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ORIGINAL ARTICLE

Elaborate evaluation of serial changes in electrocardiograms of atrial septal defects after transcatheter closure for a better understanding of the recovery process

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Abstract

Serial changes of electrocardiograms (ECG) could be used to assess their clinical features in atrial septal defects (ASD) after transcatheter closure together with other clinical parameters. We retrospectively studied 100 ASD patients who underwent transcatheter closure. Complications of persistent atrial fibrillation occurred in five ASD patients, and they were excluded. We divided the other 95 patients according to PQ intervals before closure (normal: < 200 ms, $n = 51$; prolonged: ≥ 200 ms, $n = 44$) to evaluate their clinical characteristics and parameters such as echocardiography, chest X-rays, and brain natriuretic protein (BNP) levels. Individuals in the prolonged PQ group were significantly older, had higher incidences of paroxysmal atrial fibrillation (PAF) and heart failure (HF) treated with more β-blockers and diuretics, and with a higher tendency of NYHA functional classification and BNP levels than the normal PQ group. The prolonged PQ group also had a significantly higher incidence of complete right bundle branch block, wider QRS intervals, and larger cardiothoracic ratios in chest X-rays accompanied by larger right atrial-areas and larger left atrial dimensions in echocardiograms. Furthermore, the prolonged PQ intervals with less PQ interval shortening after transcatheter closure revealed that the patients were the oldest at the time of closures and showed less structural normalization of the right heart and left atrium after ASD closure. PAF and HF also occurred more frequently in this subgroup. These results suggested that the ASD patients with prolonged PQ intervals with less PQ shortening were accompanied by more advanced clinical conditions. Together with other clinical parameters, detailed analyses of ECG and their changes after closure could elucidate the clinical characteristics and status of ASD patients with transcatheter closure and were useful for predicting structural normalization after transcatheter closure.

Keywords Atrial septal defect · Transcatheter closure · Electrocardiogram · PQ interval

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Introduction

Atrial septal defects (ASD) are the second most common congenital heart disease (CHD), accounting for 10–17% of all CHD [1–4]. If significant ASD is untreated, then it may result in worse long-term outcomes, including right-sided heart failure, more arrhythmias, and a greater degree of pulmonary hypertension (PAH) [5–8]. For those patients, guidelines recommend transcatheter or surgical closure to reduce right atrial and right ventricle (RV) volume and improve long-term prognoses [9, 10]. Although surgical closure of ASD is considered safe and has excellent long-term results, it requires open-heart surgery and longer hospitalization. The transcatheter closure for ASD has shown many therapeutic advantages such as significant improvements in symptoms without thoracotomy and cardiopulmonary bypass procedure [6, 11]. When transcatheter closure is therapeutically applicable, it is used as the first-line treatment instead of surgery at many institutions [12, 13].

The absence of thoracotomy and direct incisions in the pericardium and right atrium (RA) has led to different conditions of the body surface according to electrocardiograms (ECG) because there is no resultant scar tissue in the atrium that might interfere with electrical conduction in the heart [14, 15]. Therefore, it is possible to study changes in serial ECG results after transcatheter closure without interference from scar tissue in the atrium. Experienced cardiologists review ECG, which has contributed significantly to the early detection of ASD in children and adolescents [16]. Serial changes of ECG after closure may help medical staff understand the clinical course.

There have been some reports of electrophysiological, structural, and hemodynamic changes after ASD closure by open heart surgery and device closure [8, 17, 18]. Changes found on ECG that were attributable to the lessened burden on the right heart and affected electrical conduction in the myocardium were reported. Furthermore, changes observed on ECG indicated improvements in or normal hemodynamic parameters [19, 20]. However, irreversible structural changes of the right heart despite the improvements in hemodynamics of right heart circulation have been reported [18, 21, 22].

We have noticed wide ranges of PQ and QRS intervals and morphological changes of the QRS complex of V1 leads (R' or r' waves) in ASD patients not only before transcatheter closure but also after successful ASD closure. Therefore, we examined the serial changes apparent on ECG, other hemodynamic parameters, and complications before and after the closure of ASD. We also evaluated those patients based on the changes apparent on serial ECG to provide an alternate view that might help increase the understanding of the concordance between electrophysiological parameters and structural normalization related to the clinical severity of ASD patients.

Materials and methods

This was a single-center, retrospective, 1-year cohort study. We retrospectively recruited 108 consecutive patients who underwent transcatheter closure for ASD. Patients with atrioventricular septal defects and those aged < 13 years were not included in our study. We excluded eight patients because four were followed-up at other hospitals after closure; three had severe complications, such as severe renal failure with dialysis, a history of myocardial infarction, and persistent atrial fibrillation with pacemaker implantation, and one died of factor V deficiency (Owren's disease) during follow-up. Complete follow-up data up to 12 months after transcatheter closure were available for 100 patients. These patients fulfilled the following criteria for ASD closure: ASD diameter < 38 mm; pulmonary/systemic blood flow ratio (Qp/Qs) ≥ 1.5 or enlarged RV due to increased right-side cardiac load; and distance from the ASD to the coronary sinus, atrioventricular valve, and right superior pulmonary vein ≥ 5 mm. All patients were administered optimized pharmacotherapy for ASD before and after ASD closure. Patients underwent general anesthesia and ASD closure using an Amplatzer septal occluder ($n = 65$, Abbott Vascular Inc., Santa Clara, CA, USA) or Occlutech Figulla Flex II ($n = 35$, Occlutech Inc., Jena, Germany) under transesophageal echocardiographic guidance. The sizes of ASD were measured as a maximum diameter of the defect by transesophageal echocardiography at the closure.

