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Original Paper

Increased Incidence of Interatrial Block in Younger Adults with Cryptogenic Stroke and Patent Foramen Ovale

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Key Words
Electrocardiography · Patent foramen ovale · Cardiac arrhythmias · Stroke · Young adults

Abstract
Background: Stroke is often unexplained in younger adults, although it is often associated with a patent foramen ovale (PFO). The reason for the association is not fully explained, and mechanisms other than paradoxical embolism may be involved. Young stroke patients with PFO have more atrial vulnerability than those without PFO. It is plausible that stretching of the interatrial septum may disrupt the interatrial conduction pathways causing interatrial block (IAB). IAB is associated with atrial fibrillation, dysfunctional left atria and stroke. ***Methods:*** Electrocardiogram (ECG) characteristics of prospectively recruited young patients (≤55 years of age) with unexplained stroke (TOAST and A-S-C-O) were compared with control data. All stroke cases underwent bubble contrast transthoracic and transoesophageal echography. IAB was defined as a P-wave duration of ≥110 ms. ECG data were converted to electronic format and analysed in a blind manner. ***Results:*** Fifty-five patients and 23 datasets were analysed. Patients with unexplained stroke had longer P-wave duration ($p = 0.013$) and a greater prevalence of IAB ($p = 0.02$) than healthy controls. Case status was an independent predictor of P-wave duration in a significant multivariate model. There was a significant increase in the proportion of cases with a PFO with IAB compared with cases without PFO and with controls ($p = 0.005$). ***Conclusions:*** Young patients with unexplained stroke, particularly those with PFO, exhibit abnormal atrial electrical characteristics suggesting atrial arrhythmia or atrial dysfunction as a possible mechanism of stroke.

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Introduction

Stroke in younger adults is frequently unexplained [1]. A strong association with patent foramen ovale (PFO) has been repeatedly observed and, while paradoxical embolus does occur, it alone may not account for the association [2]. It is possible that undiagnosed atrial arrhythmia may be involved, which is suggested by the finding of excessive atrial vulnerability in those with a PFO and stroke [3].

The P wave on the electrocardiogram (ECG) is prolonged in some patient groups (such as those with stroke [4]). Prolonged P-wave duration, or interatrial block (IAB), occurs when conduction from the right to the left atrium (LA) is disrupted, usually at a point close to the atrial septum [5]. IAB is common [6] and is associated with atrial fibrillation (AF) [7] and LA dysfunction [8].

We hypothesised a priori that those with cryptogenic stroke and a PFO may have altered interatrial conduction due to the physical effect of the atrial septal abnormality (or related shunt) on the interatrial conduction pathways. We investigated the prevalence of atrial conduction abnormalities among young patients with unexplained stroke, with and without a PFO, compared with a cohort of healthy recordings.

Materials and Methods

Participants

Younger patients with cryptogenic stroke were prospectively recruited. Inclusion criteria were age ≤55 years at the time of stroke and an index cerebral infarct for which no cause was found despite extensive investigation. Investigation included at least: cerebral imaging (CT or MRI of the head); cervical vascular imaging (carotid Doppler, or CT or MR angiography), and cardiac investigation (structural imaging with transthoracic echocardiography and rhythm monitoring). All patients fulfilled the TOAST criteria for unexplained stroke and in addition must not have had level 1 evidence in any phenotype of the A-S-C-O criteria [9, 10]. Control data were obtained from a database of digital recordings for use by the biomedical research community [11].

Measurement

All cases underwent a standardised interview for eligibility, demographic details and stroke subtyping. An ECG was performed at a sweep speed of 50 mm/s and an amplitude of 20 mm/mV. All images were converted to electronic portable document format (Canoscan LiDE 200, Canon, UK; resolution 4,800 × 4,800 dpi). Electron callipers (Screen Calipers; Iconico, Inc. [12]) were used to measure distances. PDF files were coded using a patient identifier only and analysed in a blinded manner. PDF files were analysed at 200% zoom, on a high-resolution screen (Dell P2210; resolution 1,680 × 1,050 at 60 Hz). Callipers were individually calibrated for each ECG. Similar electronic analysis has been favourably compared with traditional manual measurement, with lower inter- and intra-observer error [13]. Only leads with good quality P waves were analysed, and ECGs with at least 9 leads of good quality were used. The P wave was measured from the onset of the P wave (which is defined as the junction between the iso-electric line and the beginning of the P deflection) and the offset (defined as the junction between the end of the P deflection and the PR segment) [14]. P-wave duration was averaged over at least 3 consecutive cycles with good quality tracing and over the interpretable leads.

