Advanced interatrial block: An electrocardiographic marker for stroke recurrence

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ABSTRACT

The presence of interatrial block (IAB) has been directly related to the appearance of various atrial tachyarrhythmias and therefore could be a risk factor for stroke. The objective of this study is to establish whether the presence of IAB could predict stroke recurrence in patients with a previous episode.

Methods: We included all patients discharged from our hospital in 2011 following treatment for stroke, excluding those of cardioembolic or lacunar etiology. For all patients we analyzed the ECG recordings, determined whether the patient presented cardiovascular risk factors, and determined the presence and type of IAB. An IAB was defined as partial if the P-wave duration was ≥120 ms, and advanced if the duration was ≥120 ms and presented biphasic morphology in the inferior leads. The primary endpoint was the recurrence of stroke and the secondary endpoint was the incidence of atrial tachyarrhythmias after the first episode.

Results: A total of 149 patients were identified (80 (71.5–86.0) years, 41% men). After a median follow-up of 3.96 (0.63–5.35) years, 54 deaths (36%) were observed, 27 patients (18%) had experienced stroke recurrence, and 20 (13%) had developed atrial tachyarrhythmias. On multivariate analysis, the presence of advanced IAB [HR: 2.3, 95% CI (1.0–5.5); $p = 0.043$] and diabetes [HR: 2.5, 95% CI (1.1–5.4); $p = 0.018$] were significantly associated with stroke recurrence.

Conclusion: The presence of advanced IAB predicts the recurrence of stroke in patients with a previous episode. Further studies should be performed to investigate possible interventions.

Introduction

Interatrial block (IAB), defined as a P-wave duration ≥ 120 ms on the electrocardiogram (ECG) resulting from the presence of conduction disturbances between both atria, [1] has been directly related to the appearance of various atrial tachyarrhythmias, especially atrial fibrillation (AF) [2]. Different studies have correlated this ECG pattern with fibrosis in both atria, and established that it is a very specific (90%) but insensitive marker of left atrial enlargement [3].

The prevalence of IAB depends on a variety of factors, including age (9% in subjects under 35 years and up to 60% in those over 50 years) [2]

and presence of hypertension, diabetes mellitus, hypercholesterolemia, and coronary disease [4].

Several cross-sectional studies have indicated that, on average, subjects with AF have longer P-wave duration compared to healthy controls [5,6]. More recently, a prolonged P-wave duration was shown to be a marker of incident AF in two independent cohort studies [7], and it has also been shown that the development of AF is an independent risk factor for the onset of stroke [8]. Several reports indicate that anticoagulation is an effective strategy for reducing the incidence of stroke in patients with AF [9]. In fact, some authors claim that, in patients with IAB, anticoagulation can be beneficial even before the onset of AF, [10] although to date no randomized studies have proven the validity of such claims.

In this observational study, we set out to assess whether the presence of IAB acts as a predictor of stroke recurrence.

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Methods

This retrospective cohort study was jointly carried out by members of the departments of cardiology and neurology of our institution. We included all patients discharged in 2011 following a diagnosis of stroke, defined as a neurological deficit attributed to an acute focal injury of the central nervous system (CNS) due to a vascular cause [11]. Exclusion criteria were the presence of a cardioembolic stroke (defined as an arterial occlusion presumably due to an embolus arising in the heart, we excluded all patients with a high-risk source of embolism according to the TOAST classification, including presence of atrial fibrillation, mechanical prosthetic valve, left atrial/atrial appendage thrombus, sick sinus syndrome, myocardial infarction in the previous four weeks, left ventricular thrombus, dilated cardiomyopathy, akinetic left ventricular segment, atrial myxoma, and infective endocarditis) [12] and lacunar stroke (defined as small subcortical infarcts resulting from the occlusion of a single penetrating artery caused by an intrinsic cerebral small arteriolar abnormality) [13]; while patients with previous anticoagulation were excluded due to the potential of this therapy to affect the incidence of future events.

In order to detect atrial tachyarrhythmias and stroke recurrence, we reviewed all relevant post-discharge medical records through December 2016, examining the electronic clinical history, where all data concerning patient admissions and consultations are recorded in our facility. We further reviewed the Horus model of clinical information (a shared system of electronic medical records that includes all hospital facilities in the region of Madrid). We did not use data obtained using the Holter or ISR device.

