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Atrial premature activity detected after an ischaemic stroke unveils atrial myopathy

Abbreviated title: Atrial premature activity after ischaemic stroke unveils atrial myopathy

Agathe Py[a], Mathieu Schaaf[a], Suzanne Duhamel[a], Salim Si-Mohamed[b], Jessica Daher[a], Mikhaïl Altman[c], Brigitte de Breyne[d], Laura Mechtouff[e], Joël Placide[f], Samuel Chauveau[d], Philippe Chevalier[d], Norbert Nighoghossian[e], Cyrille Bergerot[a], Hélène Thibault[a,*]

[a] *Service d'Explorations Fonctionnelles Cardiovasculaires, Groupement Hospitalier Est, Hospices Civils de Lyon, 69677 Bron, France*

[b] *Department of Thoracic and Cardiac Imaging, Groupement Hospitalier Est, Hospices Civils de Lyon, 69677 Bron, France*

[c] *Cardiology Department, Westmead Hospital, Westmead, NSW 2145; University of Sydney, Camperdown, NSW 2006, Australia*

[d] *Rhythmology Division, Groupement Hospitalier Est, Hôpital Louis Pradel, Hospices Civils de Lyon, 69677 Bron, France*

[e] *Stroke Department, Groupement Hospitalier Est, Hospices Civils de Lyon, 69677 Bron, France*

[f] *Centre d'Investigation Clinique de Lyon, Hospices Civils de Lyon, CIC1407, 69677 Bron, France*

* Corresponding author at: Cardiology Division, Service d'Explorations Fonctionnelles Cardiovasculaires, Hôpital Louis Pradel, Hospices Civils de Lyon, France.

E-mail address: helene.thibault@chu-lyon.fr (H. Thibault).

Agathe Py and Mathieu Schaaf are equal first authors.

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Summary

Background. – Recent publications suggest that left atrial (LA) myopathy is a potential source of thromboembolism, independent of atrial fibrillation.

Aims. – We sought to investigate whether the presence of atrial premature activity after an ischaemic stroke is associated with LA remodelling and dysfunction, and might be a surrogate marker of LA myopathy.

Methods. – After an ischaemic stroke or a transient ischaemic attack, patients without known atrial fibrillation or overt heart disease were included prospectively in the study. All patients had a standard workup, including ambulatory Holter electrocardiogram monitoring and transthoracic echocardiography. In some patients, transoesophageal echocardiography was also performed. Anatomical and functional LA remodelling were assessed using minimal and maximal volumes and LA emptying fraction in two-dimensional and three-dimensional echocardiography. Patients were separated into two groups according to the burden of atrial premature complexes (APCs), measured by Holter electrocardiography.

Results. – Among 148 eligible patients recruited from October 2015 to May 2016, 93 were included in the group with non-frequent APCs (nf-APC: < 100 APCs/24 hours) and 43 in the group with frequent APCs (f-APC: > 100 APCs/24 hours). Twelve patients had paroxysmal atrial fibrillation, and were not included in the statistical analysis. Maximal and minimal indexed LA volumes were significantly higher in the f-APC group than in the nf-APC group ($P < 0.01$). LA emptying fraction was worse in the f-APC group than in the nf-APC group. In addition, LA appendage emptying velocity was impaired in the f-APC group, and was correlated with LA remodelling variables, especially LA emptying fraction ($r = 0.621$).

Conclusions. – After an ischaemic stroke or a transient ischaemic attack, excessive APCs are associated with LA remodelling. Thus, LA dilatation and dysfunction reflect early LA myopathy, which might itself be responsible for cardioembolic stroke.

Résumé

Contexte. – Des travaux récents suggèrent que la myopathie atriale est une source potentielle d'évènements thromboemboliques indépendamment de la fibrillation auriculaire.

Objectif. – Le but de notre étude est d'examiner si après un accident vasculaire ischémique (AVC), la présence d'une extrasystolie atriale (ESA) est associée à un remodelage et à une dysfonction de l'oreillette gauche (OG) ; les ESA pouvant ainsi être un marqueur de myopathie atriale.

Méthodes. – Les patients ayant subi un accident vasculaire ischémique ou un accident ischémique transitoire sans fibrillation auriculaire ni cardiopathie manifeste, ont été inclus de façon prospective. Ils ont bénéficié d'un bilan systématique incluant un Holter électrocardiogramme et une échocardiographie cardiaque transthoracique. Une échocardiographie trans-oesophagienne a également été effectuée chez certains patients. Le remodelage anatomique et fonctionnel de l'OG a été évalué par la mesure du volume minimum et maximum et de la fraction d'éjection de l'OG en échographie 2D et 3D. Les patients ont été séparés en 2 groupes en fonction du nombre d'ESA enregistrées sur le Holter électrocardiogramme.

Résultats. – Parmi les 148 patients de notre étude, 93 patients ont été inclus dans le groupe extrasystoles non fréquentes (ESA-nf : nombre d'ESA < 100/24 heures), 43 patients dans le groupe extrasystoles atriales fréquentes (ESA-f : nombre d'ESA > 100/24 heures). Douze patients ont présenté une FA paroxystique et n'ont pas été inclus dans l'analyse statistique. Les volumes maximum et minimum indexés des OG étaient plus grands dans le groupe ESA-f que dans le groupe ESA-nf ($P < 0,006$). La fraction d'éjection de l'OG était plus basse dans le groupe ESA-f que dans le groupe ESA-nf. De plus, la vitesse de vidange de l'auricule gauche était diminuée dans le groupe ESA-f et était corrélée avec les paramètres de remodelage de l'OG, en particulier la fraction d'éjection de l'OG ($r = 0,621$).

