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Original article

Etiology of atrial fibrillation in patients with complex congenital heart disease — for a better treatment strategy

Aya Miyazaki (MD, FJCC)[a,b,c,*], Jun Negishi (MD)[c], Yohsuke Hayama (MD)[c], Etsuko Tsuda (MD, PhD)[c], Osamu Yamada (MD)[c], Hajime Ichikawa (MD, PhD)[d], Hideki Uemura (MD, MPhil, FRCS)[a], Hideo Ohuchi (MD, PhD, FJCC)[c]

[a] Congenital Heart Disease Center, Nara Medical University, Nara, Japan
[b] Department of Transition Medicine, Division of Congenital Heart Disease, Shizuoka General Hospital, Shizuoka, Japan
[c] Department of Pediatric Cardiology, National Cerebral and Cardiovascular Center, Osaka, Japan
[d] Department of Pediatric Cardiovascular Surgery, National Cerebral and Cardiovascular Center, Osaka, Japan

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ABSTRACT

Background: The demographics of patients with congenital heart disease (CHD) and atrial fibrillation (AF) differ significantly from the general population. The etiology and treatment strategy for AF in CHD patients have been investigated but are to date inconclusive.
Methods: To determine the etiology of AF in CHD and to seek a better treatment strategy, we retrospectively evaluated the atrial overload in 42 complex CHD cases with normal atrial arrangements and AF (age 25; range, 9–66 years) and the impact of a reduction in the atrial overload on the atrial rhythm.
Results: Cardiac defect diagnoses varied, with 17% of the patients having a persistent left superior vena cava (PLSVC). In regard to the volume overload, the frequencies of an overload in the right atrium (RA), left atrium (LA), or both, were 50 %, 23%, and 10%, respectively ($p = 0.015$). Other sustained supraventricular tachycardias were observed in 29 patients (69%) before and after the onset of AF. Among these 29 patients, 26 had intra-atrial reentrant tachycardia. Fifteen patients (36%), 10 of whom had chronic AF, died during the follow-up including 3 with arrhythmias and 10 because of heart failure. Fourteen (33%) patients had no AF at the last follow-up due to medical interventions, 8 of which underwent solely an RA-sided catheter ablation and/or surgical RA overload reduction.
Conclusions: AF in complex CHD with a normal atrial arrangement correlates with a higher RA-sided overload than an LA-sided and exhibits a high incidence of PLSVCs, high comorbidity of intra-atrial reentrant tachycardias, and high mortality rate. In a substantial number of patients, RA-sided interventions were effective in controlling AF. To effectively manage AF in complex CHD it is essential to understand each individual's hemodynamics and consider hemodynamic interventions.
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Introduction

Atrial fibrillation (AF) is more commonly seen in patients with congenital heart disease (CHD) as the patients of this cohort are growing older owing to great strides in surgical techniques and medical care during the last decades. In particular, the complex form of CHD is known to be the greatest risk factor of developing AF [1,2]. Since demographics in CHD patients differ from those of the non-CHD population [1,3], the knowledge established thus far in the latter group is not necessarily applicable for the CHD field. Thus, the precise etiology of AF and its treatment strategy are yet to be determined in the CHD cohort.

The incidence of AF increases exponentially after the age of 20, reaching approximately 8.3% by the age of 42 in patients with CHD [1]. The right atrial (RA) size is reported to be more associated with chronic AF in right-sided CHD than in left sided CHD, while the left atrial (LA) size is associated in left-sided CHD [3].

* Corresponding author at: Department of Transition Medicine, Division of Congenital Heart Disease, Shizuoka General Hospital, 4-27-1 Kita Ando, Aoi-ku, Shizuoka, 420-8527, Japan.
E-mail address: ayamiya@pc4.so-net.ne.jp (A. Miyazaki).

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The purpose of this study was to identify whether an atrial overload was crucial in terms of the etiology of AF in adults with complex CHD and to recognize how to seek a better strategy to deal with this difficult entity.

Methods

Patients

Fifty-four patients (age >15 years) with complex CHD and AF were followed up at the National Cerebral and Cardiovascular Center, Japan, from January 1985 to November 2015. Of those, patients with an atrial septal defect (ASD) and patients with AF during the perioperative period (<one month) were excluded. In addition, we excluded 11 patients with a left atrial isomerism, in order not to confound the extent of the anatomical enlargement of the morphological RA and morphological LA. Another patient who underwent a so-called atrial switch was also excluded for the same reason. Accordingly, 42 patients, all with atrial situs solitus, were retrospectively investigated.

The authors assert that all procedures contributing to this work complied with the ethical standards of the relevant national guidelines on human experimentation (Japan) and with the Helsinki Declaration of 1975 (as revised in 2008) and were approved by the institutional ethics committees (M28-027). Obtaining each individual consent was waived for this type of retrospective study, and comprehensive consent with the opt-out method was admitted.

Classification of AF

Paroxysmal AF was defined as AF that terminated spontaneously within 7 days, and persistent AF as AF that was sustained for longer than 7 days [4,5]. AF that required either direct current or chemical cardioversion within 7 days was classified as persistent [6]. Long-standing AF was defined as AF lasting for over 1 year. Permanent AF was defined when the patient and clinician made a decision to stop further attempts to restore and/or maintain sinus rhythm [4,5]. We classified long-standing and permanent AF as chronic AF.

Atrial overload

We evaluated the volume- and pressure-overload in the RA and LA at the onset of AF. We utilized the echocardiographic or catheterization data at the time of the onset of AF, and not during an AF rhythm.

