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Characterization of mid-term atrial geometrical and electrical remodeling following device closure of atrial septal defects in adults

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ABSTRACT

Purpose: Late-onset atrial arrhythmia after successful closure of atrial septal defect (ASD) is not uncommon. Right atrial (RA) enlargement and increased electrocardiographic P-wave dispersion (Pd) independently predict the development of atrial arrhythmia. Data on the degree of right atrial (RA) geometrical and electrical remodeling following device closure of ASD are limited.

Methods: Echocardiography and electrocardiography (ECG) were performed in 58 consecutive patients (47 ± 17 years) before and at 3 months after ASD closure. Persistent RA enlargement was defined as RA volume index (RAVI) ≥21 ml/m^2 at 3 months. Pd was calculated as the difference between maximal and minimal P-wave durations in 12-lead ECG.

Results: RA size reduced (RAVI: 50 ± 28 vs. 26 ± 16 ml/m^2, $p<0.001$) and Pd on ECG decreased (53 ± 17 vs. 49 ± 20 ms, $p<0.05$) significantly at 3 months when compared to baseline. However, persistent RA enlargement remained evident in 31 patients (53%). As a group, they were older with higher pulmonary arterial systolic pressure, larger Qp/Qs, longer maximal P-wave duration and Pd than those with normalized RA. Pd reduction only occurred in patients with normalized RA size. The 3-month Pd (hazard ratio: 1.033, $p<0.001$) predicted the presence of incomplete RA geometrical remodeling. ROC curve revealed that Pd ≥45 ms at 3 months was 77% sensitive and 86% specific in revealing residual RA enlargement.

Conclusion: Both atrial geometrical and electrical reverse remodeling were evident at 3 months following ASD closure. However, only half of the included patients had normalization of RA size which could be revealed by a simple ECG surrogate of intra-atrial conduction disturbance.

1. Introduction

Successful device closure of atrial septal defect (ASD) significantly reduces right heart volume and dimensions, leading to an improvement of symptoms [1–4]. However, late-onset atrial arrhythmia after successful surgical or device closure of ASD is not uncommon and it compromises prognosis and survival in patients [5,6]. Although the precise mechanism remains unclear, evidence suggested that both atrial enlargement and electrocardiography (ECG) P-wave dispersion (Pd) are important independent predictors for development of atrial arrhythmia [7]. We previously reported that 50% of adult ASD patients had residual right atrial (RA) enlargement at mid-term follow-up after closure as a result of excessive pre-closure RA dilatation [8]. In these patients, residual RA enlargement may be associated with a higher risk of developing late-onset of atrial arrhythmias. Transthoracic echocardiography can correctly examine the cardiac function and dimensions but it is not as frequently performed as ECG especially years after apparently successful surgical or device closure of ASD. Given the fact that Pd is a surrogate of intra-atrial conduction disturbance and is decreased after ASD closure [9], we hence hypothesized that there is a close link between RA geometrical and electrical changes after transcatheter ASD transcatheter closure. Therefore, the aims of this study were to characterize the atrial geometrical–electrical changes and to evaluate whether ECG markers could reveal residual RA enlargement following ASD closure.

2. Methods

2.1. Study population

Sixty-seven consecutive adult patients with successful device closure of isolated secundum-type ASD were enrolled in the present study. This was an extension study

Abbreviations: ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blockers; ASD, atrial septal defect; CI, confidence interval; ECG, electrocardiography; HR, hazard ratio; LV, left ventricular; Pd, P-wave dispersion; Qp/Qs ratio, ratio of pulmonary-to-systemic blood flow; RA, right atrial; RAVI, right atrial volume index; RV, right ventricular.

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for our previous work [8]. Transthoracic echocardiography was performed in all patients shortly before and at 3 months after closure. Those with a history of atrial arrhythmia, cardiac surgery or RA ablation, left ventricular (LV) systolic dysfunction (ejection fraction <50%), significant residual shunt after closure (2-dimensional color-flow Doppler width >3 mm), more-than-mild mitral or aortic valve diseases and concomitant congenital cardiac defects were excluded from this study. Subjects with suboptimal echocardiographic images were also excluded. Demographic and clinical information of all patients was recorded, including presence of comorbidities (coronary artery disease, hypertension, diabetes), symptoms (reduced exercise tolerance, chest pain and palpitation, dizziness) and systemic arterial blood pressure. An age- and gender-matched control group of 30 healthy volunteers was also studied. They had no history of systemic or chronic illness, and had normal physical examination, ECG as well as echocardiographic examinations. Informed consent was obtained from all participants and the study was approved by the local ethics committee of the institution.

2.2. Atrial septal defect closure

Interventional ASD closure was performed in all patients under continuous guidance of intracardiac echocardiography (Acunav, Acuson, Mountain View, CA). Amplatzer septal occluders (AGA Medical Corp., Golden Valley, MN, USA) of adequate size were delivered and deployed as previously described [10]. Pulmonary arterial systolic pressure (PASP) was assessed with standard fluid-filled catheters and the ratio of pulmonary to systemic flow (Qp/Qs ratio) was measured by oximetry using the Fick's principle [11]. Large shunt was defined as Qp/Qs ≥1.5:1. Oral aspirin and clopidogrel treatment was initiated one day before closure and lasted for 6 months [6].