This study was approved by the ethics committee of the faculty of medicine at Kyushu University (approval #29-407) and followed the Declaration of Helsinki and the ethical standards of the responsible committee on human experimentation. This research program has been disclosed on the web page of the Department of Health Sciences of Kyushu University, and the right to opt-out of this study was guaranteed for all candidates.

Measurements

We obtained data such as baseline demographic characteristics, medical history (heart failure, stroke/transient ischemic attack, and deep vein thrombosis), medication use, comorbidities, and catheterization data (mean pulmonary arterial pressure [PAP]; Qp/Qs) before occlusion. New York Heart Association (NYHA) functional classification and brain natriuretic peptide (BNP) levels were assessed before and 12 months after occlusion. Follow-up measurements and schedules were standardized as follows: electrocardiography, chest X-rays, and transthoracic echocardiography (TTE)

examinations were scheduled before and 1 month, 3 months, 6 months, and 12 months after ASD occlusion. The cardiothoracic ratio (CTR) was measured using chest X-rays. All measurements were performed in the outpatient department.

ECG was obtained using the Cardiofax G ECG-2550 (Nihon Koden Corporation, Tokyo, Japan) with a sampling rate of 1000 Hz. Two trained physicians blinded to the information of the patients measured PQ intervals (lead II), QRS intervals (lead II and V5), R' or r' wave amplitudes of QRS complexes in the V1 lead, and electrical axes. The R' or r' waves were defined as the second positive wave of QRS complexes in the V1 lead that were thought to reflect the electrical force and additive conduction time due to RV enlargement in ASD. The established physicians performed the measurements on quintupled ECG using a magnifying glass, referring the automatic measurements by the built-in program (Electro Cardiograph Analysis Program System ECAPS12C; Nihon Koden Corporation, Tokyo, Japan). Patients with persistent atrial fibrillation (perAF, $n=5$) were excluded from PQ interval measurements, and those with complete right bundle branch block (cRBBB, $n=5$) and/or left anterior hemiblock (LAH, $n=2$) were excluded from measurements of QRS intervals and electrical axes. In the measurements of R' or r' waves, we excluded 12 patients with QRS complexes without r' waves in the V1 lead ($n=7$) and those with cRBBB ($n=5$).

TTE was performed as a routine hospital examination. Echocardiography, including 2-dimensional and Doppler studies, was performed using the EPIQ7 echocardiographic system with the X5-1 transducer and the iE33 echocardiographic system with the S5-1 transducer (Philips Medical Systems, Andover, MA, USA) to obtain images with standard parasternal and apical views. Left ventricular end-diastolic diameter (LVDd), left ventricular end-systolic diameter (LVDs) and left atrial diameter (LAD) were measured using 2-dimensional parasternal long-axis views. The left ventricular ejection fraction (LVEF) was derived using the biplane modified Simpson method. The RA area was calculated during the end-systolic phase and the RV area was measured during the end-diastolic phase in the apical 4-chamber view. Each value was an average of more than five determinations and was assessed by two independent echo-technicians and cardiologists.

Statistical analysis

The obtained data are shown as mean ± SD, median (interquartile ranges), and numbers or frequencies (percentages). The differences between groups were evaluated by unpaired *t* test or Mann–Whitney *U* test after evaluation of the Gaussian distribution using the Kolmogorov–Smirnov test. For binary data, Fisher's exact test was used. Regarding data for repeated measurement, an analysis of variance (ANOVA) or Friedman test was also used to evaluate differences among groups, and the Bonferroni test was used as the post hoc test. As for data for non-repeated measurement, an ANOVA or Kruskal–Wallis test with a Bonferroni test was used. All statistics were compiled using Stata v.15.1 (StataCorp, College Station, TX, USA), and we considered a 2-sided p value <0.05 to be statistically significant and p value <0.10 to have a statistical tendency.

Results

ECG changes after the closure of ASD: a representative case

We present serial ECG of a representative case (42-year-old woman). Figure 1 describes the typical changes found on ECG after transcatheter closure. Her clinical features before intervention were as follows: NYHA class I; CTR of 43%; Qp/Qs of 3.26; PAP of 14 mmHg; defect size of 23.3 mm; BNP of 48.4 pg/dL; RA area of 14 cm^2; RV area of 25 cm^2; no complications; and no medications. Twelve months after closure, the RA and RV areas and BNP experienced changes toward normal values (9 cm^2, 16 cm^2, and 33.5 pg/dL, respectively), suggesting a lessened hemodynamic burden of the volume overload on right heart circulation. The ECG showed that PQ intervals shortened from 180 ms before closure to 150 ms at 12 months after closure (shortening of 30 ms; 16.7%). Furthermore, the incomplete bundle branch block of the QRS complex before transcatheter closure (QRS interval, 110 ms) disappeared gradually, leading to normal results (90 ms), and the electrical axes of the QRS complex changed from deviation of the right axis (100 degrees) to a normal axis (73°). The amplitudes of R' or r' waves in the V1 lead were also decreased after transcatheter closure and disappeared after 6 months. This was a representative case, but there were several different responsiveness of ECG after closure.