Conclusions. – Après un accident ischémique cérébral, une extrasystolie atriale excessive est associée à un remodelage et une dysfonction de l'OG. Ces altérations suggèrent une myopathie atriale qui pourrait en elle-même être responsable d'évènements thromboemboliques.

KEYWORDS

Atrial premature activity;

Cardioembolic stroke;

Atrial myopathy;

Left atrial remodelling;

Left atrial dysfunction

MOTS CLÉS

Extrasystole auriculaire ;

Accident vasculaire cérébral cardioembolique ;

Myopathie atriale ;

Remodelage de l'oreillette gauche ;

Dysfonction atriale gauche

Abbreviations: 2D, two-dimensional; 3D, three-dimensional; AF, atrial fibrillation; APC, atrial premature complex; nf-APC, non-frequent atrial premature complexes; f-APC, frequent atrial premature complexes; LA, left atrium/atrial; LV, left ventricular; PAF, paroxysmal atrial fibrillation.

Background

Ischaemic stroke is a frequent cause of morbidity and mortality [1]. About one-fifth of cases of ischaemic stroke have a cardioembolic mechanism [2]. Atrial fibrillation (AF) is the most frequently recognized cause of cardioembolic ischaemic stroke [3], and these patients will benefit from anticoagulation to decrease the risk of recurrence [4]. However, for many patients, the aetiology of an ischaemic stroke remains undetermined, despite a thorough workup; this has major clinical implications, as these patients will, by default, benefit from standard treatment, but remain at higher risk of stroke recurrence [5].

Recent studies failed to demonstrate the benefit of oral anticoagulation treatment for the prevention of recurrent stroke in all patients with embolic stroke of undetermined source [6-8]. This highlights the need for other markers to guide the clinician in determining the appropriateness of anticoagulant therapy.

Excessive atrial premature complexes (AyyPCs) have been reported to be associated with an increased risk of ischaemic stroke, as a marker of paroxysmal AF (PAF) [9], but also independent of the diagnosis of AF [10]. Recent studies have suggested that the left atrium (LA) may be a source of thromboembolism in ischaemic stroke, as a potential complication of underlying atrial myopathy, even in the absence of AF [10-16]. Our hypothesis is that, after an ischaemic stroke, excessive APCs are associated with left atrial (LA) remodelling and dysfunction, reflecting early LA myopathy.

To test our hypothesis, we investigated whether, after an ischaemic stroke or a transient ischaemic attack, frequent APCs are associated with LA dilatation and dysfunction, assessed by two-dimensional (2D) and three-dimensional (3D) echocardiography.

Methods

Study population

From October 2015 to May 2016, consecutive patients aged > 18 years, with an ischaemic stroke or a transient ischaemic attack and referred for transthoracic echocardiography and cardiac Holter monitoring, were included in this prospective study conducted in the Louis Pradel Hospital in Bron (France). Diagnosis of ischaemic stroke or transient ischaemic attack was established by a neurologist based on correlation between clinical symptoms and imaging (either brain magnetic resonance

imaging or computed tomography). Patients with a transient ischaemic attack were enrolled only if symptoms at presentation were related to speech problems, limb weakness or hemianopia.

Patients underwent brain computed tomography or magnetic resonance imaging, a 12-lead electrocardiogram, cardiac Holter monitoring for ≥ 24 hours, imaging of the extracranial and intracranial arteries supplying the area of brain ischaemia (magnetic resonance imaging or computed tomography angiography or Doppler ultrasonography) and transthoracic echocardiography [6, 8, 17]. Transoesophageal echocardiography was also performed for some patients in our institution. The other inclusion criterion was the presence of sinus rhythm at the time of examination.

Exclusion criteria included previous history of AF or atrial flutter, left ventricular (LV) ejection fraction < 40%, significant valvular disease or the presence of a prosthetic valve, infective endocarditis, left ventricular thrombus, atrial myxoma or other tumours, recent (< 4 weeks) myocardial infarction and poor echogenicity.

The cardiologist who performed and analysed the echocardiography was blinded to the results of electrocardiogram monitoring. This study was approved by the local ethics committee, under the agreement number IRB 00009118.

Cardiac monitoring and definitions

The Holter electrocardiogram was analysed by two electrophysiologists (B. de B. and M. S.). An atrial complex with < 80% coupling interval to the preceding QRS compared with the mean RR interval was defined as an APC. AF was defined as a supraventricular run lasting > 30 seconds.

Patients were separated into two groups according to number of APCs. Patients with < 100 APCs over 24 hours were included in the group with non-frequent APCs (nf-APC); patients with > 100 APCs over 24 hours were included in the group with frequent APCs (f-APC).

Off note, patients with PAF (the PAF group) were excluded from the main analysis. However, their results are displayed, as they constituted a reference group for patients with known atrial myopathy.

Echocardiography

All transthoracic echocardiography was performed using either a Vivid™ 9 ultrasound system with a M5S transducer for 2D measurements or a 4V transducer for 3D measurements (GE Healthcare,

Chicago, IL, USA), or an iE33™ ultrasound system with an X5-1 transducer for 2D and 3D measurements (Philips, Amsterdam, Netherlands).