All cases underwent further cardiac investigation for the presence or absence of a PFO with a bubble contrast transthoracic echocardiography [15]. This was performed with a GE Vivid 7 machine. Intravenous peripheral access was obtained in the left arm. Contrast was a mixture of 8 ml of heparinised saline, 1 ml own blood and 1 ml air. Two contrast injections were performed at rest, and up to 5 injections with a combination of early and late provocation (Valsalva, cough and sniff).

Definitions

PFO was diagnosed if ≥5 microbubbles were visualised in the left-sided chambers within 3 cardiac cycles of arrival of contrast in the right atrium or release of Valsalva. The degree of shunting was used as

Table 1. Characteristics and parameters for the case and control groups

	All controls	All cases	Cases without PFO	Cases with a PFO	Cases with a small PFO	Cases with a large PFO
Subjects, n	23	55	14	41	12	29
Age, years	36.9 ± 12.6	42.5 ± 11.2	46.7 ± 10.4	41.1 ± 10.4	44.2 ± 10.6	39.8 ± 11.4
Male sex, %	78.3	56.4	73.3	56.4	45.5	51.7
Mean P-wave duration, ms	98.4 ± 10.6*	105.6 ± 11.9*	103.3 ± 13.3	106.5 ± 11.4	105.9 ± 14.1	106.7 ± 10.3
Mean P-wave dispersion, ms	22.3 ± 7.9†	29.6 ± 11.9†	32.4 ± 13.1	28.6 ± 11.5	24.7 ± 10.2	30.2 ± 11.8
IAB, %	13.0‡	40.0	21.4‡	46.3‡	50.0	44.8

Figures are means ± SD for continuous variables and percentages for binary variables.
* Primary outcome analysis: $p < 0.05$. † $p < 0.01$; ‡ $p < 0.01$ for trend.

a marker of PFO size and was classified quantitatively by the maximum number of left ventricular bubbles per frame as small (<50 bubbles) or large (≥50 bubbles). IAB was defined as a P-wave duration of ≥110 ms, in line with previous publications [7]. P-wave dispersion (a related parameter also associated with AF) was calculated as the difference between the longest and the shortest P wave [16].

Statistical Analysis

Parametric statistics were used to compare parameters between the groups: unpaired t test for continuous and χ^2 test for categorical variables. Multivariate analysis was used to control for differences in baseline characteristics (as matching with controls was not possible). PFO status was not included in a multivariate model with controls, as these data were unavailable.

The pre-specified primary outcome measures were the differences in the mean P-wave duration and proportion with IAB between the stroke participants and controls. The secondary outcomes included the differences in P-wave characteristics between stroke groups with and without PFO. Measurement error was assessed by intra-class correlation coefficient (for continuous variables) and κ statistic (for categorical variables) [17].

For the primary outcome, with 56 cases and 18 controls, an unpaired t test would detect a difference in the primary outcome measure of 10 ms, with an anticipated standard deviation of 13 ms, an α of 0.05 and an 80% power. In addition, a stroke group with 56 cases, 28 with and 28 without a PFO, would allow detection of a 10-ms difference in P-wave duration, with a similar anticipated standard deviation, and values of α and β.

Written consent was obtained from all stroke patients. Ethical approval was granted in advance of the study by the research ethics committee (09/H0308/146).

Results

A total of 59 patients with stroke were recruited. Four were excluded because of poor quality data. ECG data were analysed on 23 control subjects. The characteristics of the controls, and of cases without PFO and with small and large PFO are displayed in table 1 and the ASCO classification of all stroke participants in table 2.

For the primary outcome measures, P-wave duration was longer in cases than controls (105.6 vs. 98.4 ms; t = –2.56, p = 0.013). IAB was more frequent in cases than in controls (40 vs. 13%; Pearson $\chi^2 = 5.411$, p = 0.02). P-wave dispersion was also longer in cases than controls (29.6 vs. 22.3 ms; t = –2.68, p = 0.009; table 1).

Of the 55 stroke cases, 41 (74.6%) had a PFO, of which 29 were large. Mean P-wave duration was not significantly longer in those with than without a PFO (106.5 vs. 103.3 ms; p = 0.39). The proportion of cases with IAB was greater in those with than without a PFO (46.3

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Table 2. A-S-C-O classification of all stroke participants