An RA volume overload was defined on the basis of the RA area index (RAAI) (RA area/body surface area); an RAAI $> 16\,cm^2/m^2$ was regarded as the cut-off value for the risk of atrial arrhythmias as had been reported in tetralogy of Fallot (TOF) [7]. The RAAI was measured by echocardiography in the apical 4-chamber view according to the previous report [8]. The RA pressure overload was defined as an RA pressure of >12 mmHg, measured by catheterization.

An LA volume overload was defined as the LA volume index (LAVI), (LA volume/body surface area). An LAVI $>34\,mL/m^2$ represented the value of moderate enlargement of the LA as per the American and European Societies of Echocardiography [9]. The LAVI was measured by echocardiography using the previously reported ellipsoid formula [9,10]. An LA pressure overload was defined as an LA pressure or pulmonary arterial wedge pressure of >12 mmHg, measured by catheterization.

Patient characteristics and treatment outcomes

To evaluate the patient characteristics at the onset of AF, the following parameters were assessed: age, diagnosis of cardiac defects, gender, number of previous open heart surgeries, types of previous surgical procedures, history of an atrioventricular valve replacement, previous implantation of a permanent pacemaker, concomitant bradycardia, history of other sustained supraventricular tachycardias (SVT), New York Heart Association Functional Classification (NHYA), medication, cardio-thoracic ratio (CTR) based on chest radiography, brain natriuretic peptide (BNP) levels, α-human atrial natriuretic polypeptide (α-hANP) levels, electrocardiography (ECG) findings such as the PR interval and QRS duration, echocardiography findings such as the presence of atrioventricular valve regurgitation, systemic ventricular ejection fraction, RAAI, LAVI, right atrial pressure (RAp), and left atrial pressure (LAp). In addition, the type of sustained atrial tachyarrhythmia if any, whether the atrial overload was treated or not, and the survival outcome or cause of death were investigated during the follow-up.

Analysis

We analyzed the data gathered from mainly four aspects; namely, the patient characteristics at the onset of AF, presence or absence of an atrial overload at the onset of AF, the latest atrial rhythm and survival outcome at the last follow-up, and what were the successful treatments during the follow-up in those patients who had not suffered from AF for more than 1 year or since the last surgery.

Continuous values are presented as the mean ± standard deviation, unless otherwise specified. Skewed data are presented as the median and range. A two-tailed unpaired Student's test or Wilcoxon signed-rank sum test was used for comparisons between the types of AF and between deaths and surviving cases, as appropriate with regards to a normal distribution (Shapiro–Wilk test). A Chi-square or Fisher's exact test was used for comparisons of the presence of an atrial overload between the types of AF and the RA and LA, and for comparisons of the patient characteristics between death and survival, as appropriate. The JMP 13 statistical software (SAS Institute, Cary, NC, USA) was used to perform all statistical analyses. A p-value of <0.05 was considered statistically significant.

Results

Patient characteristics at the onset of AF

The diagnosis of cardiac defects varied in the 42 patients (Fig. 1A), with the most common diagnosis being a repaired TOF. Seven patients (17%) possessed a persistent left superior vena cava (PLSVC) (Fig. 1B). The AF classification was paroxysmal in 4 patients (10%), persistent in 29 (69%), and in the remaining 9 (21%) chronic from the onset of AF. The detailed patient characteristics are listed in Table 1. Seventeen patients (40%) had a history of other sustained SVTs before the AF started. There were no statistically significant differences in the patient characteristics except for being medicated with antiplatelet agents and the cardiothoracic ratio (CTR) between the groups with paroxysmal/persistent AF and chronic AF including the number of previous open heart surgeries, surgical procedures, and a history of an atrioventricular valve replacement.

Atrial overload at the onset of AF

A volume overload alone was seen more often on the RA side than LA side ($p = 0.015$) (Table 2). Twenty-four out of forty patients (60%) had an RA volume overload with or without an LA volume overload. A volume and/or pressure overload was more common in the RA than LA ($p = 0.04$) among 25 patients in whom both echo