Cardiac chamber size, LV ejection fraction, LV mass and LA dimensions were evaluated according to the recommendations of the European Society of Echocardiography. LV mass was indexed to body surface area. Pulsed-wave Doppler at the tip of mitral valve leaflets was used to measure early (E) and late (A) diastolic filling velocities, E/A ratio, E deceleration time and A-wave duration. An early diastolic mitral annular peak velocity (E') was measured, allowing calculation of E/E'. Duration of atrial pulmonary flow reversal (Ar) was measured in a pulmonary vein. E/E' and the difference in mitral (Am) and pulmonary venous (Ar) A wave duration (Am – Ar) were used to estimate LV filling pressure. Patients were classified as having high, low or undetermined LV filling pressure.

LA size and function

Acquisition and analysis of LA size and function were performed using a standardized protocol. 2D and 3D full-volume acquisitions of the LA were obtained from the apical view during a short breath-hold. 2D LA images were acquired from apical four- and two-chamber views. For 3D acquisition, four small wedge-shaped subvolumes from four consecutive cardiac cycles were required to acquire a full-volume data set, resulting in a volume rate of more than 20 volumes/s. All acquisitions of the LA were analysed by two trained sonographers (A. P. and M. S.) in our core laboratory. For analysis in both 2D and 3D acquisitions, LA appendage and pulmonary veins were excluded. 2D LA volumes were estimated using Simpson's method.

3D image analysis was based on semiautomated tracing of the LA endocardial border for the calculation of LA volumes. The endocardium was defined on two orthogonal planes of the LA. Edges of the mitral annulus were the limits of the LA endocardium. From these reference points, the software detected the LA endocardium using a semiautomated contour-tracing algorithm. Manual modifications were made to correct automatic tracing on three cross-sectional short-axis planes.

Minimal and maximal LA volumes were obtained at mitral valve closure and just before mitral valve opening, respectively. LA reservoir function was estimated by the total LA emptying fraction, calculated using the following formula: LA emptying fraction (%) = ([LA $volume_{max}$ - LA $volume_{min}$]/LA $volume_{max}$) x 100%. LA volumes were indexed to body surface area.

Transoesophageal echocardiography

Transoesophageal echocardiography was performed according to current guidelines [18], and enabled measurement of the emptying velocity of the LA appendage.

Statistical analysis

Results are expressed as mean ± standard deviation or median (interquartile range), depending on the normal distribution, as assessed by the Shapiro-Wilk test.

Relationships between APCs and echocardiographic atrial remodelling have not yet been published. Therefore, no calculation could be made for patient sample size. To avoid a non-parametric test, we had to include at least 35 patients in the f-APC group. According to the prevalence of APCs based on 24-hour electrocardiogram monitoring reported in the literature [19, 20], we anticipated that inclusion of 140 patients in total would be sufficient to ensure more than 35 patients in the f-APC group.

Comparisons between APCs groups were performed using the unpaired *t* test or Wilcoxon's rank sum test, as appropriate. Linear regressions were performed to investigate the independent relationship between each atrial remodelling variable and APCs. Each regression was adjusted for variables significantly associated with the burden of APCs (> 100 APCs/24 hours). Six different atrial remodelling variables were tested. Therefore, tests with P values < 0.01 were considered to be statistically significant, to avoid alpha risk inflation. In addition, 2D atrial remodelling variables were also compared with LA appendage emptying velocity using Pearson's test.

Off note, we expected to find very few cases of PAF by 24-hour Holter monitoring (5% reported by Wachter et al. [21]); thus, only descriptive results were reported for this group (reference group of patients with known atrial myopathy).

Statistical tests were performed using SPSS software, version 20 (SPSS Inc., Chicago, IL, USA).

Results

Population characteristics

A total of 148 patients were included in the study; 111 (75%) were diagnosed with ischaemic stroke and 37 (25%) with transient ischaemic attack. Eighty patients (59%) were male, and the mean age

was 71 ± 14 years. The mean body mass index was 25.91 ± 4.5 kg/m^2 and the mean CHA_2DS_2-VASc score was 2.8 ± 1.8.

All subjects had Holter electrocardiogram monitoring (mean duration 48 hours and 10 minutes). According to the Holter results, 93 patients were in the nf-APC group, 43 were in the f-APC group and 12 patients had PAF. Table 1 summarizes the baseline characteristics for each group. Patients in the f-APC group were older than those in the nf-APC group (79 ± 8 vs 66.3 ± 15 years; $P < 0.01$). Hypertension was significantly more prevalent in the f-APC group (76.7% vs 46.2% in the nf-APC group; $P < 0.01$). The CHA_2DS_2-VASc score was higher in the f-APC group than in the nf-APC group. Smoking was more prevalent in nf-APC group ($P = 0.02$). There were no significant differences between groups in relation to heart rate, body mass index, rates of diabetes mellitus and dyslipidaemia or prevalence of family history of cardiovascular disease.

At the end of the workup, a potentially causal significant atherosclerotic disease was diagnosed for 13 patients (six in the f-APC group and seven in the nf-APC group), four patients had a potentially causal small vessel disease (two in the f-APC group and two in the nf-APC group) and seven patients had a diagnosis of arterial dissection (one in the f-APC group and six in the nf-APC group) [6, 17].

Echocardiographic characteristics

2D echocardiography was performed in all patients. 3D echocardiography was obtained with good recording quality in 114 patients, representing 77% of the total population.

Echocardiographic characteristics according to patient group

Differences were observed in mitral Doppler measurement between the nf-APC and f-APC groups (Table 2). However, LV end diastolic pressures were not statistically different between these two groups. Other LV echocardiographic characteristics were not different between groups (Table 2).

Excessive APCs are associated with LA dilatation and dysfunction

Both 2D and 3D analysis of LA minimal and maximal volumes were significantly higher in the f-APC group than in the nf-APC group (Table 3, Fig. 1 and Fig. 2). The functional analyses showed significant impairment of LA function in the f-APC group compared with the nf-APC group, with a decrease in LA emptying fraction.