We recorded the presence of several cardiovascular risk factors such as hypertension, diabetes (DM), hyperlipidemia, smoking status, and studied the ECG recordings obtained during admission. The surface 12 lead ECG (TraceMasterVue_R, Philips, Amsterdam, the Netherlands) obtained during admission (filtered at 0.05–150 Hz, 10 mm/mV, 25 mm/s) was analyzed and the P-wave was measured with digital calipers with quadruple magnification. The P-wave onset was defined as the point of initial upward or downward deflection from the baseline and the offset as the return of the waveform to the initial baseline. IAB was defined as partial if the P-wave duration was ≥120 ms, and advanced if the P-wave was ≥120 ms and presented biphasic morphology in the inferior leads. Patient clinical records were analyzed in search of a relationship between the presence of IAB and the development of new events during follow-up, particularly the recurrence of stroke, but also to evaluate the appearance of new episodes of atrial tachyarrhythmias until the conclusion of the study period (December 2016).

The study was presented and approved by the ethics committee of our institution (FJD, Madrid, Spain), which waived the requirement for informed consent due to the retrospective nature of this research.

Statistical analysis

Quantitative variables are expressed as the median (interquartile range) because they did not follow a normal distribution. Qualitative variables are expressed with frequencies and percentages. Qualitative variables were compared using the chi-square test, and quantitative variables were evaluated using the Mann-Whitney U test. P-values of <0.05 were considered statistically significant.

The following variables were included in the univariate Cox regression model: age, gender, hypertension, diabetes mellitus, dyslipidemia, treatment with clopidogrel and aspirin, presence of IAB or advanced IAB, and AF during follow-up. All variables with a P-value < 0.2 were entered into a multivariate Cox regression model, where the dependent variable was the recurrence of stroke or the appearance of atrial tachyarrhythmias.

Results are expressed as hazard ratio (HR) and 95% confidence interval (CI). The recurrence of stroke in the first 30 days is considered an important prognostic marker and has been tested in several studies related to stroke prognosis. According to Mohan et al., it is the period in which most stroke recurrences take place, as well the period with the highest mortality (up to 25% according to Hankei et al). As a result, we considered it important to make this distinction in our analysis, and we performed a Cox regression model for the 30 days after the first episode of stroke so as to distinguish those variables that predicted early recurrence and which served as predictors of late recurrence [14,15].

All analyses were performed with SPSS 22, (IBM corporation, Edicott, NY).

Results

Baseline characteristics

In 2011, a total of 381 ischemic strokes were diagnosed in our facility, 194 of which were treated with anticoagulation or were labeled cardioembolic, or the patient died during admission. Of the remaining 187, 38 were found to be of lacunar etiology, leaving a total of 149 patients for the analysis of this study. The mean age was 80 (71.5–86.0) years, and 41% were men. Thirty-four patients presented IAB, 22 presenting advanced IAB and the rest (12) partial IAB. The baseline characteristics of the patients according to the presence and type of IAB are listed in (Table 1).

After a mean follow-up of 3.96 (0.63–5.35) years, 54 deaths were observed (36.2%). During this time, there were 27 recurrences of stroke (18.1%), and 20 patients (13.4%) developed atrial tachyarrhythmias.

We performed a univariate Cox analysis for all the variables appearing in Table 1, with the exception of death. The variable DM reached statistical significance (HR: 6.6; $p = 0.010$). We then carried out a multivariate Cox analysis to establish whether any of the variables could independently predict the recurrence of stroke. For this analysis,

Table 1
Baseline characteristics of the patients according to presence and type of interatrial block.

	IAB	No IAB	p-Value	Advanced IAB	No advanced IAB	p-Value
n	34	115		22	126	
Age (years)	78 (63.5–83.7)	80 (73–86)	0.26	79 (73–84.5)	80 (71–86)	0.98
Male gender % (n)	44.1 (15)	47 (41)	0.74	40.9 (9)	41.7 (53)	0.94
Hypertension % (n)	64.9 (22)	82 (71)	0.46	68 (15)	70 (88)	0.86
DM % (n)	35.3 (12)	25 (22)	0.11	31.8 (7)	23.6 (30)	0.41
DL % (n)	32.4 (11)	46 (40)	0.42	36.4 (8)	38.6 (49)	0.84
Smoker % (n)	32.4 (11)	34 (30)	0.76	18 (4)	32.3 (41)	0.19
Aspirin % (n)	70 (24)	70.3 (81)	0.98	60 (13)	72.1(91)	0.29
Clopidogrel % (n)	26.7 (9)	31.7 (36)	0.60	35 (8)	29.7 (37)	0.64
Death % (n)	35.3 (12)	42 (37)	0.89	40.9 (9)	41.7 (53)	0.99
AF % (n)	5.9 (2)	13 (11)	0.37	9.1 (2)	10.2 (13)	0.87