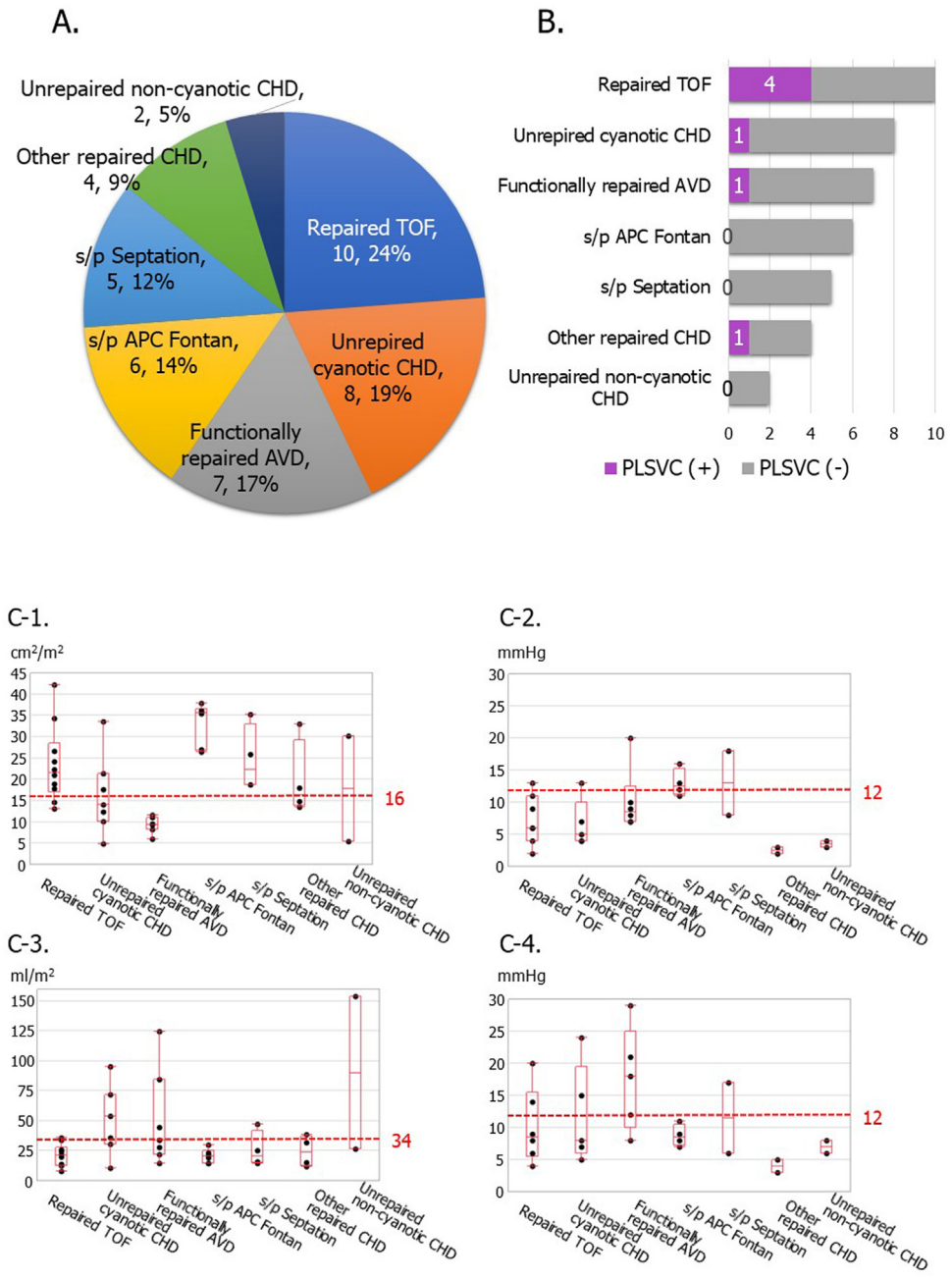

Fig. 1. Anatomical diagnosis and atrial overloads. (A) Cardiac defects in 42 CHD patients with AF. Other repaired CHD included one patient each with a dysplastic tricuspid valve, interruption of the aortic arch, truncus arteriosus, and total anomalous pulmonary venous connection. (B) A concomitant persistent left superior vena cava (PLSVC) with or without an unroofed coronary sinus. Seven patients (17% of 42 patients) had a PLSVC. (C) Atrial size and pressure for each cardiac defect: (C-1) Right atrial area index. (C-2) Right atrial pressure. (C-3) Left atrial volume index. (C-4) Left atrial pressure.
AF, atrial fibrillation; APC, Fontan-type atrio-pulmonary connection Fontan; AVD, atrioventricular discordant; CHD, congenital heart disease; TOF, tetralogy of Fallot.

and catheter data were available. In 64% of those patients, the RA was volume- or pressure-overloaded.

Fig. 1C shows the atrial size and pressure for each cardiac defect. Although the statistical differences were not evaluated due to the small number of patients, the RAAI was larger than 16 cm^2/m^2 in most patients with a repaired TOF, Fontan circulation of the atrio-pulmonary connection type (APC), and circumstances after the so-called septation procedure. The LAVI was higher than 34 mL/m^2 in a substantial number of patients with unrepaired cyanotic CHD and functionally repaired atrio-ventricular discordance.

Clinical course of the atrial rhythm and survival outcome at the last follow-up

The follow-up period was 9.7 ± 6.4 years in all 42 patients. In the patients with paroxysmal, persistent, and chronic AF, the follow up periods were 4.0 (2.3–11.0), 11.7 (0.3–26.0), and 7.3 (5.4–16.1) years, respectively. Other sustained SVTs were observed in 29 patients (69%) before and after the onset of AF. Among those 29 patients, 26 had intra-atrial reentrant tachycardia (IART).

In Fig. 2A, shown are an atrial rhythm and the survival outcomes at the last follow-up. Among four patients with paroxysmal AF at

Table 1
Patient characteristics at the onset of atrial fibrillation.