Excessive APCs are associated with LA remodelling, independent of age and hypertension

Patients in the f-APC group were older and more frequently had hypertension than patients in the nf-APC group. Therefore, to evaluate the independent association between excessive APCs (> 100 APCs/24 hours) and atrial remodelling, multivariable stepwise regression analyses were performed to analyse the influence of age, hypertension and frequent APCs on each LA remodelling variable (Table 4). We found that frequent APCs remained significantly associated with all 2D echocardiographic variables of anatomical and functional LA remodelling. Therefore frequent APCs might be a surrogate marker of LA remodelling and dysfunction.

In 3D echocardiography, frequent APCs remained significantly associated with minimal volume, but not with maximal LA volume. There was a trend toward an independent association between 3D LA emptying fraction and frequent APCs ($P = 0.02$).

Excessive APCs are associated with lower LA appendage emptying velocity

Fifty-nine patients underwent transoesophageal echocardiography. Patients in the nf-APC group had a higher LA appendage emptying velocity than patients in the f-APC and PAF groups (80.5 ± 28.4 vs 66.9 ± 23.3 cm/s and 47 ± 40.4 cm/s, respectively; $P = 0.03$). Interestingly, LA appendage emptying velocity was positively associated with 2D LA emptying fraction (Fig. 3; $r = 0.621$; $P < 0.001$) and negatively associated with 2D LA maximal and minimal volumes: $r = –0.371$ ($P = 0.004$) and $r = –0.582$ ($P < 0.0001$), respectively.

Discussion

In this prospective study of patients after an ischaemic stroke, without overt heart disease or documented AF, we found that excessive APCs were associated with the presence of LA remodelling assessed by 2D and 3D echocardiography. In addition, increased LA volumes and impaired LA function were associated with decreased LA appendage emptying velocity. These results suggest that frequent APCs after ischaemic stroke are associated with LA myopathy characterized by LA dilatation and dysfunction, both conditions that might lead to cardiac embolism even in the absence of AF.

Excessive atrial premature activity is associated with stroke

Excessive atrial premature activity has been shown to be associated with occurrence and recurrence of ischaemic stroke. In a population-based cohort of 678 healthy individuals, Binici et al. [9] demonstrated that risk of death or stroke was significantly higher in subjects with frequent APCs than in those without APCs, after adjustment for conventional risk factors (hazard ratio 1.64). More recently, Larsen et al. [22] showed that frequent APCs were associated with an increased risk of ischaemic stroke beyond documented AF (hazard ratio 1.96). In addition, in their recent paper, Pinho et al. [10] showed an independent relationship between the number of APCs and the annual recurrence rate of ischaemic stroke or transient ischaemic attack after a first ischaemic stroke.

Excessive atrial activity is associated with LA remodelling, and might reflect underlying atrial myopathy

Regarding the assessment of LA size and function in our study, we noticed that 2D and 3D atrial volumes and emptying fractions in the nf-APC group were in accordance with normal reference ranges described recently in the NORRE study [23, 24]. Our study demonstrates that LA remodelling, assessed by volumetric and functional echocardiographic variables, was evident in the f-APC group compared with the nf-APC group. 2D and 3D measurements of LA maximal and minimal volumes were significantly higher in the f-APC group than in the nf-APC group. The functional analysis also demonstrated significant impairment of LA function in the f-APC group compared with the nf-APC group, characterized by a decrease in LA emptying fraction.

This link between frequent APCs and LA remodelling has not been studied extensively in the literature. One study by Pinho et al. [10] reported that patients with frequent APCs had a greater median LA diameter than patients with non-frequent APCs. Assessment of LA remodelling was based only on evaluation of LA diameter, and the authors did not provide information on LA volumes and function. To our knowledge, our study is the first to carefully assess and characterize LA remodelling and dysfunction associated with excessive APCs after a stroke.

Interestingly, Kamel et al. [11] recently reported the concept of atrial myopathy as a possible explanation for the phenomenon of thromboembolism in the absence of AF. The authors hypothesized that atrial thromboembolism originates from the combination of LA anatomical and functional abnormalities, which might be associated with atrial dysrhythmia. This hypothesis is supported by

papers reporting that only a small percentage of patients had device-detected subclinical AF in the 30 days before a stroke (8% in the ASSERT trial [25]).

In addition, other studies have reported that patients in sinus rhythm with LA enlargement are at higher risk of stroke than patients without LA enlargement [13]. The hypothesis of LA myopathy is also directly supported by Russo et al. [14], who demonstrated a correlation between LA remodelling and subclinical cerebrovascular disease (detected by systematic brain magnetic resonance imaging), independent of AF.

Of note, in our study, we did not follow the patients, and did not explore the link between LA remodelling and thromboembolic recurrence.

From a haemodynamic point of view, we showed that LA remodelling was associated with reduced LA appendage emptying velocity. These results are in accordance with previous studies [26, 27] investigating the association of spontaneous echo contrast and reduced LA appendage emptying velocity with LA remodelling and dysfunction assessed by various techniques. Decreased LA appendage emptying velocity is known to be associated with embolic events [27]. Therefore, our results confirm that LA remodelling is associated with reduced LA appendage emptying velocity after a stroke, and suggest a potential atrial cardiac source of embolism in the ischaemic stroke.

Is LA myopathy a common substrate of stroke in patients with excessive APCs and those with AF?

Alteration of LA structure and function is well known to be the substrate for AF. Our group and others have already shown that, even at the PAF stage, LA structure and function are already impaired [28-31].

