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Catheter Ablation for Atrial Fibrillation in Adults With Congenital Heart Disease

Lessons Learned From More Than 10 Years Following a Sequential Ablation Approach

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ABSTRACT

OBJECTIVES This study aimed to evaluate the impact, safety, and success of atrial fibrillation (AF) ablation in adults with congenital heart disease (ACHD) transferring ablation strategies established in normal hearts.

BACKGROUND AF is an emerging arrhythmia in ACHD.

METHODS Fifty-seven consecutive ACHD (median age 51.1 ± 14.8 years) with drug-refractory AF were analyzed who underwent catheter ablation between 2004 and 2017. CHD was classified according to its complexity into mild (61.4%), moderate (17.5%), and severe (21.1%) lesions. AF ablation was performed in 104 procedures following a sequential ablation approach.

RESULTS Of the 57 patients, 30 underwent corrective surgery, 6 underwent palliative surgery, 5 had catheter interventions, and 16 were natural survivors. Follow-up was available for all patients (median 41 ± 36 months). The median duration of cyanosis was 9.2 ± 19.7 years, and the time of volume or pressure overload prior to corrective surgery or intervention was 26.1 ± 21.2 years and 18.1 ± 15.8 years, respectively. The Kaplan-Meier estimate for arrhythmia-free survival following the index ablation procedure was 63% for 1 year and 22% for 5 years. Performing subsequent ablation procedures (2.0 ± 0.5), the Kaplan-Meier estimate significantly improved, with 99% for 1 year and 83% for 5 years ($p < 0.01$). Five patients died during follow-up due to their underlying CHD condition or underwent transplantation.

CONCLUSIONS AF ablation strategies established in normal hearts can be transferred to ACHD. The treatment is safe and effective with acceptable long-term results. Varying anatomical pre-conditions and the heterogeneous population itself are challenging and contribute toward a higher reablation rate. Therefore, AF ablation in ACHD should be reserved for dedicated and highly specialized teams. (J Am Coll Cardiol EP 2018;4:733–43)

Atrial fibrillation (AF) is an emerging arrhythmia in adults with congenital heart disease (ACHD). Long-term antiarrhythmic drug therapy has significant limitations in ACHD, prospective studies of its efficacy are lacking, and furthermore, pharmacological strategies with proven effectiveness in adults without congenital heart disease (CHD) may be less effective in ACHD or even proarrhythmic (1). The Pediatric and Congenital Electrophysiology Society and Heart Rhythm

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ABBREVIATIONS AND ACRONYMS

ACHD = adults with congenital heart disease

AF = atrial fibrillation

AT = atrial tachycardia

CFAE = complex fractionated atrial electrogram

CHD = congenital heart disease

CI = confidence interval

DC = direct current

LA = left atrium

LAA = left atrial appendage

PAF = paroxysmal atrial fibrillation

PERS = persistent atrial fibrillation

PV = pulmonary vein

PVI = pulmonary vein isolation

SR = sinus rhythm

Society expert consensus document on the recognition and management of arrhythmias in ACHD recommends that AF ablation might be considered after failure of trials of cardioversion with pharmacologic rhythm control (1). There is lacking evidence regarding individual risk stratification, ablation strategies, and long-term follow-up after AF ablation in ACHD. Predominantly, operators have largely transferred ablation approaches including pulmonary vein isolation (PVI), connecting linear lesion sets to the left-sided mitral isthmus, and cavotricuspid isthmus ablation (1), and no reliable data currently exist for substrate-based ablation approaches. In addition, individual disorders and cardiac lesions contribute to the arrhythmogenesis and perpetuation of cardiac arrhythmias and therefore increase the severity of AF ablation in ACHD. Recently, Tilz et al. (2) reported their findings following a sequential ablation strategy for persistent AF (PERS) in patients with structurally normal hearts. This approach included basically PVI, linear lesion sets, and complex fractionated atrial electrogram (CFAE) ablation, and leads to a long-term maintenance of sinus rhythm (SR) with a rate of 45% after multiple ablation procedures (2). These findings are in line with the data from O'Neill et al. (3) demonstrating that a stepwise ablation approach focusing on termination of AF during ablation leads to improved outcomes in patients with PERS without CHD. AF ablation in the setting of ACHD remains challenging and therefore, this study aimed to evaluate the impact, safety, and mid- to long-term success of AF ablation in ACHD transferring AF ablation strategies from patients without cardiac anomalies to ACHD.