Baseline characteristics and differences between patients stratified according to PQ intervals before ASD closure: normal PQ and prolonged PQ groups

Among 100 patients, we excluded five with persistent AF (perAF) from the ECG analyses. Patients with perAF were older, had a higher NYHA functional class, had higher mean PAP and larger CTR, had a larger RA area and had a larger LAD than the other 95 patients without perAF. They experienced more episodes of heart failure (HF) with more administrations of β-blockers and diuretics compared to those without perAF.

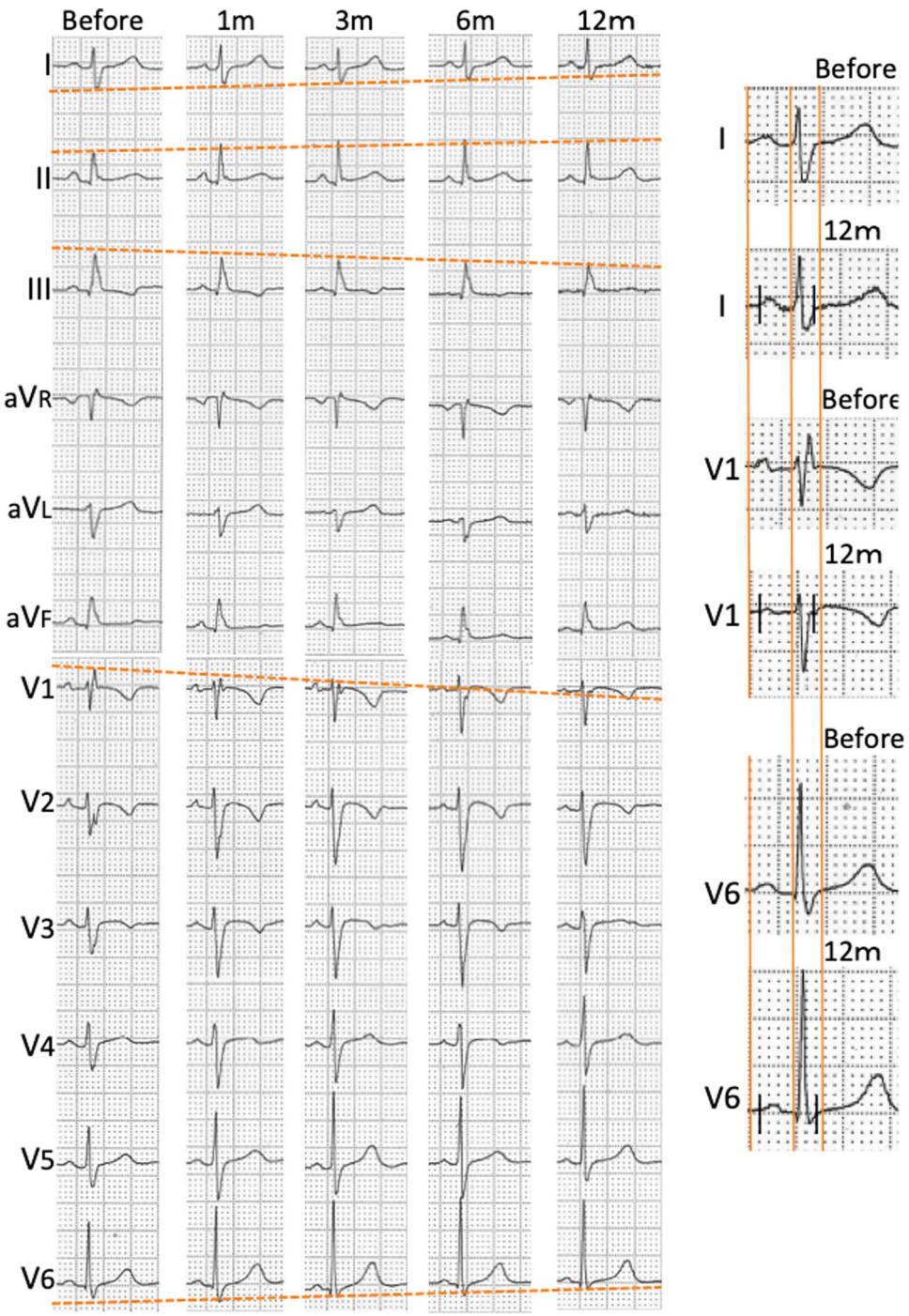

Fig. 1 Representative ECG of an ASD case before and up to 12 months after transcatheter closure. Explanations are in the text

We analyzed 95 patients without perAF and stratified them into two groups according to the lengths of the PQ intervals before closure: those with PQ intervals < 200 ms (normal PQ group) and those with PQ intervals ≥ 200 ms (prolonged PQ group) (Table 1). Because PQ intervals represent the conduction time from the sinus node to the end of the atrioventricular node and also are normally longer than QRS intervals, changes of PQ intervals were more recognizable than those of QRS intervals.