AF: atrial fibrillation; DL: dyslipidemia; DM: diabetes mellitus; IAB: interatrial block;

Table 2
Univariate and multivariate analysis of stroke recurrence.

Stroke recurrence	Univariate analysis	Multivariate analysis		
	p-Value	HR	95% CI	p-Value
IAB	0.07	1.8	0.80–3.93	0.16
Age	0.34			
Gender (male)	0.45			
Hypertension	0.43			
Diabetes mellitus	**0.01**	2.5	1.17–5.53	**0.02**
Hyperlipidemia	0.39			
Smoker	0.43			
Aspirin treatment	0.19			
Clopidogrel treatment	0.45			
AF	0.87			

Stroke recurrence	Univariate analysis	Multivariate analysis		
	p-Value	HR	95% CI	p-Value
Advanced IAB	**0.03**	2.4	1.03–5.51	**0.04**
Age	0.34			
Gender (male)	0.45			
Hypertension	0.43			
Diabetes mellitus	**0.01**	2.5	1.17–5.47	**0.02**
Hyperlipidemia	0.39			
Smoker	0.43			
Aspirin treatment	0.19			
Clopidogrel treatment	0.45			
AF	0.87			

AF: atrial fibrillation; IAB: interatrial block.

Table 3
Univariate and multivariate analysis of late stroke recurrence.

Late stroke recurrence	Univariate analysis	Multivariate analysis		
	p-Value	HR	95% CI	p-Value
IAB (any type)	0.43	1.8	0.681–4.686	0.24
Age	0.10	1.0	0.995–1.081	**0.09**
Gender (male)	0,83			
Hypertension	0.62			
Diabetes mellitus	0.21			
Hyperlipidemia	0.50			
Smoker	0.97			
Aspirin treatment	0.34			
Clopidogrel treatment	0.73			

Late stroke recurrence	Univariate analysis	Multivariate analysis		
	p-Value	HR	95% CI	p-Value
Advanced IAB	**0.05**	2.9	1.145–7.698	**0.03**
Age	0.10	1.0	0.993–1.081	0.10
Gender (male)	0.83			
Hypertension	0.62			
Diabetes mellitus	0.21			
Hyperlipidemia	0.50			
Smoker	0.97			
Aspirin treatment	0.34			
Clopidogrel treatment	0.73			

AF: atrial fibrillation; IAB: interatrial block.

in addition to DM, treatment with aspirin (ASA) ($p = 0.191$) and IAB ($p = 0.071$) was included, as the p value was <0.2. The results of the multivariate analysis showed that DM maintained its ability to independently predict the recurrence of stroke [HR: 2.5, 95% CI (1.169–5.526); $p = 0.019$]. In general, IAB did not predict the recurrence of stroke [HR: 1.8, 95% CI (0.795–3.931); $p = 0.162$].

We carried out another univariate Cox analysis, replacing the 'IAB' variable with 'advanced IAB' next to all the variables in Table 1, except death. Again, the presence of diabetes was a significant predictor of stroke recurrence [HR: 6.6; $p = 0.010$], but the presence of advanced IAB [HR: 5.0; $p = 0.025$] predicted the recurrence of stroke.

We subsequently performed a multivariate Cox analysis to investigate whether any of the variables could independently predict the recurrence of stroke. For this multivariate analysis, treatment with ASA ($P = 0.191$) was included, as were DM and presence of advanced IAB. The results of this analysis showed that advanced IAB [HR: 2.4, 95% CI (1.03–5.51); $p = 0.043$] and DM [HR: 2.5, 95% CI (1.17–5.47); $p = 0.018$] remained statistically significant and independent predictors of recurrence of stroke. (Table 2).