	N	All	n	Paroxysmal or persistent	n	Chronic	*p*
n		42		33		9	
Age (years)	42	25.7, 9.8–66.4	33	27.2, 10.5–66.4	9	24.1, 9.8–66.0	n.s.
Gender (Female)	42	12 (28.6%)	33	11 (33.3%)	9	1 (11.1%)	n.s.
Concomitant persistent left superior vena cava	42	7 (16.7%)	33	6 (18.2%)		1 (11.1%)	n.s.
Number of previous open heart surgeries	42	1, 0–4	33	1, 0–4	9	1, 1–2	n.s.
Surgical procedure	42		33		9		
BVR		19 (45.2%)		12 (36.4%)		7 (77.8%)	n.s.
Functional BVR		7 (16.7%)		6 (18.2%)		1 (11.1%)	
APC Fontan		6 (14.3%)		6 (18.2%)		0	
No corrective surgery		10 (23.8%)		9 (27.3%)		1 (11.1%)	
History of an AVV replacement	42	4 (9.5%)	33	3 (9.1%)	9	1 (11.1%)	n.s.
Pacemaker implantation	42	4 (9.5%)	33	3 (9.0%)	9	1 (11.1%)	n.s.
Concomitant bradycardia	42	11 (26.2%)	33	7 (21.2%)	9	1 (11.1%)	n.s.
Sinus node dysfunction		1 (2.4%)		1 (3.0%)		0	n.s.
Atrioventricular block		10 (23.8%)		6 (18.2%)		4 (44.4%)	n.s.
History of other atrial tachycardia	42	17 (40.4%)	33	12 (36.3%)	9	5 (55.6%)	n.s.
NYHA Functional Classification	42	2, 1–4	33	2, 1–3	9	2, 2–4	n.s.
Medication							
Diuretics	39	25 (64.1%)	31	20 (64.5%)	8	5 (62.5%)	n.s.
ACE-I/ARB	39	10 (25.6%)	31	9 (29.0%)	8	1 (12.5%)	n.s.
β blockers	39	4 (10.2%)	31	4 (12.9%)	8	0	n.s.
Digoxin	39	20 (51.2%)	31	15 (48.4%)	8	5 (62.5%)	n.s.
Antiarrhythmic drugs (Na or K channel blockers)	39	11 (28.2%)	31	8 (25.8%)	8	3 (37.5%)	n.s.
Warfarin	39	8 (20.5%)	31	7 (22.6%)	8	1 (12.5%)	n.s.
Antiplatelet agent	39	8 (20.5%)	31	8 (25.8%)	8	0	0.04
CTR (%)	31	62.5 ± 7.8	23	60.4 ± 6.9	8	68.6 ± 7.5	0.008
BNP (pg/mL)	20	204, 13–1056	18	236, 13–1056	2	53, 103	–
α-hANP (pg/mL)	17	128, 28–770	16	140, 28–770	1	29	–
ECG findings							
PR interval (ms)	31	200, 140–360	27	200, 140–360	4	190, 160–220	n.s.
QRS duration (ms)[a]	38	120, 80–200	31	120, 80–200	7	120, 100–200	n.s.
Atrial volume by echocardiography							
RAAI (cm^2/m^2)	40	18.3, 4.8–42.1	31	17.6, 4.8–38.0	9	22.3, 8.3–42.1	n.s.
LAVI (ml/m^2)	40	25.7, 7.8–153.7	31	28.0, 7.8–153.7	9	24.1, 12.9–72.3	n.s.
RA volume overload	40	24 (60%)	32	17 (53.1%)	8	7 (87.5%)	0.058
LA volume overload	40	13 (32.5%)	32	11 (34.4%)	8	2 (25.0%)	n.s.
Atrial pressure by catheterization							
RAp (mmHg)	28	8.4 ± 4.8	26	8.0 ± 4.6	2	9, 18	–
LAp (mmHg)[b]	26	8, 3–29	25	8, 3–29	1	17	–
RA pressure overload	28	8 (28.6%)	26	7 (26.9%)	2	1 (50.0%)	–
LA pressure overload	26	9 (34.6%)	25	8 (32.0%)	1	1 (100.0%)	–

ACE-I/ARB, angiotensin-converting-enzyme inhibitor/angiotensin II receptor blocker; α-hANP, α-human atrial natriuretic polypeptide; APC Fontan, atriopulmonary connection type Fontan; AVV, atrioventricular valve; BNP, B-type natriuretic peptide; BVR, biventricular repair; CTR, cardiothoracic ratio; ECG, electrocardiogram; LA, left atrium; LAp, left atrial pressure; LAVI, left atrial volume index; NHYA, New York Heart Association; RA, right atrium; RAAI, right atrial area index; RAp, right atrial pressure.
[a] Three patients were under ventricular pacing.
[b] The pulmonary arterial wedge pressure was used in cases when the LAp was not directly measured.

Table 2
Presence of an atrial overload.

	n	RA	LA	RA + LA	None	*p*
Volume overload	40	20 (50%)	9 (23%)	4 (10%)	7 (18%)	0.015
Pressure overload	26	3 (15%)	4 (12%)	5 (19%)	14 (54%)	0.078
Volume or pressure overload	25	11 (44%)	7 (28%)	5 (20%)	2 (8%)	0.04

RA, right atrium; LA, left atrium.

the onset, three developed persistent or chronic AF at the last follow-up. Two patients eventually died of arrhythmias: ventricular tachycardia (VF) in one and uncontrollable atrial tachyarrhythmias in the other. As for the 29 patients with persistent AF at the onset, no AF was detected at the last follow-up in 13 patients, while 8 patients developed chronic AF. Seven patients died, including one arrhythmia-related death (uncontrollable atrial arrhythmias). Out of 9 with chronic AF at the onset, 6 patients died. As a whole, 14 patients (33%) had no AF after >1 year or since the last surgery, and 19 patients (45%) were in chronic AF at the last follow-up. Fifteen patients (36%), 10 of whom had chronic AF, died during the follow-up including 3 with arrhythmias and 9 because of heart failure.

Among the seven patients with a PLSVC two had no AF, two paroxysmal AF, two persistent AF, and one chronic AF at the last-follow-up. The one with chronic AF died due to heart failure.