Baseline characteristics of the prolonged PQ group were significantly older age, more comorbidities of heart failure (HF) and paroxysmal AF (PAF), the higher tendency for poorer NYHA functional classification, higher serum BNP levels, higher mean pulmonary arterial pressure (mPAP), higher incidence of incomplete RBBB (iRBBB), and more frequent use of medication (β-blockers and diuretics) compared to the normal PQ group. Eight patients had paroxysmal AF but were not accompanied by strokes. Another six

Table 1 Baseline characteristics, ECG, and TTE data between the normal and prolonged PQ-interval groups

	All patients	Normal-PQ group (PQ < 200 ms)	Prolonged-PQ group (PQ ≥ 200 ms)	*p* value
Number	95	51	44	–
Age, years	50.0 (35.0, 66.0)	45.0 (25.0, 62.0)	61.5 (46.0, 68.0)	0.005
Male, *n* (%)	19 (20.0)	10 (19.6)	9 (20.5)	1.00
NYHA functional Classification, *n* (%)				
I	53 (55.8)	33 (64.7)	20 (45.5)	
II	40 (42.1)	18 (35.3)	22 (50.0)	0.06
III	2 (2.1)	0 (0.0)	2 (4.6)	
BNP, pg/dl	24.7 (15.1, 50.1)	23.0 (14.4, 42.4)	35.0 (16.3, 62.9)	0.09
Catheterization				
mPAP, mmHg	16.0 (14.0, 20.0)	15.5 (13.0, 19.0)	17.0 (15.0, 21.0)	0.09
Qp/Qs	2.3 (1.8, 2.9)	2.2 (1.7, 3.0)	2.4 (1.9, 2.8)	0.54
Defect Size, mm	18.1 ± 5.4	17.3 ± 6.1	18.9 ± 4.4	0.16
Comorbidities, *n* (%)				
HT	18 (19.0)	6 (11.8)	12 (27.3)	0.07
HF	14 (14.7)	2 (3.9)	12 (27.3)	0.003
pAF	8 (8.4)	1 (2.0)	7 (15.9)	0.02
Stroke/TIA	6 (6.3)	3 (5.9)	3 (6.8)	1.00
DVT	2 (2.1)	1 (2.0)	1 (2.3)	1.00
Medications, *n* (%)				
β-blocker	8 (8.4)	1 (2.0)	7 (15.9)	0.02
ACE/ARB	17 (17.9)	6 (11.8)	11 (25.0)	0.11
Diuretics	13 (13.7)	1 (2.0)	12 (27.3)	< 0.0001
ECG				
PQ interval, ms	180 (160, 200)	160 (160, 180	200 (200, 220)	
QRS interval, ms	99 ± 12	96 ± 12	103 ± 12	0.01
r' wave amplitude, mV	0.30 (0.25, 0.40)	0.35 (0.25, 0.50)	0.30 (0.23, 0.40)	0.15
Electrical axis, degree	78 (50, 90)	75 (50, 90)	80 (45, 100)	0.42
cRBBB, *n* (%)	5 (5.3)	0 (0.0)	5 (11.4)	0.02
iRBBB, *n* (%)	46 (48.4)	20 (39.2)	26 (59.1)	0.07
LAH, *n* (%)	2 (2.1)	0 (0.0)	2 (4.6)	0.21
TTE				
RA area, cm^2	21.2 ± 5.6	19.8 ± 5.3	22.7 ± 5.6	0.01
LAD, mm	34.0 (30.0, 41.0)	33.4 (28.0, 36.0)	37.5 (31.5, 44.5)	0.004
RV area, cm^2	27.8 (23.0, 32.9)	27.1 (22.6, 31.2)	29.1 (24.4, 34.7)	0.13
LVDs, mm	25.0 (23.0, 27.0)	25.0 (23.0, 27.0)	24.5 (22.0, 28.0)	0.82
LVDd, mm	40.0 (37.0, 43.0)	40.0 (37.0, 43.0)	39.0 (37.0, 44.0)	0.99
LVEF, %	68.7 ± 6.0	69.4 ± 5.6	68.0 ± 6.4	0.28
CTR, %	51.8 ± 6.5	50.6 ± 6.2	53.3 ± 6.7	0.04

n number, *BNP* brain natriuretic peptide, *NYHA* New York Heart Association, *mPAP* mean pulmonary arterial pressure, *HT* hypertension, *HF* Heart failure, *pAF* paroxysmal atrial fibrillation, *cRBBB* complete right bundle branch block, *iRBBB* incomplete RBBB, *LAH* left anterior hemiblock, *TIA* transient ischemic attack, *DVT* deep vein thrombosis, *ACE* angiotensin-converting enzyme inhibitor, *ARB* angiotensin receptor blocker, *ECG* electrocardiogram, *ms* millisecond, *CTR* cardiothoracic ratio, *TTE* transthoracic echocardiography, *RA* right atrium, *LAD* left atrium dimension, *RV* right ventricular, *LVDs* left ventricular end-systolic dimension, *LVDd* left ventricular end-diastolic dimension, *LVEF* left ventricular ejection fraction

patients had a history of stroke without documented PAF and the cause of the stroke was unknown.

In ECG findings, longer QRS intervals and cRBBB occurred significantly more frequent in the prolonged PQ group than in the normal group. The amplitudes of R' or r' waves in the V1 lead were not significantly different between the two groups. Distribution of iRBBB had a frequent tendency in the prolonged PQ group.

The atrial size (RA area and LAD) by TTE and CTR, reflecting atrial enlargement, were significantly larger in the

prolonged PQ group than in the normal group; however, those of the RV, left ventricle (LV), and LVEF were not significantly different between the 2 groups (Table 1).