To discriminate those variables that predict early or late recurrence of stroke, we conducted a Cox analysis, excluding from this analysis all cases in which recurrence took place in the first 30 days after discharge. We found that in the multivariate analysis only the presence of advanced IAB [HR: 2.9, 95% CI (1.15–7.69); $p = 0.025$] reached a statistically significant value as a predictor of late recurrence. Of interest, diabetes was not a predictor of recurrence after 30 days of discharge (Table 3).

Predictive value of IAB in the development of atrial tachyarrhythmias

To establish the relationship between IAB and atrial tachyarrhythmias, we performed a univariate Cox analysis for all variables in Table 1, except death. The age variable reached statistical significance on univariate analysis ($p = 0.09$). For the multivariate analysis, we included age, presence of IAB ($p = 0.696$), and hypertension ($p = 0.198$), revealing that only age remained as a predictor of atrial tachyarrhythmias [HR: 1.1, 95% CI (1.01–1.13); $p = 0.021$] (Table 4).

We also carried out a Cox analysis with advanced IAB alongside the same variables analyzed previously (except IAB). Age again reached clinical significance ($p = 0.023$), and this relationship remained unchanged on multivariate analysis [HR: 1.1, 95% CI (1.01–1.13); $p = 0.020$].

Table 4
Univariate and multivariate analysis of incidence of atrial tachyarrhythmias.

Incidence of atrial tachyarrhythmias	Univariate analysis	Multivariate analysis		
	p-Value	HR	95% CI	p-Value
IAB	0.70	0.9	0.26–3.19	0.88
Age	**0.01**	1.1	1.01–1.13	**0.02**
Gender (male)	0.75			
Hypertension	0.20			
Diabetes mellitus	0.49			
Hyperlipidemia	0.79			
Smoker	0.79			
Aspirin treatment	0.33			
Clopidogrel treatment	0.29			

Incidence of atrial tachyarrhythmias	Univariate analysis	Multivariate analysis		
	p-Value	HR	95% CI	p-Value
Advanced IAB	0.60	1.4	0.40–4.97	0.59
Age	**0.01**	1.1	1.01–1.13	**0.02**
Gender (male)	0.75			
Hypertension	0.20			
Diabetes mellitus	0.49			
Hyperlipidemia	0.79			
Smoker	0.79			
Aspirin treatment	0.33			
Clopidogrel treatment	0.29			

IAB: interatrial block.

Predictive value of IAB for the incidence of all-cause mortality and after 30 days post-stroke

Variables predicting all-cause mortality on multivariate analysis were age [HR: 1.0, 95% CI (1.06–1.14); *p* ≤0.001] and the presence of DM in the first 30 days [HR: 2.2, 95% CI (1.25–4.32); *p* = 0.011], (Table 5); advanced IAB did not reach statistical significance [HR: 0.9, 95% CI (0.47–2.11); *p* = 0.98]. Regarding the combined endpoint of all-cause mortality/stroke recurrence, advanced IAB [HR: 2.1, 95% CI (1.09–3.93); *p* = 0.039] and age [HR: 1.1, 95% CI (1.03–1.09); p ≤0.001] were identified as risk factors (Table 5).

Discussion

In this study, we have found that patients with advanced IAB presented a higher rate of stroke recurrence, and this association remained statistically significant after adjusting for established risk factors for stroke. However, not all types of IAB worsened prognosis in patients with a history of stroke. These findings are consistent with the study conducted by O'Neals et al., who found that advanced IAB was associated with incident ischemic stroke among the general population [16]. This finding is also consistent those of a recent study conducted by Escobar-Robledo et al. in which a multivariable comprehensive Cox regression analysis revealed that advanced IAB was associated with ischemic stroke [17]. We did not find previous studies that evaluated the presence of advanced IAB with stroke recurrence.

We have documented that DM was a predictor of early recurrence of stroke and all cause mortality, but this association disappeared after 30 days. DM is a known risk factor for stroke and is associated with higher mortality in these events [18,19].

In our study, age was the only variable that remained an independent predictor of development of atrial tachyarrhythmias on multivariate analysis. We have not found any association between the presence of advanced or partial IAB and AF, though this relationship has been established in several previous studies. [5,6,20] Particularly, a recent study conducted by Skov et al. demonstrated that the 10-year risk of

AF was 50% in those with advanced IAB compared to 10% in subjects with a normal P-wave. The authors concluded that individuals with advanced IAB and absence of cardiovascular disease had a higher risk of AF than patients with cardiovascular disease and no IAB [20].