Case No.	PFO status	Sex	Age years	A-S-C-O classification	Case No.	PFO status	Sex	Age years	A-S-C-O classification
1	large	female	46.9	A0-S0-C2-O0	29	large	male	16.6	A0-S0-C3-O0
2	large	male	40.3	A0-S0-C2-O0	30	large	male	50.3	A0-S0-C2-O9
3	large	male	49.8	A0-S0-C3-O0	31	small	female	33.7	A0-S0-C3-O0
4	small	male	40.0	A0-S0-C2-O0	32	none	female	51.0	A3-S0-C0-O0
5	none	male	52.2	A3-S0-C0-O0	33	small	female	54.7	A3-S0-C3-O0
6	large	male	33.1	A0-S0-C2-O0	34	large	female	0.0	A0-S0-C3-O3
7	large	male	55.5	A3-S0-C3-O0	35	large	male	51.2	A0-S3-C3-O9
8	none	female	26.7	A0-S3-C0-O9	36	small	male	45.3	A0-S9-C3-O3
9	large	female	40.6	A0-S0-C3-O0	37	none	male	48.6	A3-S3-C3-O0
10	none	male	49.7	A3-S3-C0-O9	38	large	female	54.6	A0-S9-C2-O9
11	none	male	52.5	A0-S9-C0-O9	39	large	male	26.6	A0-S0-C3-O0
12	large	female	35.5	A0-S0-C3-O0	40	small	male	56.0	A0-S0-C3-O0
13	none	female	20.1	A0-S0-C0-O9	41	large	female	45.0	A0-S0-C3-O0
14	small	female	24.8	A0-S0-C3-O0	42	large	male	35.0	A0-S0-C2-O0
15	large	female	38.6	A0-S0-C3-O0	43	large	female	24.0	A0-S0-C3-O0
16	large	male	48.3	A0-S9-C3-O0	44	small	female	55.0	A0-S3-C3-O0
17	small	male	37.8	A0-S0-C3-O9	45	large	female	21.0	A0-S0-C3-O9
18	none	male	46.3	A0-S0-C0-O0	46	large	male	50.0	A0-S0-C3-O0
19	none	male	54.5	A0-S2-C0-O0	47	small	male	48.0	A0-S0-C0-O0
20	none	male	44.9	A0-S0-C0-O9	48	large	female	49.0	A0-S0-C3-O0
21	small	female	31.2	A0-S0-C3-O1	49	large	female	30.0	A0-S0-C3-O1
22	large	male	45.0	A0-S0-C3-O0	50	none	male	56.0	A0-S0-C0-O0
23	large	female	43.7	A0-S0-C2-O9	51	large	male	49.0	A0-S0-C3-O9
24	none	male	53.7	A3-S2-C0-O9	52	none	female	49.0	A3-S0-C0-O0
25	large	female	48.8	A0-S3-C2-O9	53	small	female	48	A0-S0-C3-O0
26	none	male	48.5	A0-S0-C0-O0	54	large	female	22.0	A0-S0-C2-O0
27	large	male	44.3	A0-S0-C3-O0	55	large	male	42.0	A0-S0-C2-O0
28	small	male	55.3	A3-S1-C3-O0					

Table 3. Multiple regression model of the predictors of P-wave duration

	B	SE (B)	β
Step 1			
Constant	90.87	4.7	
Age	0.31	0.11	0.31
Step 2			
Constant	92.55	4.8	
Age	0.2	0.11	0.2*
Female sex	–6.41	2.67	–0.26†
Case status	7.59	2.85	0.29‡

R^2 = 0.094 for step 1 and 0.2 for step 2 (p = 0.001). * p = 0.08; † p = 0.019; ‡ p = 0.01.

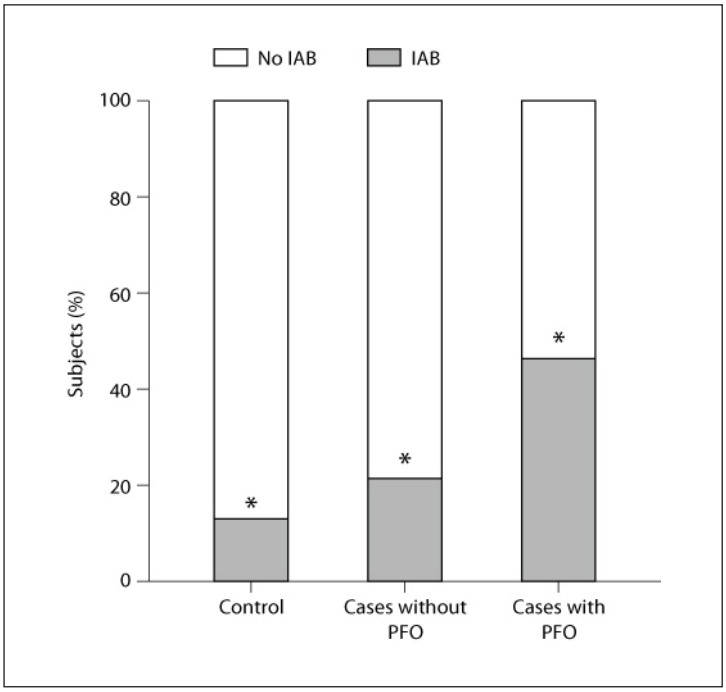

Fig. 1. Proportion of subjects in each group with and without IAB. * $p < 0.01$ for trend.

vs. 21.4%; $\chi^2 = 2.7$, $p = 0.1$). IAB occurred in 13% of controls, 21.4% without PFO and 46.3% with a PFO (χ^2 test for trend = 7.93, $p = 0.005$; fig. 1).

