated ablations, (ii) non-CTI-dependent circuits, (iii) use of antiarrhythmic drugs after the ablation, (iv) paced or ectopic atrial rhythm, or (v) lost during follow-up. All participants provided written informed consent, and all study procedures were in accord with the ethical standards outlined in the Helsinki Declaration of 1975, as revised in 1983.

Electronic charts were reviewed for demographics, co-morbid conditions, history of cardiac disease, score for the $CHADS_2$ evaluation, and echocardiographic parameters prior to ablation, including LA diameter and left ventricular ejection fraction (LVEF).

Electrocardiogram analysis

In all patients, a blinded evaluation of a post-ablation, 12-lead ECG in sinus rhythm (filter 150 Hz, 25 mm/s, 10 mm/mV) was performed to detect the presence of advanced IAB. The ECGs were scanned at 300 DPI, and the images were amplified ×10. The P-wave duration was measured with semi-automatic callipers (Iconico). The onset of the P-wave was identified as the point of initial upward or downward deflection from the baseline, and the P-wave endpoint was defined as the point where the waveform returned to the baseline. Partial IAB was defined as a P-wave duration ≥120 ms; advanced IAB was defined as a P-wave ≥120 ms accompanied by a biphasic morphology (±) in the inferior leads[10] (*Figure 1*).

Electrophysiology study

After obtaining informed consent from patients, the procedure was performed in a fasting state under conscious sedation. Catheter ablation was performed with a maximum voltage guided approach, as per routine practice. This technique has been described elsewhere.[10] An 8 mm large tip (Dual-8™, Saint Jude Medical or Blazer™, Boston Scientific) or a 4 mm irrigated catheter (Coolflex™, Saint Jude Medical) was used for ablation at the operator's discretion.

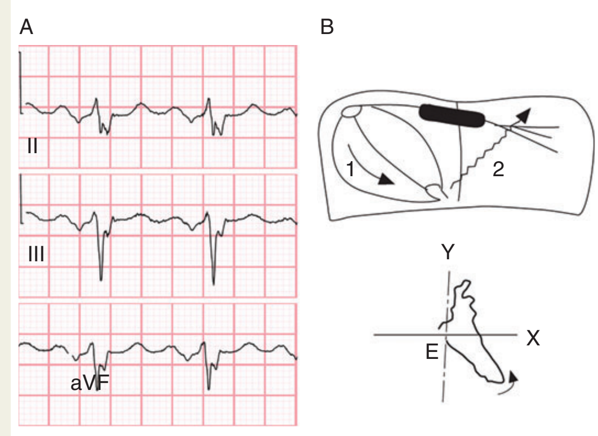

Figure 1 The interatrial block. Panel A: Typical ECG of advanced IAB with a P-wave duration >120 ms and biphasic morphology in inferior leads. Panel B: Diagram of atrial conduction, showing a block of the electrical impulse in the upper and middle parts of the interatrial septum and retrograde LA activation via muscular connections in the vicinity of the coronary sinus. The typical vectorcardiogram of the P-wave is also shown (modified from[20]). ECG, electrocardiogram; IAB, interatrial block; LA, left atrium.

Post-ablation follow-up

Episodes of new-onset AF were identified from 12-lead ECGs, Holter monitoring, and device interrogations. As per routine practice within participating centres, patients wore a 24 or 48 h Holter monitor at 3 months after ablation before considering anticoagulant discontinuation. In addition, any extra ECGs, Holter monitoring, or event recordings, driven by the patient's symptoms, were also considered during the follow-up.

Statistical analysis

Data were expressed as means and standard deviations for continuous variables, and as frequencies and percentages for categorical variables. After performing univariate comparisons (independent samples *t*-tests and χ^2 tests), we performed a multivariate logistic regression analysis to identify predictors of new-onset AF. Variables that were $P < 0.10$ on univariate analyses were entered into the model. A manual stepwise approach was used to delete variables from the model, based on lack of statistical significance, until only variables that were significant or close to significant (to avoid missing potentially important trends) remained. A Kaplan–Meier analysis of AF-free survival was also performed. Parameters of patients with and without advanced IAB were compared with the log-rank test. Comparison of P waves before and after ablation (in a sub-group of patients in sinus rhythm at the time of ablation) was done with the Bland–Altman method for P-wave duration and the Kappa index of agreement for P-wave morphology. The *P* values <0.05 were considered statistically significant.