The lack of a relationship between IAB and atrial tachyarrhythmias may be due to the fact that our patients had a lower average age than in previous studies. For example, in the study carried out by Martínez-Selles et al., the mean participant age was 101 ± 1.5 years, [21] whereas in our study the median age in the group of advanced IAB was 79 (73–84.5) years. Another potential explanation is that many events perhaps have gone unidentified since, as explained above, we did not use Holter monitoring or ISR to detect atrial tachyarrhythmias.

Our findings lead us to consider the possibility that, regardless of the presence of atrial tachyarrhythmias, left atrial disease should be considered an independent risk factor of stroke. In fact, previous studies established the possibility that mechanisms other than AF contribute to the development of thromboembolic events [22]. Kottkamp et al. suggested the term fibrotic atrial cardiomyopathy to describe a specific, primary form of biatrial pathology characterized by extensive fibrosis as the substrate underlying atrial arrhythmias and thromboembolism [23,24]. Other studies have found an association between other ECG patterns beyond abnormal P-wave terminal force in lead V1, a marker of left atrial fibrosis, and ischemic stroke [25–27]. These studies and our findings lead us to hypothesize that in the presence of risk factors for recurrence of stroke such as advanced IAB or left atrium cardiomyopathy, preventive interventions could be carried out. It has been established that even patients without AF could benefit from early anticoagulation if they have certain risk factors. [28,29] Indeed, Martinez-Selles et al. proposed a series of high-risk characteristics that should be considered linked to the microembolic processes frequently occurring in these patients before a stroke, and established that patients with advanced IAB have a higher risk of stroke regardless of whether they have documented AF [10].

We believe that it is important to conduct future studies to investigate whether this intervention could reduce the incidence of stroke and cognitive decline in these patients.

Study limitations

Limitations such as the small sample size and retrospective nature of the study do not allow us to draw any final conclusions. As in previous studies on the search for atrial tachyarrhythmias, these episodes are likely to be under-ascertained, which would decrease our power to detect associations rather than result in spurious false-positive results.

Another of our limitations is that we did not determine atrial size; however, the main point of interest of our study was to demonstrate the predictive ability of the ECG, as it is a simple and accessible diagnostic technique.

Larger long-term prospective series are needed to confirm the relationship between advanced IAB and poor prognosis in patients with stroke. However, we believe that the present work can set a precedent for future prospective studies searching for new preventive and therapeutic strategies.

Conclusion

In our series of patients, the presence of advanced IAB and DM were significant predictors of stroke recurrence. Further studies should be performed to confirm this association and investigate possible interventions and therapeutic measures.

Acknowledgments

Table 5
Univariate and multivariate analysis of all-cause mortality, all-cause mortality or stroke recurrence and all-cause mortality or stroke recurrence after 30 days post-stroke.

All-cause mortality				All-cause mortality after 30 days post-stroke		
	Multivariate analysis			Multivariate analysis		
	HR	95% CI	p-Value	HR	95% CI	p-Value
IAB	1.1	0.60–2.17	0.70	1.3	0.62–2.55	0.53
Age	1.1	1.06–1.14	<**0.001**	1.1	1.04–1.11	<**0.001**
Diabetes mellitus	2.2	1.24–4.28	**0.012**			

All-cause mortality				All-cause mortality after 30 days post-stroke		
	Multivariate analysis			Multivariate analysis		
	HR	95% CI	p-Value	HR	95% CI	p-Value
Advanced IAB	0.9	0.47–2.11	0.98	1.4	0.63–2.91	0.45
Age	1.1	1.06–1.14	<**0.001**	1.1	1.04–1.11	<**0.001**
Diabetes mellitus	2.3	1.25–4.32	**0.011**			

All-cause mortality or stroke recurrence				All-cause mortality or stroke recurrence after 30 days post-stroke		
	Multivariate analysis			Multivariate analysis		
	HR	95% CI	p-Value	HR	95% CI	p-Value
Advanced IAB	1.5	0.82–2.82	0.20	2.1	1.09–3.93	**0.039**
Age	1.1	1.03–1.09	<**0.001**	1.1	1.03–1.09	<**0.001**
Diabetes mellitus	1.5	0.82–2.82	**0.20**			

IAB: interatrial block.

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