Changes of ECG, TTE, and other clinical parameters during 12 months after transcatheter closure

The PQ and QRS intervals were significantly shortened and the amplitudes of R' or r' waves in the V1 lead were also significantly decreased after transcatheter closure in both groups (Fig. 2a, b, c). Furthermore, the electrical axes of the QRS complex were significantly shifted toward the left only in the prolonged PQ group (Fig. 2d). The PQ intervals were significantly longer in the prolonged PQ interval group even 12 months after transcatheter closure.

The RA and RV areas were significantly decreased, and the LVDd and LVDs were significantly increased after closure; however, the LAD did not significantly change after closure in both groups (Fig. 3a, b, d, e). The changes of LVEF varied over time and their clinical significance was not clear (Fig. 3f). In addition to the changes in TTE parameters, the CTR also gradually decreased corresponding with decreases in the RA and RV areas (Fig. 3c). The RA and RV areas, LAD, and CTR were significantly larger in the prolonged PQ interval group than in the normal PQ group even 12 months after transcatheter closure.

The NYHA functional classification significantly improved 12 months after closure in both groups (NYHA I, II, and III; normal group before closure: 64.7%, 35.3%, and 0%; normal group 12 months after closure: 98.0%, 2.0%, and 0% [$p < 0.0001$]; prolonged group before closure: 45.4%, 50%, and 4.6%; prolonged group 12 months after closures: 90.9%, 9.1%, and 0.0% [$p < 0.0001$]). Despite these changes, the serum BNP levels did not significantly change after closure because most baseline BNP

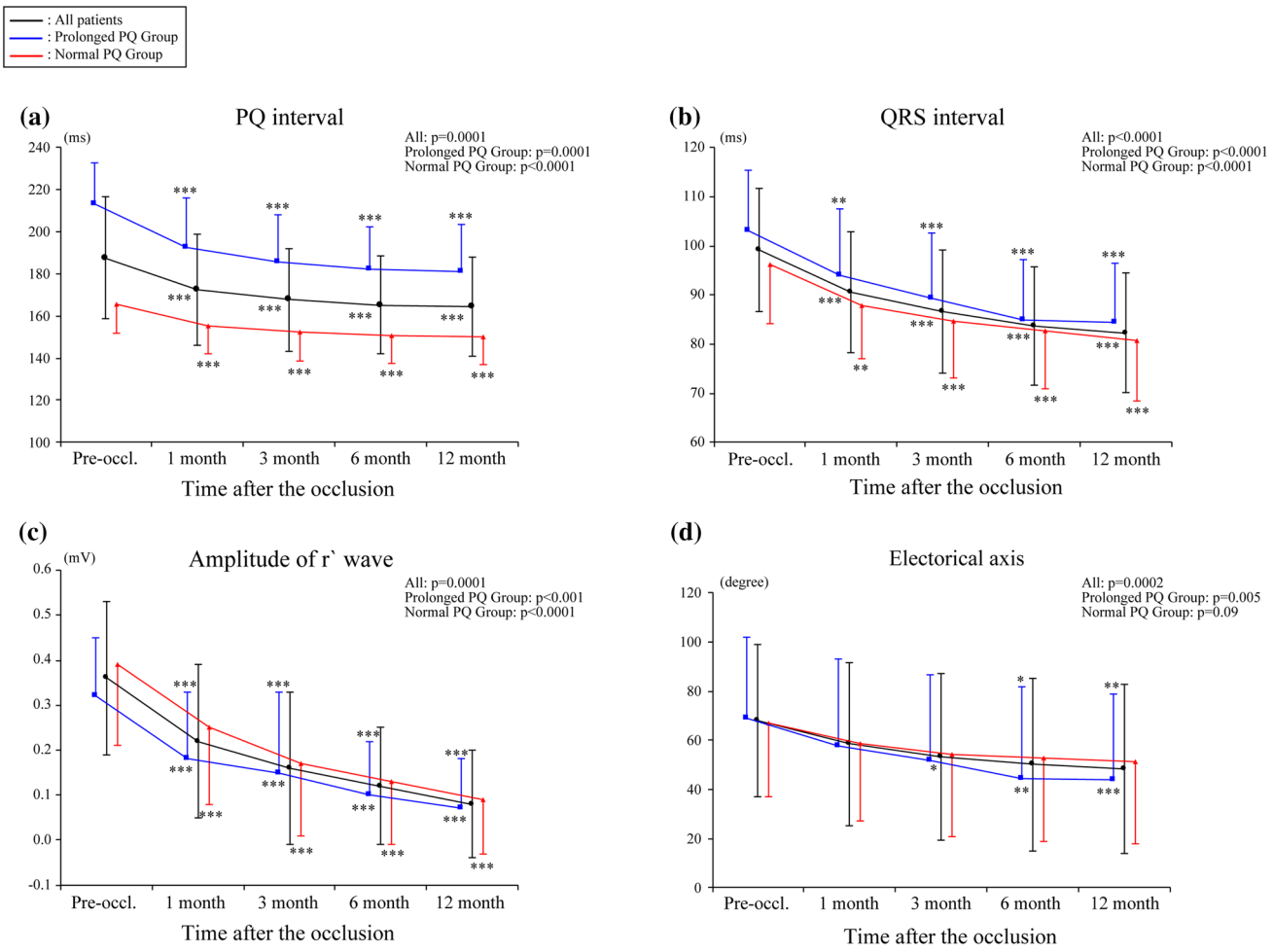

Fig. 2 Serial changes in ECG parameters before occlusion and up to 12 months after transcatheter closure. Serial changes in PQ intervals, QRS intervals, amplitudes of R' or r' waves and electrical axes are shown before occlusion (pre-occl.) and up to 12 months after transcatheter closure in the prolonged PQ group and the normal PQ group.*$p < 0.05$, **$p < 0.001$, ***$p < 0.0001$