Results

During the study period, a total of 187 patients fulfilled the inclusion criteria. The mean age was 67 ± 10.7 years, and 146 patients were males (78.1%). The mean LA size was 43.8 ± 6.1 mm, the mean LVEF was 55.8 ± 11.2%, and LV systolic dysfunction (EF < 50%) was present in 23% of patients. Hypertension was present in 60.9% ($n = 114$), ischaemic heart disease in 28.3% ($n = 53$), and 28.9% were diabetic ($n = 54$). For the cohort, the average $CHADS_2$ score was 1.5 ± 1.2 points. The CHADS scores were distributed as follows: scores = 0, 1, 2, and ≥ 3 points were observed in 19.8, 40.1, 21.4, and 18.7% of patients, respectively. The mean follow-up was 25.5 ± 15.1 months, and the follow-up periods were normally distributed (median 24.2 months, range 3–65).

At the time of the electrophysiology study, 108 patients were in AFl (57.8%) and 79 were in sinus rhythm (42.2%) but all had ECG evidence of previous typical AFl; thus, the latter group received an empiric CTI ablation. After the ablation, 154 patients (82.4%) were discharged with instructions to continue anticoagulation therapy (warfarin/acenocoumarol for 136 patients and new oral anticoagulants for 18 patients). Anticoagulation was not prescribed for 33 patients (17.6%), primarily based on the evidence of sinus rhythm prior to the procedure and small atrial size. In most of these patients (29/33), the $CHADS_2$ score was 0–1. Recurrence of typical AFl was observed in 7% of patients, and all of these required a repeat ablation.

Advanced IAB was detected in 34 patients (18.2%); partial IAB was detected in 107 (57.2%); and P-wave duration was normal in 46 patients (24.6%). The mean P-wave duration was 136.8 ± 20.5 ms. Compared with patients without advanced IAB, those with advanced IAB were, on average, older (70.5 ± 10.2 vs. 66.1 ± 10.7 years; $P = 0.03$), and they had larger LAs (46.2 ± 5.9 vs. 43.1 ± 6.0 mm; $P = 0.01$); the prevalence of hypertension was also higher, but the difference did not reach statistical significance (73.5 vs. 58.2%; $P = 0.12$).

In a subgroup of patients in sinus rhythm ($n = 25$), pre- and post-ablation ECGs were recorded in order to assess a potential effect of ablation on the P-wave duration and morphology. The P-wave duration was not different for pre- and post-ablation (mean difference 1.5 ms, 95% limits of agreement −5.1 to 8.2 ms with the Bland–Altman method), and the P-wave morphology (presence or absence of IAB) did not change either (Kappa = 1), thus suggesting that the ablation line did not significantly alter inter-atrial conduction assessed by ECG.

At the end of the follow-up, 67 patients had displayed at least one episode of AF (35.8%). Of these episodes, 22.4% ($n = 15$) presented early after the procedure (within 3 months) and 59.7% in total ($n = 40$) occurred within the first 12 months. The incidence of AF was 64.7 and 29.4% in patients with and without advanced IAB, respectively ($P < 0.001$). *Table 1* shows the characteristics of patients who did and did not develop new-onset AF after AFl ablation. Patients who developed AF had longer absolute P-wave durations (141.0 ± 19.7 vs. 134.5 ± 20.6 ms; $P = 0.04$) and higher prevalence of ischaemic heart disease (37.3 vs. 23.3%; $P = 0.06$) compared with those who did not. The temporal pattern of AF onset was not different in patients with or without advanced IAB (14.0 ± 11.1 vs. 15.6 ± 17.0 months, respectively; $P = 0.69$).