Comparison of patient characteristics at the follow-up between the deaths and surviving cases

The follow-up duration from the onset of AF was longer in the surviving cases (Table 3). In the death cases 66.7% had chronic AF,

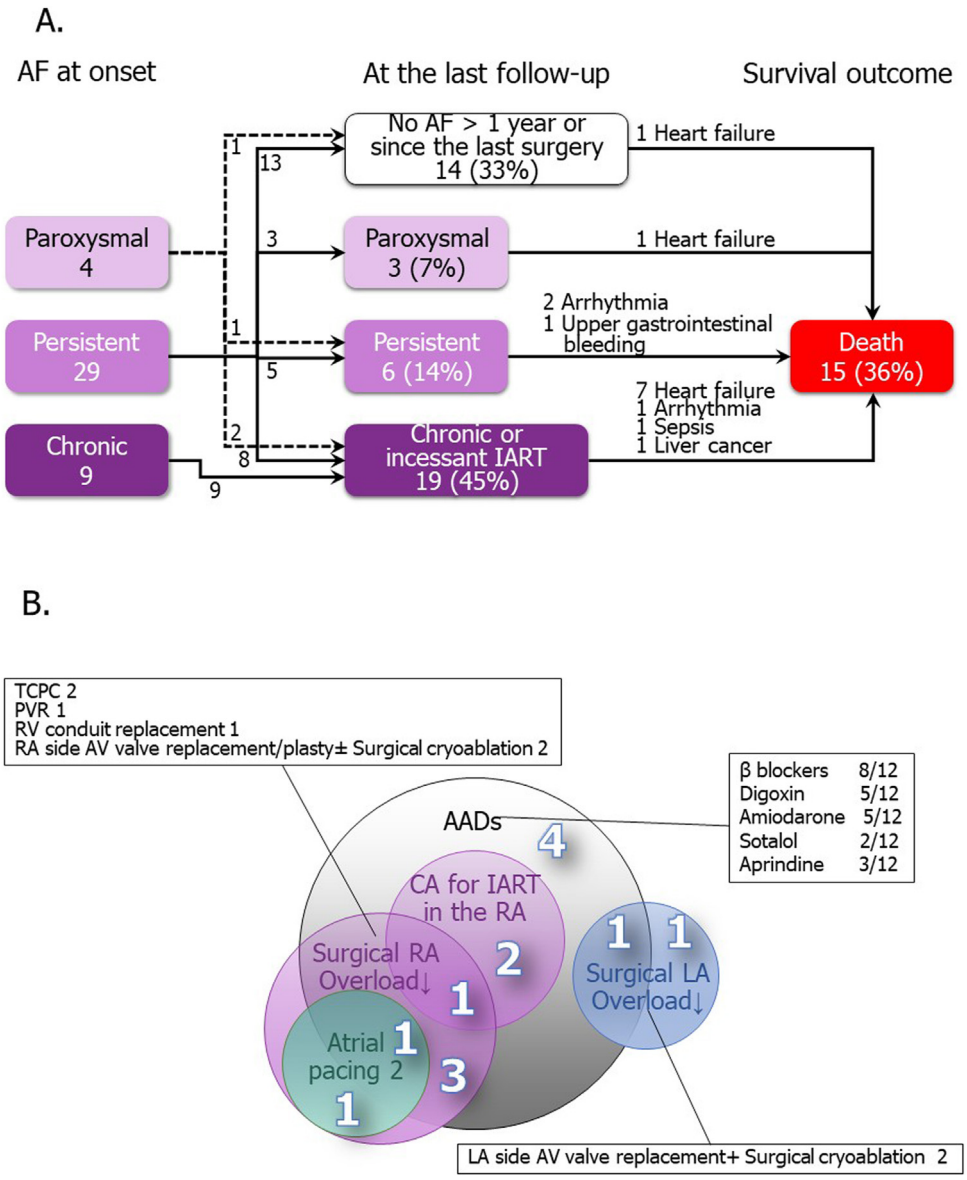

Fig. 2. Clinical course during the follow-up. (A) Atrial rhythm and survival outcomes during the follow-up. The left and middle squares show the classification of AF at the onset and last follow-up, respectively. The right square shows the survival outcomes at the last follow-up. (B) Effective treatment in 14 patients who had no AF for >1 year or since the last surgery at the last follow-up.
AADs were administered in 12 patients, and 3 underwent catheter ablation of IART in the RA. Surgical interventions were performed to reduce the RA overload in 6 patients and the LA overload in 2. Atrial pacing was performed in 2 patients.
AADs, antiarrhythmic drugs; AF, atrial fibrillation; AV, atrioventricular; CA, catheter ablation; IART, intra-atrial reentrant tachycardia; LA, left atrium; PVR, pulmonary valve replacement; RA, right atrium; RV, right ventricle; TCPC, total cavo-pulmonary connection.

while 48.2% of the surviving cases had no AF at the last follow-up. Moreover, the CTR and BNP and α-hANP levels were higher and the systemic ventricular ejection fraction was lower in the death cases than in the surviving cases.

Effective treatment for arrhythmias

Antiarrhythmic drugs (AAD), catheter ablation for IART in the RA, surgical interventions, and atrial pacing appeared successful in 14 patients who had no AF > 1 year or since the last surgery (Fig. 2B). Four patients with controlled AF were medicated with AADs. Eight patients underwent an RA-sided catheter ablation and/or surgical RA volume reduction. Two patients had a surgical therapy for an LA volume reduction.