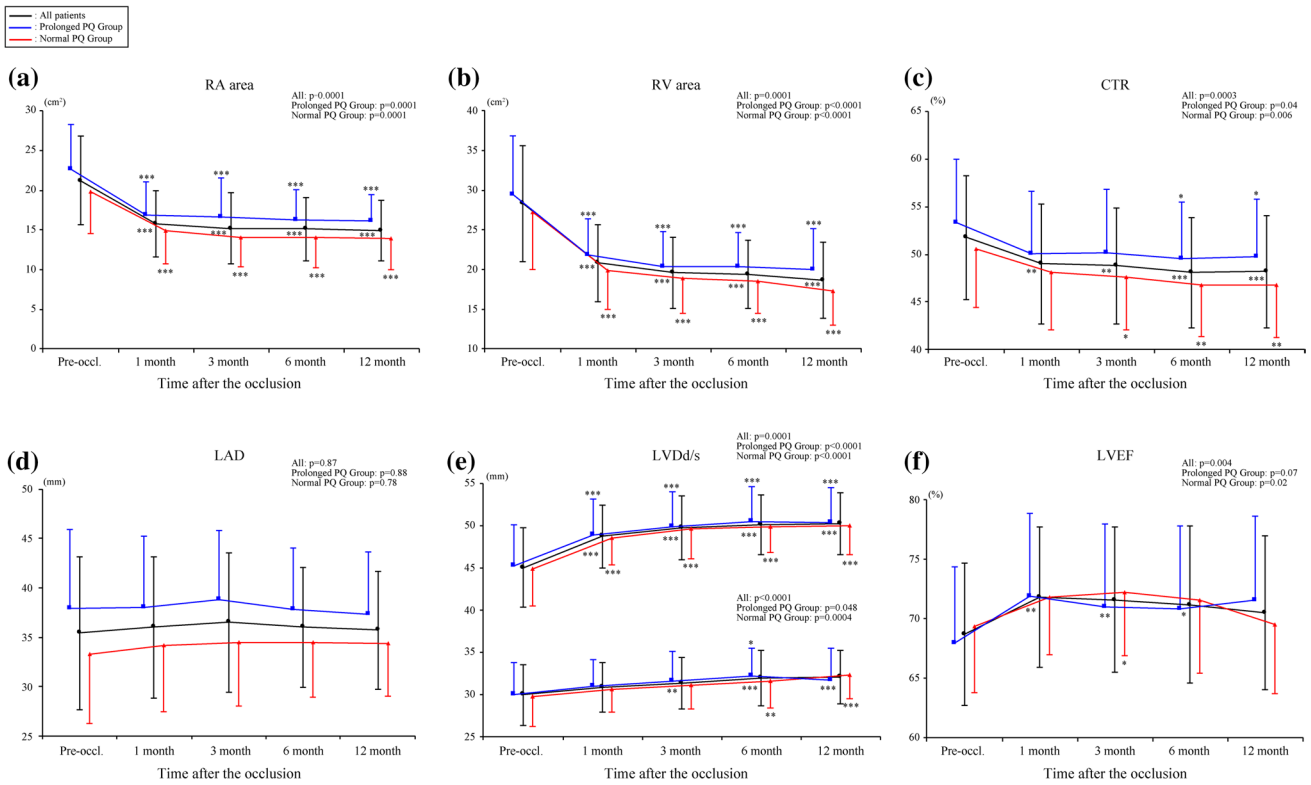

Fig. 3 Serial changes in TTE parameters and CTR before occlusion and up to 12 months after transcatheter closure. Serial changes in RA areas (**a**), RV areas (**b**), LAD (**d**), LVDd and LVDs (**e**), LVEF (**f**), and CTR (**c**) are shown before occlusion (pre-occl.) and up to 12 months after transcatheter closure in the prolonged PQ group and the normal PQ group. $*p < 0.05$, $**p < 0.001$, $***p < 0.0001$

values, except for those of severe ASD cases, were within the normal range even before transcatheter closure.

Baseline clinical characteristics of four subgroups of patients stratified according to baseline PQ intervals and their shortening after transcatheter closure

We divided individuals in both normal PQ and prolonged PQ groups into 2 subgroups according to the shortening ratio of PQ intervals after closure (Table 2). We used an 11% change in the normal PQ group and a 20% change in the prolonged PQ group as references. These values were the average changes in the PQ interval of each group. Individuals in the prolonged PQ group with less shortening in PQ intervals (PQ change < 20%) after closure were the oldest among all subgroups. The median age gradually increased with smaller PQ changes in both normal PQ and prolonged PQ groups. Significantly more patients with a history of HT, PAF, and HF and who used diuretics were in the prolonged PQ group with smaller PQ changes than in the normal PQ group with larger PQ changes. A cRBBB was also observed only on the ECG of the prolonged PQ group with smaller PQ changes. The PQ intervals, RV areas, LAD, and CTR of the prolonged PQ group with less PQ shortening remained largest among the four groups even 12 months after closure. In the normal PQ group, the presence or absence of the PQ shortening was not related to so many clinical indices except for QRS intervals, electrical axis, and LAD at 12 months after the closure.