The multivariable logistic regression model included the presence of ischaemic heart disease ($P = 0.06$), LVEF ($P = 0.09$), P-wave duration ($P = 0.04$), and advanced IAB ($P < 0.001$). The multivariable analysis showed that neither P-wave duration ($P = 0.89$) nor LVEF ($P = 0.26$) were significant factors in predicting new-onset AF. However, advanced IAB emerged as the strongest predictor of AF development after successful AFl ablation (OR 4.2, 95% CI: 1.9–9.3, $P < 0.001$), followed by ischaemic heart disease (OR 1.8, 95% CI: 0.9–3.6, $P = 0.09$). The Kaplan–Meier analyses showed the cumulative AF-free survival rates (*Figure 2*). For patients with advanced IAB, the incidence of AF was 39.3 and 69.4% at 1 and 3 years, respectively; in patients without advanced IAB, the incidence of AF was 23.7 and 35.6% at 1 and 3 years, respectively ($P = 0.02$, log-rank test).

Table 1 Clinical variables in patients that did and did not develop atrial fibrillation after CTI ablation procedure

Clinical variable	No AF (n = 120)	AF (n = 67)	P-value
Age, years ± SD	66.2 ± 11.3	68.0 ± 9.6	0.27
Male sex, %	80.0	74.6	0.46
Hypertension, %	60.8	61.2	1.00
Prior stroke/TIA, %	8.3	9.0	1.00
Ischaemic heart disease, %	23.3	37.3	0.06
$CHADS_2$ score, mean ± SD	1.5 ± 1.2	1.4 ± 1.1	0.36
LA dimension, mm	43.7 ± 6.4	44.0 ± 5.8	0.81
LVEF, % ± SD	57.6 ± 9.8	53.8 ± 12.4	0.09
Advanced IAB, %	9.2	32.8	<0.001
P-wave duration, ms	134.5 ± 20.6	141.0 ± 19.7	0.04

TIA, transient ischemic attack; $CHADS_2$: stroke risk assessment based on a combination of risk factors, including cardiac failure, hypertension, age, diabetes, and stroke. AF, atrial fibrillation; LA, left atrium; LVEF, left ventricular ejection fraction; IAB, interatrial block.

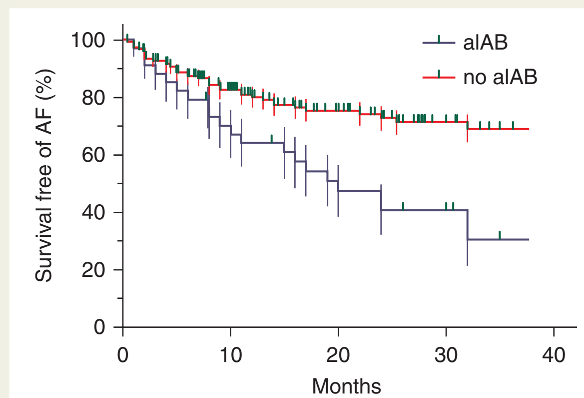

Figure 2 Kaplan–Meier analysis of AF-free survival during follow-up in patients with (red line) or without (blue line) advanced IAB. AF, atrial fibrillation; aIAB, advanced interatrial block.

Discussion

Atrial fibrillation is commonly observed after ablation of typical AFl; thus, the optimal duration of anticoagulation is unknown after successful AFl ablation. A previous history of AF is the strongest predictor of post-ablation AF.[1,3,4] Therefore, it is reasonable to assume that, in patients with pre-ablation AF, anticoagulation should be continued according to their estimated embolic risk. However, the approach is less clear for patients with typical AFl that have not had a previously documented AF. In this group, clinical predictors of AF have not been consistently demonstrated, and a follow-up monitoring strategy has not been well defined.

In this study, over one-third of patients developed new-onset AF after a mean follow-up of 25.5 ± 15.1 months; and most AFs occurred within the first post-ablation year. This observation was consistent with previous studies, which reported the development of new-onset AF in a significant proportion of patients with isolated, typical AFl, after a variable follow-up period.[2,5] This has led to the suggestion made by some authors that pulmonary vein isolation should be performed at the time of the CTI ablation.[5,11] In an analysis of the factors associated with AF occurrence, Lee *et al.*[6] found that the only independent predictor was LA volume index. Ellis *et al.*[5] determined that LA size and LVEF were associated with a high incidence of AF, but that association did not reach statistical significance. Other associated variables that have been suggested include the presence of significant mitral regurgitation[3] and the inducibility of sustained AF during the electrophysiology study.[3] On the other hand, Chinitz *et al.*[2] did not demonstrate any predictive value for age, hypertension, LA size, LV systolic dysfunction, or structural heart disease.