Discussion

Cardiac defects

It was not surprising to find those with a repaired TOF as the largest subgroup among our patients with a normal atrial arrangement. It has been reported that this is the largest entity in adult CHD with a moderate complexity [11]. Also, patients with cono-truncal heart defects had the highest risk of AF among those with CHD [1]. AF in adult TOF is the second most common following AF in adult ASD [12].

On the other hand, it was interesting to find a PLSVC in 17% of patients; it was obviously more frequent than that seen in the non-CHD population (1/200) or in those with CHD (1/20) [13]. In

Table 3
Comparison between the deaths and surviving cases at the last follow-up.

	n	death	n	survival	*p*
n		15 (35.7%)		27 (64.2%)	
Follow-up duration from the onset of AF (years)	15	6.7 ± 1.6	27	11.4 ± 1.2	0.02
The cause of death	15				
Heart failure		9 (60%)		–	
Arrhythmia		3 (20%)		–	
Liver cancer		1 (7%)		–	
Sepsis		1 (7%)		–	
Upper gastrointestinal bleeding		1 (7%)		–	
Type of AF	15		27		
No AF		1 (6.7%)		13 (48.2%)	0.01
Paroxysmal or persistent AF		4 (44.4%)		5 (18.5%)	
Chronic AF		10 (66.7%)		9 (33.3%)	
Concomitant persistent left superior vena cava	15	1 (6.7%)	27	6 (22.2%)	n.s.
Number of previous open heart surgeries	15	2, 0-4	27	2, 0-5	n.s.
Surgical procedure	15		27		
BVR		6 (40.0%)		13 (48.2%)	n.s.
Functional BVR		2 (13.3%)		6 (22.2%)	
Fontan		4 (26.7%)		3 (11.1%)	
No corrective surgery		3 (20.0%)		5 (18.5%)	
History of AVV replacement	15	4 (26.7%)	27	9 (33.3%)	n.s.
CTR (%)	12	68.1 ± 7.5	27	57.1 ± 8.2	0.0003
BNP (pg/mL)	8	690, 75-3481	26	64, 8-502	0.002
α-hANP (pg/mL)	7	351, 74-2870	23	43, 18-422	0.001
ECG findings					
QRS duration (ms)[a]	14	152 ± 50	27	150 ± 34	n.s.
Echocardiographic findings	13		27		
≧moderate AVV regurgitation		7 (53.9%)		8 (29.6%)	n.s.
Systemic ventricular ejection fraction (%)		49 ± 19		61 ± 13	0.02

AF, atrial fibrillation; α-hANP, α-human atrial natriuretic polypeptide; AVV, atrioventricular valve; BNP, B-type natriuretic peptide; BVR, biventricular repair; CTR, cardiothoracic ratio; ECG, electrocardiogram.
[a] Six patients were under ventricular pacing.

particular, in those with a repaired TOF, the prevalence of a PLSVC was 40% in the current study with AF, however, it was reported to be 4–25% in general repaired TOF patients in the previous reports [14,15]. The coronary sinus (CS) is usually dilated in patients with a PLSVC in the setting of situs solitus, and therefore, it can be an arrhythmogenic source of AF [16]. Indeed, the CS receiving the PLSVC is more dilated when the RA is overloaded, and is occasionally documented with such as a giant CS [17]. We regarded that, in the present study, the presence of a PLSVC was a potential factor of AF. Also, a careful recognition and technical modification may be needed when catheter ablation is carried out in the RA for atrial arrhythmias to be treated.

Etiology of AF in CHD patients

An overload of the RA appears to be a common cause of AF in the adult CHD field. This is contrary to the circumstance seen in the non-CHD adult population; it is well established that a pressure and/or volume overload stretches the LA and the mechanical dilatation results in atrial remodeling [18,19]. Subsequently, the connecting area between the pulmonary veins and scarred LA acts as a main focus triggering AF, and a dilated LA starts to accommodate an electronic circuit to maintain AF [3,20,21].

Even in the CHD group, of course, the LA can start the development of AF, but it is up to the nature of the malformations. Our findings this time, nevertheless, found that an overload of the RA was more common and clearly indicated that a right-sided problem needs careful attention regarding initiating AF. In right-sided CHD patients with AF, it has been reported that progressive and predominant RA dilatation parallels the development of AF [3]. On the other hand, LA dilatation has been reported to be an indicator of AF even in those with a repaired TOF [7,22,23]. These observations sound inconsistent. We speculated that a right heart problem can solely produce an overload of the RA, while an initial right heart problem could induce left heart dysfunction through an interventricular reaction resulting in an overload of the LA. Once an episode of AF starts, both atria would still further be affected by progressive histopathological changes. These steps should provide different circumstances of a detectable overload of the RA or LA and eventually both in the clinical setting. We judged that this was the reason why the status of a mechanical overload of the RA, LA, or bilaterally remains somehow equivocal in the heterogeneous clinical groups.

Comorbidities induced by SVTs, particularly IART, were frequent in the present study; this was comparable to the previous reports regarding CHD patients with AF [12]. In the CHD cohort, IART is often confined to the right atrial tissue [24]. Chronic IART leads to atrial electrical remodeling, with a shortening of the atrial effective refractory period and conduction velocity [25]. IART is caused by an RA overload and progresses to AF in many cases [26].