In this study, we showed that excessive APCs were associated with LA remodelling. There was a trend towards bigger volumes and a smaller LA emptying fraction in the PAF group compared with the f-APC group. However, we did not find any significant statistical difference. This could be explained either by lack of statistical power (small PAF group) or because these two dysrhythmias finally unveil a similar atrial myopathy.

Study limitations

In our study, patients in the f-APC and PAF groups were older and more frequently had hypertension compared with those in the nf-APC group. However, frequent APCs remained significantly associated with echocardiographic variables of anatomical and functional LA remodelling assessed in 2D, even after adjustment for age and hypertension. In 3D, frequent APCs remained significantly associated with LA minimal volume, but not with LA maximal volume, and there was a trend towards an association with 3D LA emptying fraction. This could be explained by a higher variability in 3D measurements.

A decrease in LA longitudinal strain has been shown to be associated with AF after stroke [32]. However, in our study, we focused on volumetric assessment of the LA, which is available on all clinical ultrasound systems in 2D.

We sought to extract LA appendage emptying velocities from the transoesophageal echocardiograms that were performed in our institution, to correlate them with LA remodelling assessed by transthoracic echocardiography. However, we only found 59 patients with such data. PAF could have been undetected on the electrocardiogram monitoring. Prolonged monitoring with an implantable subcutaneous device would have been more sensitive to detect PAF, but it is invasive and expensive, and systematic implantation does not constitute common systematic clinical practice.

The patients included in our study were those referred by the neurologist for transthoracic echocardiography and cardiac Holter monitoring. Therefore, most had no obvious cause for their stroke or transient ischaemic attack at the time of the diagnosis. However, a few patients (15 in the nf-APC group and nine in the f-APC group) were finally diagnosed with a potential extracardiac cause. These patients were not excluded, as our main objective was to investigate the association between APCs and LA remodelling and dysfunction.

Benefit for clinical practice

We have shown that, after an ischaemic stroke, patients with frequent APCs have clear LA remodelling, similar to patients with PAF, suggesting atrial myopathy. However, the guidelines only recommend anticoagulant therapy for patients with PAF.

Interestingly, a recent study failed to demonstrate the benefit of oral anticoagulation treatment (rivaroxaban at a daily dose of 15 mg) for the prevention of recurrent stroke in all patients with embolic

stroke of undetermined sources [8]. In addition, anticoagulant therapy was associated with a higher risk of bleeding compared with aspirin [8].

All together, these results highlight the need for better selection of patients, and the potential benefit of integrating LA assessment (frequent APCs and/or LA remodelling and dysfunction) in the process to determine the appropriateness of anticoagulant therapy after a stroke. In this setting, the ongoing ARCADIA trial [33] aims to assess the potential benefit of apixaban versus aspirin in a population of embolic stroke of undetermined source with evidence of atrial myopathy. In this trial, atrial cardiopathy is defined by one or more criteria, including electrocardiogram (P wave terminal force in lead V1 [PTV1] > 5000 µVms), elevation of serum N-terminal prohormone of brain natriuretic peptide (NT-proBNP) and LA dilatation with a definition based on indexed diameter. We believe that further prospective studies integrating echographic assessment of LA volumes and function and information on frequent APCs might be of interest. Further prospective studies integrating these variables are needed.

Conclusions

After ischaemic stroke or transient ischaemic attack in patients without overt heart disease or confirmed AF, excessive APCs are associated with the presence of LA remodelling, determined by volumetric and functional echocardiographic variables. This remodelling is correlated with decreased LA appendage emptying velocity. Frequent APCs could reflect early LA myopathy, a condition that might be responsible for a cardioembolic phenomenon.

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None.

Disclosure of interest

The authors declare that they have no conflicts of interest relevant to the contents of this paper to disclose.

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Figure legends

Figure 1. Two-dimensional (2D) and three-dimensional (3D) variables of left atrial remodelling in the group with non-frequent atrial premature complexes (nf-APC), the group with frequent atrial premature complexes (f-APC) and the group with paroxysmal atrial fibrillation (PAF). MaxLAVI: maximal indexed left atrial volume; MinLAVI: minimal indexed left atrial volume.

Figure 2. Two-dimensional (2D) and three-dimensional (3D) variables of left atrial function (left atrial ejection fraction [LAEF]) in the group with non-frequent atrial premature complexes (nf-APC), the group with frequent atrial premature complexes (f-APC) and the group with paroxysmal atrial fibrillation (PAF).

Figure 3. Correlation between left atrial (LA) appendage emptying velocity and LA ejection fraction (LAEF) for 59 patients. 2D: two-dimensional.

Table 1 Clinical characteristics, according to patient group.

	nf-APC group (n = 93)	f-APC group (n = 43)	P^a	PAF group (n = 12)
Demographic characteristics				
Age (years)	66.3 ± 15	79 ± 8	< 0.01	79 ± 9
Male sex	50 (53.7)	24 (55.8)	0.06	6 (50.0)
Body mass index (kg/m^2)	24.8 (22.3–27.4)	25.3 (23.1–27.6)	0.68	27.3 (12.3–30.3)
Heart rate (beats/min)	73.0 ± 13	71.0 ± 13	0.49	71 ± 7
Systolic BP (mmHg)	138.9 ± 19	143.3 ± 22	0.29	150.7 ± 23
Diastolic BP (mmHg)	76.6 ± 10	74.5 ± 11	0.37	83.4 ± 8
Cardiovascular risk factors	2 (1-3)	3 (2.5-3.5)	0.67	2 (2-1)
Hypertension	43 (46.2)	33 (76.7)	< 0.01	8 (66.7)
Smoking	22 (23.7)	3 (7.0)	0.02	3 (25)
Diabetes mellitus	24 (25.8)	7 (16.3)	0.43	1 (8.3)
Dyslipidaemia	40 (43.0)	18 (41.9)	0.86	3 (25.0)
Family history	10 (10.8)	6 (14.0)	0.61	0 (0)
CHA_2DS_2-VASc score	2 (1–3)	3 (2.5–3.5)	< 0.01	3.5 (2.5–4.5)
Ischaemic event				
Cerebral infarction	70 (75.3)	29 (67.4)	0.36	12 (100)