Discussion

This study examined the serial changes apparent on ECG and other clinical parameters before and after transcatheter closure of ASD. We evaluated those patients based on the length of PQ interval before closure and the PQ interval change after the closure on serial ECG and other clinical parameters such as echocardiography, chest X-rays, and BNP levels. The results provide an alternate view that might help increase the understanding of the concordance between electrophysiological parameters and structural normalization related to the clinical severity of ASD patients.

Table 2 Baseline characteristics and changes of ECG and TTE parameters of 4 subgroups stratified by baseline PQ-intervals and their shortening ratios after the closure

	Normal-PQ group		Prolonged-PQ group		4 Groups *p* value
	PQ change ≥ 11% *n* = 30	PQ change < 11% *n* = 21	PQ change ≥ 20% *n* = 18	PQ change < 20% ***n = 26***	
Age, years	42.0 (18.0, 55.0)	47.0 (35.0, 62.0)	55.0 (43.0, 66.0)	64.5 (52.0, 71.0)**	0.001
Comorbidities, *n* (%)					
HT	3 (10.0)	3 (14.3)	2 (11.1)	10 (38.5)**	0.047
HF	1 (3.3)	1 (4.8)	5 (27.8)*	7 (26.9)*	0.01
pAF	0 (0.0)	1 (4.8)	2 (11.1)	5 (19.2)*	0.04
Medications, *n* (%)					
β-blocker	1 (3.3)	0 (0.0)	3 (16.7)	4 (15.4)	0.08
Diuretics	1 (3.3)	0 (0.0)	4 (22.2)	8 (30.8)**	0.002
ECG					
cRBBB, *n* (%)	0 (0.0)	0 (0.0)	0 (0.0)	5(27.4)***	0.003
QRS interval, ms, Baseline	95 ± 13	98 ± 11	103 ± 14	103 ± 11	0.06
12 m	78 ± 11	85 ± 13*	85 ± 12	84 ± 12	0.10
r' wave amplitud, mV, Baseline	0.33 (0.25, 0.50)	0.40 (0.25, 0.40)	0.30 (0.25, 0.30)	0.35 (0.23, 0.48)	0.32
12 m	0.05 (0.00, 0.15)	0.05 (0.0, 0.15)	0.00 (0.00, 0.05)	0.03 (0.00, 0.25)	0.11
Electrical axis, degree, Baseline	82 (60, 90)	60 (30, 80) *	80 (45, 90)	70 (45, 100)	0.04
12 m	70 (50, 80)	30 (0, 60) *	60 (35, 70)	50 (15, 70)	0.02
TTE					
RA area, cm^2 Baseline	19.3 ± 5.6	20.6 ± 5.0	23.2 ± 6.8	22.4 ± 4.7	0.07
12 m	13.9 ± 3.8	13.9 ± 4.2	16.1 ± 3.8*	16.0 ± 3.1*	0.053
LAD, mm Baseline	32.5 ± 5.7	34.5 ± 8.8	38.0 ± 8.9*	37.9 ± 7.4*	0.03
12 m	33.0 ± 4.4	36.3 ± 6.1*	36.1 ± 6.1	38.1 ± 6.6**	0.01
RV area, cm^2 Baseline	26.5 ± 6.9	28.5 ± 7.8	30.6 ± 7.9	28.7 ± 6.8	0.34
12 m	16.8 ± 3.3	18.2 ± 5.3	19.9 ± 5.1	20.0 ± 5.3*	0.045
CTR, %					
Baseline	49.6 ± 6.2	51.9 ± 6.1	51.4 ± 7.0*	54.6 ± 6.2*	0.04
12 m	46.0 ± 5.2	48.0 ± 5.9	47.2 ± 6.0	51.6 ± 5.4**	0.003

n number, *HT* hypertension, *HF* Heart failure, *pAF* paroxysmal atrial fibrillation, *cRBBB* complete right bundle branch block, *ECG* electrocardiogram, *ms* millisecond, *TTE* transthoracic echocardiography, *RA* right atrium, *LAD* left atrium dimension, *RV* right ventricular, *CTR* cardiothoracic ratio

vs. PQ < 200 ms + PQ change ≥ 11%: *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$

Validity of the analyses of PQ intervals and other ECG findings

The ECG findings for ASD patients varied according to the type of defect. ECG may look normal for young and minimum ASD patients without complications. However, the classic ECG findings of significant secundum ASD are the presence of iRBBB, right-axis deviation, and prolonged PQ interval [19, 20, 23].

Incomplete RBBB has been considered to be an important ECG finding and is possibly due to delayed conduction of the enlarged RV from RV volume overload [19]. The rSR' or rSr' pattern in lead V1 has a specificity of 80%, a sensitivity of 36.1%, a positive predictive value of 14.7%, and a negative predictive value of 92.9% for the diagnosis of ASD [24]. It is important that the amplitude of the R' or r' wave is higher than that of the initial r wave. In our representative case, the amplitude of the R' wave decreased gradually during 12 months after closure. Therefore, we also evaluated the serial changes of the amplitudes of R' or r' waves of the V1 lead in all available patients. We were able to assess the serial changes of amplitudes of the R' or r' waves of the V1 lead in each patient; however, comparisons of these amplitudes among different individuals and assessments of

relationships between the amplitudes and clinical severities of ASD or RV area were difficult because various physical characteristics of the patients and forms of the thoracic cage influenced the amplitudes of the QRS complexes of the chest leads.