In the current study, the presence of advanced IAB was a strong predictor of new-onset AF post-ablation, and the association remained significant in a multivariate analysis. Interestingly, a prolonged P-wave duration alone was insufficient to predict AF. This is because a P-wave >120 ms may also be due to a delay in the right atrium. Also, the inhomogeneous LA activation, evidenced by the biphasic P-wave, is probably more important for AF genesis than the total atrial activation time.

The association of advanced IAB with atrial arrhythmias was first described by Bayes de Luna *et al.*[12] The authors reported a high incidence of paroxysmal supraventricular tachycardias (50% AF) in 16 patients with advanced IAB at a 30-month follow-up (93.7 vs. 27.7% in controls; $P < 0.001$). In a general hospital population, Agarwal *et al.*[13] found that advanced IAB was present in 160 of 308 patients (52%) that developed AF at a 16-month follow-up, compared with 18% without IAB in the age- and gender-matched control patients that remained in sinus rhythm. Interatrial block has also been associated with AF recurrence after electrical cardioversion[14] or after pulmonary vein isolation,[15] and IAB was associated with progression of paroxysmal AF to persistent or permanent AF.[16] The mechanism of this association is not completely understood; however, some have speculated on the pathophysiology. In the early 1980s, Bayes de Luna *et al.*[12] postulated that the biphasic P-wave morphology in the inferior leads reflected predominant caudo-cranial activation of the LA through the coronary sinus. This conduction path has been later confirmed using endocardial mapping.[17] This delayed, heterogeneous electrical activation of the LA results in impaired LA mechanical function, interatrial dyssynchrony, and increased susceptibility to AF. Consistent with that hypothesis, Goyal and Spodick[18] demonstrated that patients with IAB had LAs with poor contractile properties, and the extent of the dysfunction was related to the degree of electrical delay. Thus, abnormal LA activation should be considered a risk factor for AF, because it could also lead to a diminished contribution to the LV preload, a reduced LVEF, and a predisposition to thrombus formation in the LA appendage. Recently, the association between advanced IAB and atrial arrhythmias (predominantly AF and atypical AFl) has been called 'Bayes' syndrome', in recognition of the first person to describe all aspects associated with this condition, about 30 years ago.[19]

Cavotricuspid isthmus-dependent AFl can either start spontaneously or arise from premature atrial contractions. However, in a significant proportion of cases, it actually starts as AF that organizes into a macro-reentrant circuit, due to the development of functionally blocked lines between the two venae cavae. In these patients, as suggested by Waldo and Feld[8], AF has always been present, and it simply becomes manifest after CTI ablation, because it can no longer evolve into an AFl. This group of patients may be expected to exhibit extensive atrial remodelling, reflected by an increased P-wave duration, enlarged LA dimensions, tissue fibrosis, and impaired atrial mechanical function. The presence of advanced IAB on a 12-lead ECG facilitates the identification of patients with significant atrial remodelling and a substrate predisposed to the initiation and maintenance of AF.

Limitations

Some limitations apply to the present study. First, the retrospective nature of our study may have introduced bias in the analysis, although all patients were consecutively enrolled. Second, we could not fully ascertain that all the patients in this cohort were free of AF before the ablation, because a large proportion was presented with persistent AFl. Finally, after ablation we did not perform routine monitoring for asymptomatic arrhythmias with more prolonged Holter or event monitors or implantable loop recorders, with the eventual underestimation of AF recurrence.

Conclusions

In conclusion, aIAB identified in a surface, 12-lead ECG is a strong and independent predictor of new-onset AF after successful CTI ablation in patients with typical AFl and no prior history of AF. These findings may contribute to guiding decisions regarding the maintenance of anticoagulation after AFl ablation.

Conflict of interest: none declared.

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