Data are expressed as mean ± standard deviation, number (%) or median (interquartile range; Q1–Q3). BP: blood pressure; f-APC: frequent atrial premature complexes; nf-APC: non-frequent atrial premature complexes; PAF: paroxysmal atrial fibrillation.

[a] P value assessed by Student's t test, the Wilcoxon test or the χ^2 test, as appropriate, realized between nf-APC and f-APC groups.

Table 2 Left ventricular echocardiographic characteristics, according to patient group.

	nf-APC group (n = 93)	f-APC group (n = 43)	P^a	PAF group (n = 12)
LV ejection fraction (%)	64.2 ± 8	64.9 ± 8	0.69	60.0 ± 14
LV end-diastolic diameter (mm)	47.0 ± 7	49.0 ± 8	0.27	51.0 ± 11
LV end-systolic diameter (mm)	28.6 ± 6	29.0 ± 7	0.74	30.4 ± 10
LV end-diastolic indexed volume (mL/m^2)	78.3 ± 29	86.1 ± 33	0.24	91.0 ± 39
LV end-systolic indexed volume (mL/m^2)	29.1 ± 16	32.3 ± 20	0.39	41.0 ± 31
LV mass index (g/m^2)	181.1 ± 67	193.6 ± 51	0.37	194.1 ± 50
Peak E mitral velocity (cm/s)	68.6 ± 17	75.2 ± 19	0.04	77.6 ± 22
Peak A mitral velocity (cm/s)	77.4 ± 23	86.7 ± 25	0.04	68.0 ± 31
E/A	0.82 (0.59–1.05)	0.84 (0.66–1.02)	0.95	1.34 (0.78–1.87)
E-wave deceleration time (ms)	225.3 ± 66	236 ± 78	0.42	198 ± 28
E' (cm/s)	10.0 (7–12)	9 (8–10)	0.056	9.5 (8–11)
E/E'	6.9 (5–9)	8.5 (6–10)	0.004	8.7 (7–11)
Am – Ar (ms)	13.0 ± 21	13.6 ± 26	0.91	30.5 ± 33
LV end-diastolic pressure			0.06	
High	7 (7.5)	8 (18.6)		1 (8.3)
Low	78 (83.9)	29 (67.4)		11 (91.7)
Undetermined	8 (8.6)	6 (14.0)		0 (0)

Data are expressed as mean ± standard deviation, median (interquartile range; Q1–Q3) or number (%). Am-Ar: difference in mitral (Am) and pulmonary venous (Ar) A wave duration; f-APC: frequent atrial premature complexes; LV: left ventricular; nf-APC: non-frequent atrial premature complexes; PAF: paroxysmal atrial fibrillation.

[a] P value assessed by Student's t test, the Wilcoxon test or the χ^2 test, as appropriate, realized between nf-APC and f-APC groups.

Table 3 Echocardiographic measurements assessing left atrial remodelling, according to patient group.

	nf-APC group (n = 93)	f-APC group (n = 43)	P^a	PAF group (n = 12)
LA size				
2D MaxLAVI (mL/m^2)	28.8 ± 11	33.8 ± 10	< 0.01	39.8 ± 11
3D MaxLAVI (mL/m^2)	29.1 ± 9	35.6 ± 11	< 0.01	40.3 ± 12
2D MinLAVI (mL/m^2)	12.6 ± 6	17.8 ± 9	< 0.01	23.4 ± 12
3D MinLAVI (mL/m^2)	13 ± 6	19 ± 9	< 0.01	22 ± 18
LA function				
2D LAEF (%)	56.5 ± 11	48.6 ± 15	< 0.01	43.8 ± 18
3D LAEF (%)	54.4 ± 11	48.6 ± 12	< 0.01	40.3 ± 23

Data are expressed as mean ± standard deviation. 2D: two-dimensional; 3D: three-dimensional; f-APC: frequent atrial premature complexes; LA: left atrial; LAEF: left atrial emptying fraction; MaxLAVI: maximal indexed left atrial volume; MinLAVI: minimal indexed left atrial volume; nf-APC: non-frequent atrial premature complexes; PAF: paroxysmal atrial fibrillation.

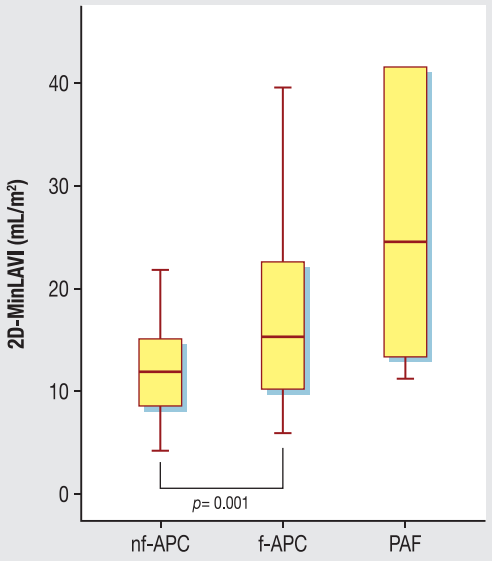
[a] *P* value assessed by Student's *t* test, the Wilcoxon test or the χ^2 test, as appropriate, realized between nf-APC and f-APC groups.