Survival outcome

Overall mortal events are known to be more frequent in those with CHD and AF; the Swedish national cohort study clearly demonstrated this fact (mortality rate 11.57 vs. 0.73 /1000 person-y in CHD and non-CHD adult patients with AF, respectively) [1]. On top of that, the risk of heart failure causing death was significantly higher than the risk of an ischemic stroke in those with CHD and AF.

Arrhythmogenic changes in the atria have been attributed to the various factors associated with CHD [2,27], some of them being rather congenital-oriented such as intrinsic structural malformations, surgical procedures peculiar to CHD, a deleterious influence during a previous cyanotic period, and so on. Once AF occurs, as a matter of fact, AF itself promotes a hemodynamic deterioration by means of a loss of the atrial transport factor, atrioventricular dyssynchrony, and an inappropriate ventricular rate. This perti-

nently explains the high mortality and comorbidity in CHD patients with AF. The current study also showed that the hemodynamic values were worse with a higher incidence of chronic AF in the death cases than survivors. Hence, a sensible treatment strategy is the key to prevent and treat AF in those with complex CHD.

Treatment strategies for AF in CHD patients

This retrospective study showed that the etiology and treatment that was effective for AF in CHD indicated a better treatment strategy. That is, the arrhythmogenic background should be carefully evaluated in each individual patient before choosing the remedy for AF.

At a stage when the RA overload and its histopathological changes just initiate AF episodes, we probably should focus mainly on the RA side. In reality, the RA-sided catheter ablation and/or surgical RA overload reduction was only effective in eight patients. There have been several case reports showing the successful AF catheter ablation of dilated RA substrates [28,29]. In a multicenter study where AF catheter ablation was performed in 84 CHD patients, an RA ablation with/without a pulmonary vein isolation was performed in 48% of the patients, and the majority of those underwent an ablation at the cavo-tricuspid isthmus [30].

When chronic AF is set, the LA is dilating and adversely remodeling as "AF begets AF" [3,21]. During this stage, the cardiologist should no longer concentrate on the initial lesions on the RA side, but should also actively treat the LA [29]. Catheter ablation is undoubtedly useful to reduce or remove the arrhythmogenic substrate and triggers of AF [31,32]. We need to consider still further whether more aggressive surgical maneuvers are reasonable, such as an LA volume reduction, the so-called full maze procedure, and a repair of structural impediments causing the RA and/or LA overload.

Study limitations

This study had several limitations. The basic cardiac anomalies were heterogeneous in nature and the exact number of the total population with CHD was not available. We did not compare the atrial overload between the CHD patients with and without AF. Therefore, we did not determine the incidence of AF in those with an atrial overload. Moreover, the sample size was small, and the catheterization data were available for only 26 patients (62%) out of the total 42 patients. The inclusion criteria might have caused a significant bias for the data evaluation. Furthermore, in this retrospective study, the treatment did undergo changes during the approximately 30-year study duration period. Finally, the relationship of the atrial overload to AF was not conclusively proved, due to the lack of an electrophysiology study. Nonetheless, we considered that these results were valuable for assessing the etiology of AF in complex CHD.

Conclusion

AF in complex CHD patients with a normal atrial arrangement is more associated with an overload of the RA than of the LA. A PLSVC was relatively common in our series of patients. SVTs, particularly IART, were frequently observed. Anti-arrhythmic interventions in the RA were effective in controlling AF. If AF is not treated successfully, the survival outcome in the long term will not be secure because of intractable heart failure or sudden arrhythmic episodes. It is essential to investigate the precise hemodynamics in each individual in order to arrange an effective treatment in patients with complex CHD and AF.

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Disclosures

The authors declare that there are no conflicts of interest.