2.3. Two-dimensional transthoracic echocardiography examination

Comprehensive transthoracic echocardiography was performed with Vivid 7 Ultrasound System (Vingmed-General Electric, Horten, Norway) and 5 consecutive beats in sinus rhythm were digitally stored for off-line analysis (EchoPac PC 7.0.0, Vingmed-General Electric). RA and left atrial (LA) volumes were measured at different cardiac phases using monoplane area-length method at apical 4-chamber view and biplane area-length method, respectively [12]. Total emptying fractions of both atria were calculated by the following formula [13]:

$$\text{Total emptying fraction} = (\text{maximal volume} - \text{minimal volume})/\text{maximal volume} \times 100\%.$$

Residual RA enlargement was defined as RA volume measured at the end-systole indexed to body surface area (RAVI) of ≥21 ml/m^2 [14]. Right ventricular (RV) and LV volumes and ejection fractions were assessed by monoplane ellipsoid method and biplane Simpson's method, respectively.

2.4. Electrocardiograhical measurement

All patients were in sinus rhythm during ECG evaluation and anti-arrhythmic drugs were stopped for three days prior to the ECG procedure. Standard 12-lead ECG (PageWriter TC 70, Phillips, USA) was recorded 24 h before closure and at 3-month follow-up in all patients with a 25 mm/s paper speed and a calibration of 1 mV/cm. P-wave duration and P-wave amplitude were measured manually and magnifying glass was used when necessary. In each lead, P-wave duration was calculated from onset to offset of P-wave by taking the average of three complexes. Pd was calculated as the difference between maximal and minimal P-wave duration. The P-wave amplitude was obtained in Lead II with the reference point of isoelectric PR interval. PR interval and QRS duration were derived from the ECG recordings. ECG results were excluded if the number of un-analyzable leads was >4. Bifid P-wave was defined as the time difference between two P-peaks of >40 ms in Lead II. ECG investigators were blinded to patients' information and echocardiographic data.

2.5. Inter- and intra-observer variability

Inter- and intra-observer variability of Pd was assessed in 20 randomly selected patients on different days. Variability was calculated as the percent error, derived as the absolute difference between two sets of measurements, divided by the mean of the observations.

2.6. Statistical analysis

Statistical software of SPSS version 17 (SPSS Inc., Chicago, Illinois, USA) was used to analyze all the data. All continuous variables were expressed as mean ± SD and Kolmogorov–Smirnov test was applied to test the normality. Paired *t*-test and independent *t*-test were used to compare the mean value of the parametric values as appropriate. Categorical variables were expressed as frequency and compared by Pearson Chi-square test or Fisher Exact test as appropriate. Cox regression analysis was used to identify the predictors of residual RA enlargement at 3 months. Receiver-operating characteristic (ROC) curve was performed to determine the cut-off value of the potential ECG parameter that predicted RA enlargement. A significant difference was defined as $p<0.05$ (2-tailed).

3. Results

3.1. Demographic data

Nine patients were excluded in the final analysis due to the undetermined P-wave measurements in more than 4 leads (n = 3), unmet inclusion criteria (n = 4) and development of persistent atrial arrhythmia at 3 months (n = 2). Majority of the remaining 58 patients (age 47 ± 17 years, 15 males) had large shunt (93%). Twenty-three (40%) patients had other comorbidities and 32 (55%) patients had symptoms. The ASD size measured by intracardiac echocardiography, the occluder size, the Qp/Qs ratio, the PASP and systolic arterial blood pressure were also listed in Table 1.

3.2. Echocardiographic and ECG changes before and after atrial septal defect

The changes of echocardiographic and ECG parameters after ASD closure are presented in Table 2. At 3 months after ASD closure, both RA and RV sizes reduced significantly with improved RA total emptying fraction. The LV volumes and ejection fraction were slightly increased while LA size and function remained similar. Regarding ECG parameters, pre- and post-closure Pd were significantly longer than those of the normal control group (28 ± 8 ms, $p<0.001$ vs. pre-closure, and $p<0.01$ vs. 3-month follow-up). Ablation of inter-atrial shunting led to a reduction of Pd although there was no difference in terms of maximal, minimal P-wave durations and the prevalence of bifid P-wave pattern. In addition, P-wave amplitude reduced, PR interval unchanged and QRS duration shortened after device closure.

3.3. Comparison of clinical, echocardiographic and ECG parameters between patients with and without right atrial enlargement at 3-month follow-up

Fifty-three patients (91%) had enlarged RA before closure (i.e. RAVI >21 ml/m^2) and residual RA enlargement was found in 31 patients (53%) at 3-month follow up ($\chi^2 = 20.89$, $p<0.001$). Patients with residual RA enlargement were older, having larger degree of inter-atrial shunting and higher PASP than other patients (Table 3).

Table 1
Baseline characteristics.

Demographic data	Whole group (n = 58)
Age at closure, years	47 ± 17
Gender, male (%)	15 (26)
Body surface area, m^2	1.60 ± 0.18
Heart rate, bpm	67 ± 12
Blood pressure, mm Hg	
Systolic	121 ± 17
Diastolic	72 ± 12
With comorbidities, n (%)	23 (40)
Hypertension, n (%)	19 (33)
Diabetes mellitus, n (%)	7 (12)
Ischemia heart disease, n (%)	3 (5)
Medication	
Anti-arrhythmia drug, n (%)	0 (0)
β-Blocker, n (%)	4 (7)
ACEI or ARB, n (%)	8 (14)
Calcium channel antagonist, n (%)	5 (9)
With symptom, n (%)	32 (55)
Qp/Qs ratio	2.36 ± 0.76
Large shunt, n (%)	54 (93)
PASP, mm Hg	43 ± 13
ASD size, mm	16 ± 7
Occluder size, mm	21 ± 7

ACEI = angiotensin converting enzyme inhibitor; ARB = angiotensin II receptor blockers; ASD = atrial septal defect; PASP = pulmonary arterial systolic pressure; Qp/Qs = the ratio of pulmonary-to-systemic flow.