In a significant linear regression model with age and sex ($R^2 = 0.21$, $p = 0.001$), case-control status remained a significant predictor of P-wave duration ($\beta = 0.29$, $p = 0.01$; table 3). 20% of cases (randomly selected) were re-analysed for measurement error. For P-wave duration, the intra-class correlation coefficient was 0.954. For IAB, the κ statistic was 0.737.

Discussion

This is the first report of altered P-wave characteristics in younger cryptogenic stroke patients and the first suggestion of an association with PFO. This is important both in understanding the possible causes of unexplained stroke and the role played by a PFO.

The duration of the P wave is the time taken for atrial depolarisation. Prolongation of the P wave represents interatrial conduction delay or IAB. Conduction of an impulse from the right to the LA occurs via discrete communications, the most prominent of which is the Bachmann bundle, which courses along the superior aspect of the interatrial septum [18]. It has been suggested that stretch or pressure build-up on the superior portion of the atrial septum could alter the function of the Bachmann bundle and therefore delay interatrial conduction [19].

There are two main consequences of IAB. Firstly, IAB is a substrate to sustain AF, and the association between AF and IAB has been demonstrated [20]. Secondly, IAB results in delayed contraction of the LA (as depolarisation is delayed), which can result in LA dysfunction, with reduced LA kinetic energy and smaller 'atrial kick' contribution to ventricular filling [8]. Such a delay in LA contraction has haemodynamic consequences including raised

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LA pressure and LA dilatation, which again is a substrate for AF. Interestingly, LA dysfunction has been demonstrated in patients with stroke and PFO (which improved after PFO closure) [21].

There has been limited study on cardiac-electrophysiology in those with unexplained stroke, although there is some suggestion that it may be altered in the presence of a PFO. There were a number a papers which reviewed the ECG findings of those with and without PFO, looking for crochetage (a notch on the R wave which had been identified in atrial septal defects [22]). The first two small studies reported conflicting results [23, 24]. A further study found no association with crochetage, but P-wave abnormalities appeared more frequent in those with a PFO, and specifically biphasic P wave in lead III [25]. While there was no evidence of IAB, the biphasic P waves in lead III are interesting, as they are similar to the pattern expected in IAB and suggest that conduction to the LA may not have been via the Bachmann bundle.

The most relevant study on the possible impact a PFO may have on atrial conduction is the report on electrophysiological parameters of 62 younger patients with unexplained stroke [3]. Berthet et al. [3] reported a parameter 'atrial vulnerability' (a marker of the ability to sustain AF) which was significantly more likely in those with an atrial septal abnormality (OR = 4.1). The authors of the study concluded that atrial stretching induced by the atrial septal abnormality could alter the electrophysiological substrate, thereby increasing atrial vulnerability, and they suggest paroxysmal arrhythmia as a cause of stroke with PFO [3].

The strength of the current study is the prospective nature, the well-chosen and characterised patient group, and the blinded analysis. The main limitation lies in the use of control data from a database. However, these were collected and published with the intention of such use as control data.

The finding of prolonged P-wave duration in a cohort of patients with unexplained stroke raises the possibility that atrial arrhythmia is an unrecognised cause of stroke in this group. The likely increased prevalence of IAB in those with a PFO is intriguing, from which we can hypothesise an association between PFO and atrial arrhythmia, or LA dysfunction. At the least, we suggest altered LA conduction associated with the presence of a PFO (in cryptogenic stroke). It is important to understand the pathophysiology of PFO-associated stroke, especially given the uncertain benefits of PFO device closure [26].

Although we observed a large difference in the proportion of IAB in young stroke patients with a PFO when compared to those without a PFO, this difference did not reach statistical significance when those with and without PFO were directly compared. The study was not powered to detect this difference (a secondary end point).

Conclusion

This study demonstrates altered atrial depolarisation, which is associated with AF, in young patients with unexplained stroke, suggesting atrial arrhythmia as a possible cause of cryptogenic stroke. In addition, there is a possible association between PFO and atrial arrhythmia, suggesting that PFO is more than an inert communication or conduit between the atria.

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Disclosure Statement

The authors have no conflicts of interest.

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