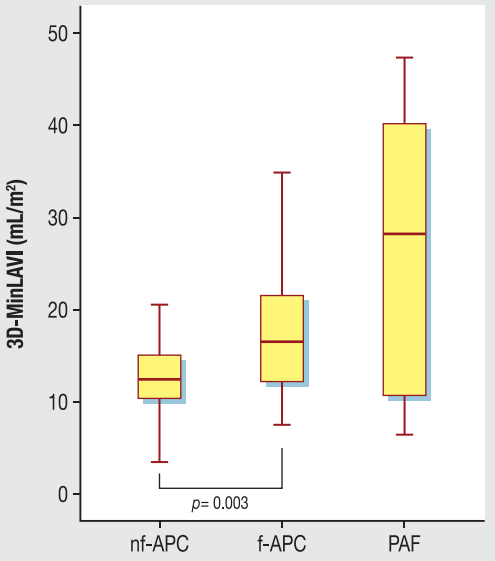
Table 4 Multivariable linear regressions between left atrial echographic variables and atrial premature complexes, adjusted for age and hypertension.

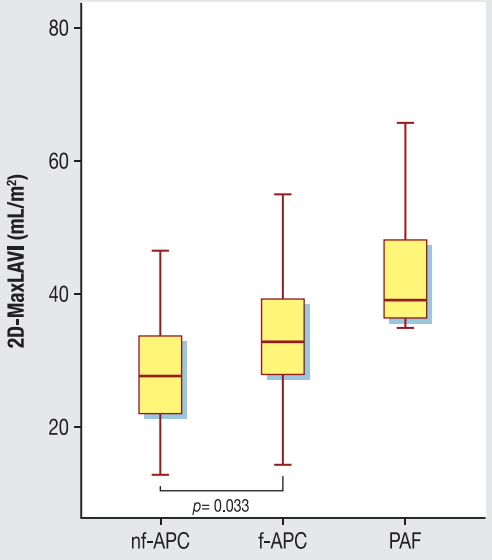
LA remodelling variables		Multivariable regression	
		Beta	*P*[a]
2D MaxLAVI	> 100 APCs/24 hours	0.23	0.009
	Age	0.13	0.14
	Hypertension	0.14	0.10
3D MaxLAVI	> 100 APCs/24 hours	0.23	0.16
	Age	0.22	0.03
	Hypertension	0.12	0.19
2D MinLAVI	> 100 APCs/24 hours	0.35	0.000
	Age	0.12	0.16
	Hypertension	0.61	0.45
3D MinLAVI	> 100 APCs/24 hours	0.27	0.004
	Age	0.17	0.08
	Hypertension	0.12	0.19
2D LAEF	> 100 APCs/24 hours	–0.29	0.001
	Age	–0.14	0.14
	Hypertension	0.03	0.76
3D LAEF	> 100 APCs/24 hours	–0.23	0.02
	Age	–0.17	0.09
	Hypertension	–0.2	0.87

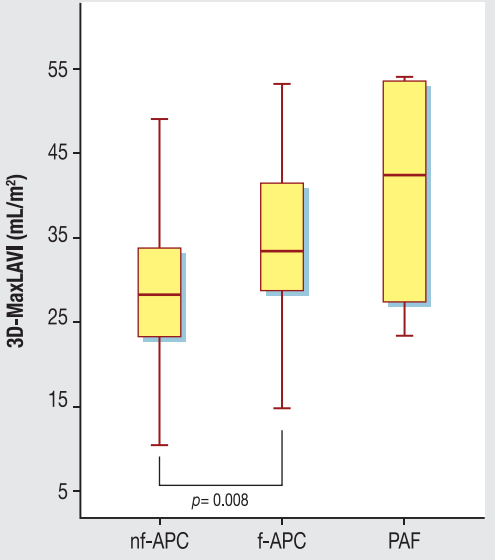
2D: two-dimensional; 3D: three-dimensional; APCs: atrial premature complexes; LAEF: left atrial ejection fraction; LAVI: indexed left atrial volume; Max: maximal; Min: minimal.

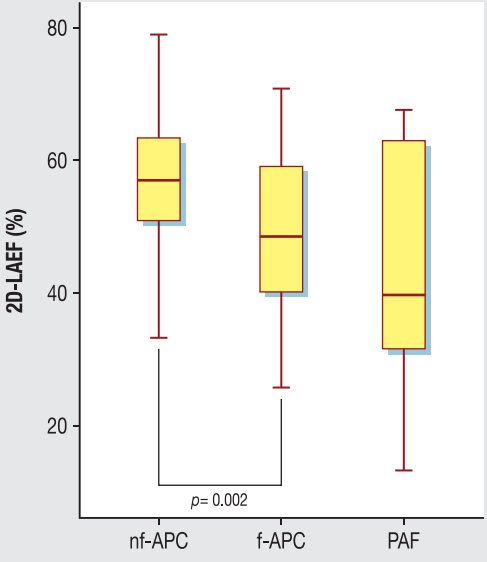
[a] *P* values < 0.01 were considered to be statistically significant.