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References

[1] Mandalenakis Z, Rosengren A, Lappas G, Eriksson P, Gilljam T, Hansson PO, et al. Atrial fibrillation burden in young patients with congenital heart disease. Circulation 2018;137:928–37.
[2] Labombarda F, Hamilton R, Shohoudi A, Aboulhosn J, Broberg CS, Chaix MA, et al. Increasing prevalence of atrial fibrillation and permanent atrial arrhythmias in congenital heart disease. J Am Coll Cardiol 2017;70:857–65.
[3] Bouchardy J, Marelli AJ, Martucci G, Bottega N, Therrien J. Mirror image atrial dilatation in adult patients with atrial fibrillation and congenital heart disease. Int J Cardiol 2013;167:816–20.
[4] Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Europace 2016;18:1609–78.
[5] January CT, Wann LS, Alpert JS, Calkins H, Cigarroa JE, Cleveland Jr JC, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines and the Heart Rhythm Society. Circulation 2014;130:e199–267.
[6] Morady F, Zipes DP. Atrial fibrillation: clinial features, mechanisms, and management. In: Zipes DP, Libby P, Bonow RO, Mann DL, Tomaselli GF, Braunwald E, editors. Braunwald's heart disease: a textbook of cardiovascular medicine. 11th ed., Philadelphia: Elsevier; 2019. p. 730–52.
[7] Bonello B, Kempny A, Uebing A, Li W, Kilner PJ, Diller GP, et al. Right atrial area and right ventricular outflow tract akinetic length predict sustained tachyarrhythmia in repaired tetralogy of Fallot. Int J Cardiol 2013;168:3280–6.
[8] Rudski LG, Lai WW, Afilalo J, Hua L, Handschumacher MD, Chandrasekaran K, et al. Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. J Am Soc Echocardiogr 2010;23:685–713.
[9] Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, et al. Recommendations for chamber quantification: a report from the American Society of Echocardiography's guidelines and standards committee and the chamber quantification writing group, developed in conjunction with the european association of echocardiography, a branch of the european society of cardiology. J Am Soc Echocardiogr 2005;18:1440–63.
[10] Ujino K, Barnes ME, Cha SS, Langins AP, Bailey KR, Seward JB, et al. Two-dimensional echocardiographic methods for assessment of left atrial volume. Am J Cardiol 2006;98:1185–8.
[11] Shiina Y, Toyoda T, Kawasoe Y, Tateno S, Shirai T, Wakisaka Y, et al. Prevalence of adult patients with congenital heart disease in Japan. Int J Cardiol 2011;146:13–6.
[12] Teuwen CP, Ramdjan TT, Gotte M, Brundel BJ, Evertz R, Vriend JW, et al. Time course of atrial fibrillation in patients with congenital heart defects. Circ Arrhythm Electrophysiol 2015;8:1065–72.
[13] Gupta SK, Spicer DE, Anderson RH, Moore RA. Anomalus systemic venous return. In: Wernovsky G, Anderson RH, Kumar K, Mussatto K, Redington AN, Tweddell JS, et al., editors. Anderson's pediatric cardiology. 4th ed., Philadelphia: Elsevier; 2020. p. 457–74.
[14] Kula S, Cevik A, Sanli C, Pektas A, Tunaoglu FS, Oguz AD, et al. Persistent left superior vena cava: experience of a tertiary health-care center. Pediatr Int 2011;53:1066–9.
[15] Fraser RS, Dvorkin J, Rossall RE, Eidem R. Left superior vena cava: a review of associated congenital heart lesions, catheterization data and roentgenologic findings. Am J Med 1961;31:711–6.
[16] Hsu LF, Jais P, Keane D, Wharton JM, Deisenhofer I, Hocini M, et al. Atrial fibrillation originating from persistent left superior vena cava. Circulation 2004;109:828–32.
[17] Nathani S, Parakh N, Chaturvedi V, Tyagi S. Giant coronary sinus. Tex Heart Inst J 2011;38:310–1.
[18] Tsang TS, Barnes ME, Bailey KR, Leibson CL, Montgomery SC, Takemoto Y, et al. Left atrial volume: important risk marker of incident atrial fibrillation in 1655 older men and women. Mayo Clin Proc 2001;76:467–75.
[19] Oakes RS, Badger TJ, Kholmovski EG, Akoum N, Burgon NS, Fish EN, et al. Detection and quantification of left atrial structural remodeling with delayed-

enhancement magnetic resonance imaging in patients with atrial fibrillation. Circulation 2009;119:1758–67.
[20] Haissaguerre M, Jais P, Shah DC, Takahashi A, Hocini M, Quiniou G, et al. Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. N Engl J Med 1998;339:659–66.
[21] Nattel S, Harada M. Atrial remodeling and atrial fibrillation: recent advances and translational perspectives. J Am Coll Cardiol 2014;63:2335–45.
[22] Khairy P, Aboulhosn J, Gurvitz MZ, Opotowsky AR, Mongeon FP, Kay J, et al. Arrhythmia burden in adults with surgically repaired tetralogy of Fallot: a multi-institutional study. Circulation 2010;122:868–75.
[23] Geva T. Repaired tetralogy of Fallot: the roles of cardiovascular magnetic resonance in evaluating pathophysiology and for pulmonary valve replacement decision support. J Cardiovasc Magn Reson 2011;13:9.
[24] Walsh EP, Cecchin F. Arrhythmias in adult patients with congenital heart disease. Circulation 2007;115:534–45.
[25] Morton JB, Byrne MJ, Power JM, Raman J, Kalman JM. Electrical remodeling of the atrium in an anatomic model of atrial flutter: relationship between substrate and triggers for conversion to atrial fibrillation. Circulation 2002;105:258–64.
[26] Mouws E, Roos-Hesselink JW, Bogers A, de Groot NMS. Coexistence of tachyarrhythmias in patients with tetralogy of Fallot. Heart Rhythm 2018;15:503–11.
[27] Moe TG, Abrich VA, Rhee EK. Atrial fibrillation in patients with congenital heart disease. J Atr Fibrillation 2017;10:1612.
[28] Takahashi K, Shoda M, Manaka T, Nakanishi T. Successful radiofrequency catheter ablation of atrial fibrillation late after modified Fontan operation. Europace 2008;10:1012–4.
[29] Guarguagli S, Kempny A, Cazzoli I, Barracano R, Gatzoulis MA, Dimopoulos K, et al. Efficacy of catheter ablation for atrial fibrillation in patients with congenital heart disease. Europace 2019;21:1334–44.
[30] Liang JJ, Frankel DS, Parikh V, Lakkireddy D, Mohanty S, Burkhardt JD, et al. Safety and outcomes of catheter ablation for atrial fibrillation in adults with congenital heart disease: a multicenter registry study. Heart Rhythm 2019;16:846–52.
[31] Ichijo S, Miyazaki S, Kusa S, Nakamura H, Hachiya H, Kajiyama T, et al. Impact of catheter ablation of atrial fibrillation on long-term clinical outcomes in patients with heart failure. J Cardiol 2018;72:240–6.
[32] Kim JO, Shim J, Lee SH, Yu HT, Kim TH, Uhm JS, et al. Clinical characteristics and rhythm outcome of catheter ablation of hemodynamically corrected valvular atrial fibrillation. J Cardiol 2019;73:488–96.