In addition to iRBBB, patients with secundum ASD often have the right-axis deviation of the QRS complex by right ventricular overload [19, 20, 23]. The electrical axes are influenced not only by the hemodynamic load of the RV by ASD but also by LV overload such as hypertension in the aged patients. In our study population, the prolonged PQ group with smaller changes of PQ intervals showed the most leftward shift electrical axes after closure, in which the comorbidity of hypertension was most frequent and was the oldest group.

The prolongation of the PQ interval is probably due to the enlargement of the RA by shunt flow via ASD and the increased distance due to the defect itself. PQ intervals were considered mostly to be reflected by atrial load due to ASD [18, 25]. Both of them could cause an increase in internodal conduction time from the SA node to the AV node. The prolonged PQ ($\geq$200 ms) group was accompanied by higher age and electrocardiologically (QRS interval, coexistence of RBBB), anatomically (RA area, LAD, CTR), and clinically (complication of HF, BNP levels, medication-uses) advanced status.

Changes of ECG parameters after ASD closure and relations to other parameters

Serial and detailed ECG evaluations provided some important information regarding not only untreated ASD but also the status after transcatheter closure of ASD. Although we should be careful about the changes of waveforms and axes of *P* waves, we could evaluate quantitatively serial changes of PQ intervals after closure. If significant ASD is untreated for long periods, it may result in irreversible changes such as fibrosis of the atrial cardiac muscles [5–8]. Thus, the electrophysiological remodeling after closure would depend on the anatomical and histological remodeling of the atrium. This would be reflected upon the smaller or larger changes in PQ intervals (electrophysiological remodeling) after closure in each normal and prolonged PQ group. However, the significant clinical factors observed in the prolonged PQ group with less PQ shortening were higher age, more comorbidities (hypertension, paroxysmal AF), diuretic use, cRBBB, larger LAD and CTR at 12 months after the closure than the other 3 subgroups. In the normal PQ group, the presence or absence of the PQ shortening was not related to many clinical indices except for QRS intervals, electrical axis, and LAD at 12 months after the closure. This suggested that the phenomenon of less PQ shortening might be influenced not only by the long-standing exposure of volume overload due to ASD but also by the existence of hypertension, aging and other clinical factors.

Since this study was not a prospective cohort study, the longer prognoses of the patients in this subgroup remained unclear. However, this suggested that the patients of this subgroup should be carefully followed up in a long span even after the closure.

Some reports indicated that the patients with AF before ASD closure were more likely to continue to have AF even after ASD closure [5, 26]. This suggests that there might be certain irreversible changes or damage to the myocardium or electrical conduction system that might lead to future complications such as arrhythmias. It is recommended that significant ASD patients older than 40 years should undergo closure instead of other treatments [5]. Akagi et al. reported that the average time before either cardiac surgery or device closure was within 3 years for 72% of patients older than 40 years [27]. We considered that earlier significant ASD closure, if not contraindicated, would be better for older patients. The intervention strategy for ASD has changed since the introduction of transcatheter occlusion, which lessens the physical burden on the patients. Additionally, minimally invasive cardiac surgery has been proven to be beneficial for certain groups of patients. Technical advances would certainly influence the treatment strategy for ASD. Those who care for ASD patients should continue learning and increasing their knowledge to support better outcomes.

Limitations

This single-center study had several limitations. First, although the data were collected retrospectively, the follow-up protocols and outcome assessments in the transcatheter treatments of ASD were standardized. Thus, we could obtain serial clinical data in most cases even after closure. However, pressure data of the treated patients from catheter examinations would have helped us to further understand the changes in hemodynamics, but we could not perform a second catheterization study after the closure. Second, our observations were based on a relatively small number of patients from a single institution. The clinical importance of our observations might increase when long-term observational data from other institutions are available, and thus must be verified by more cases and a multicenter, prospective study.

Electrocardiography is noninvasive, easy to perform, and probably the most popular method used by cardiologists. Our observational study indicated that precise chronological observations of serial ECG together with other clinical parameters after transcatheter closure in ASD patients might reflect the physical and electrical remodeling of the heart and might help us provide a better prediction of structural and clinical normalization. Especially, the patients with

prolonged PQ interval with smaller PQ interval changes after closure should be carefully followed up for longer periods even after ASD closure.

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Compliance with ethical standards

Conflict of interest H.T. received lecture fees from Otsuka Pharmaceutical Co., Ltd., Takeda Pharmaceutical Co., Ltd., Mitsubishi Tanabe Pharma Co., Ltd., Daiichi Sankyo Co., Ltd., Nippon Boehringer Ingelheim Co., Ltd., Bayer Pharmaceuticals Co., Ltd., and Pfizer Inc. H.T. received grants from Japan Tobacco Inc., Nippon Boehringer Ingelheim Co., Ltd., and Mitsubishi Tanabe Pharma Co., Ltd. H.T. received scholarship donations from MSD Co., Ltd., Daiichi Sankyo Co., Ltd., Mitsubishi Tanabe Pharma Co., Ltd., Teijin Pharma Co., Ltd., and Nippon Boehringer Ingelheim Co., Ltd. All other authors have no conflicts of interest.

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