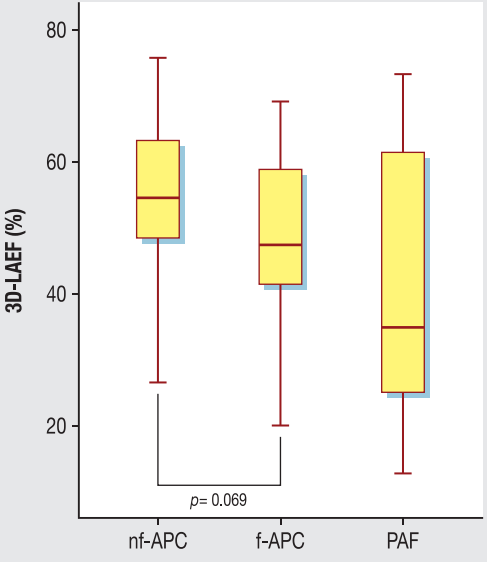

2D-MinLAVI (mL/m²)
0
10
20
30
40
p= 0.001
nf-APC
f-APC
PAF

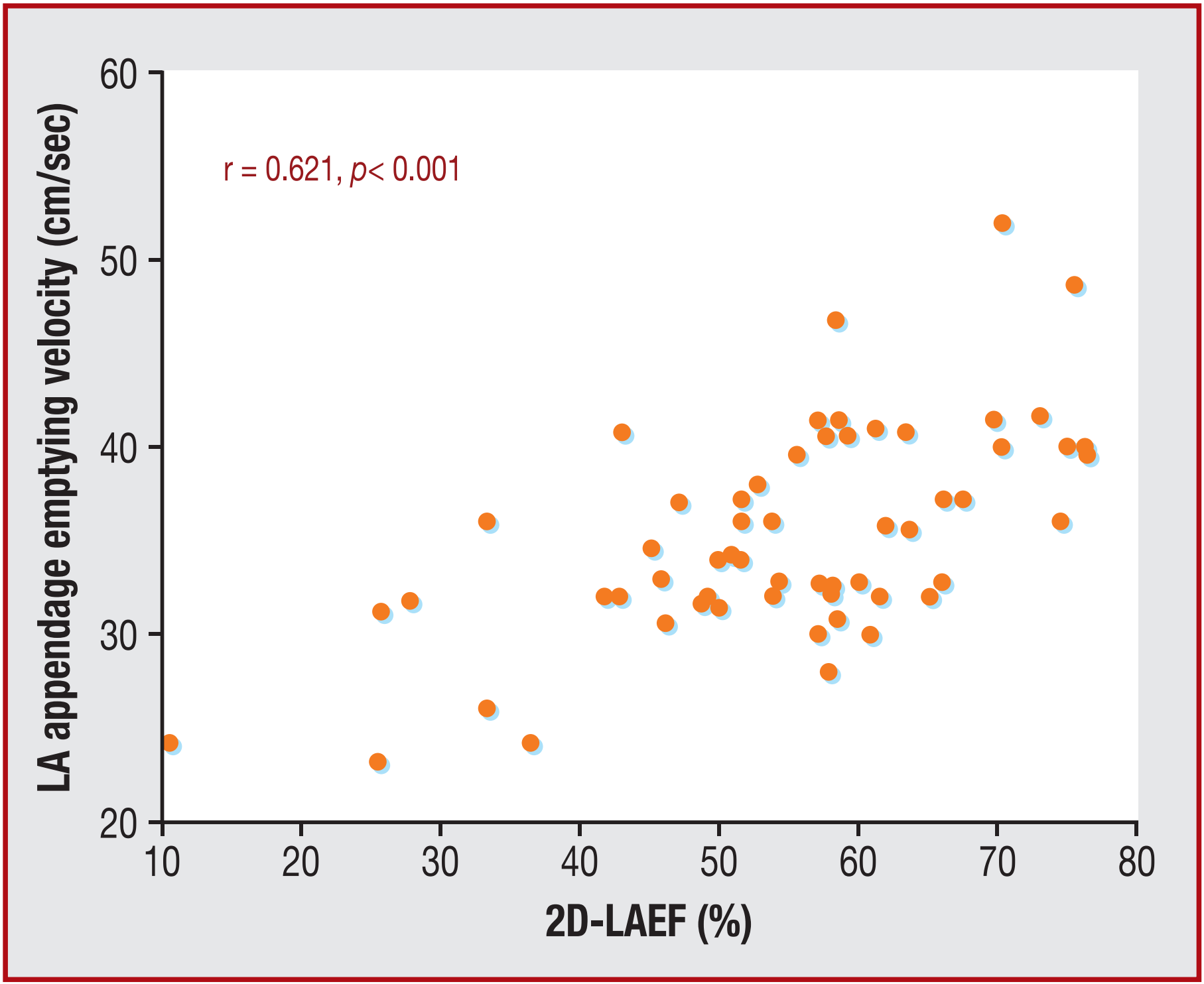

3D-MinLAVI (mL/m²)
0
10
20
30
40
50
p= 0.003
nf-APC
f-APC
PAF


2D-MaxLAVI (mL/m²)
20
40
60
80
p= 0.033
nf-APC
f-APC
PAF


3D-MaxLAVI (mL/m²)
5
15
25
35
45
55
p= 0.008
nf-APC
f-APC
PAF


2D-LAEF (%)
80
60
40
20
p= 0.002
nf-APC
f-APC
PAF


3D-LAEF (%)
80
60
40
20
p= 0.069
nf-APC
f-APC
PAF


r = 0.621, p< 0.001
LA appendage emptying velocity (cm/sec)
60
50
40
30
20
10
20
30
40
50
60
70
80
2D-LAEF (%)