METHODS

STUDY POPULATION. Between 2004 and 2017, a total number of 67 consecutive ACHD (median age 50 years; range: 17.5 to 76.3 years) with drug-refractory AF underwent a total of 150 left atrial (LA) ablation procedures for AF at our institution. Ten ACHD with preceding LA ablation attempts at another center as well as those candidates with previous surgical treatment for AF were excluded. Consequently, 57 ACHD with a primary interventional approach for drug-refractory AF at our institution remained, in whom 104 procedures were performed and analyzed in this observational single-center study. Previous catheter ablation for right atrial tachycardia (AT) has been performed in 17 of 57 patients (29.8%) focusing on re-entrant tachycardia based on either macro re-entrant and/or micro re-entrant focal mechanism. The congenital cardiac anomalies were classified according the 32nd Bethesda consensus document (4) into their levels of complexity: mild (61.4%), moderate (17.5%), and severe (21.1%) (**Table 1**). Ninety percent of patients underwent previous cardiac surgery and 21% had a history of cyanosis. Paroxysmal AF (PAF) and PERS were defined according to the recommendations of the 2012 Heart Rhythm Society/European Heart Rhythm Association /European Cardiac Arrhythmia Society Expert Consensus Statement on Catheter and Surgical Ablation of Atrial Fibrillation (5).

ELECTROPHYSIOLOGICAL STUDY. Prior to each procedure, LA thrombus formation was excluded. In patients on vitamin K antagonists, oral anticoagulation was stopped 3 days before ablation and replaced by intravenous heparin to maintain a partial thromboplastin time of 2× to 3× the normal value or bridged with low-molecular-weight heparins. Since 2012, ablation was performed under therapeutic international normalized ratio values of 2 to 3. Direct oral anticoagulants were stopped the day before and continued after the procedure when pericardial effusion had been ruled out. The intervention was performed under deep sedation utilizing midazolam, fentanyl, and a continuous infusion of propofol. One standard catheter was positioned inside the coronary sinus. Two SL1 sheaths (St. Jude Medical, Minneapolis, Minnesota) were advanced to the LA using a modified Brockenbrough technique (6). After transseptal catheterization, intravenous heparin was administered, targeting an activated clotting time of >300 s. Three-dimensional electroanatomical reconstruction using the CARTO system (Biosense Webster, Diamond Bar, California) and ablation were performed using a 3.5-mm-tip catheter (ThermoCool Navi-Star, Biosense Webster) (2,6,7). Low voltage for abnormal atrial areas was defined as an amplitude of ≤0.5 mV. In case of right atrial ablation, the anatomic course of the phrenic nerve was identified using pace mapping. The location of the esophagus was visualized using an 8-F nasogastric tube (Nutritub, B. Braun, Melsungen, Germany). Before AF intervention, a baseline electrophysiological study was performed to evaluate and, if necessary, eliminate coexisting tachycardia. Written informed consent was obtained from each patient before the procedures after intensive elucidation with special respect to the individual CHD condition. The study was approved by the Institutional Review Board.

ABLATION PROTOCOL DURING THE INITIAL PROCEDURE. All patients underwent AF ablation following a sequential ablation. Initially, wide area circumferential PVI was performed in all procedures using irrigated radiofrequency current, which is concordant to previous series (2,3,5–7). Radiofrequency energy was limited to 30 W and an infusion rate of 17 ml/min along the superior, anterior, and inferior portions of the PV and 20 W along the posterior aspect. During PVI, a circumferential mapping catheter (Lasso, Biosense Webster) was placed inside the ipsilateral PV. The endpoint of PVI was defined as the absence of any PV spike potential recorded on the Lasso catheter for at least 30 min. after PVI and demonstration of exit block by pacing from inside the PV. In case that AF persisted after initial PVI or did not convert to AT, electrical cardioversion with up to 3 biphasic direct current (DC) shocks (maximum 200 J) was performed aiming to restore SR. If DC failed to evoke SR, LA substrate modification was performed by application of linear lesions along the roof, the mitral isthmus, and the posterior wall followed by repeat cardioversion after each ablation maneuver until DC shocks accomplished SR. If AF was reinitiated by a non-PV trigger during the 30-min waiting period, such trigger was targeted for ablation. Patients were defined as acute PVI responder if stable SR could be established by means of PVI only or with the additional use of DC cardioversion. CFAE ablation was applied aiming to convert sustained AF to SR or any AT (8). The CFAEs were analyzed visually and categorized based on Nademanee et al. (9). During ablation of CFAE or AT with the use of a linear lesions concept, the lasso catheter was positioned in the LA appendage (LAA). For the latter ablation strategy, bidirectional block of the designated area was attempted as an endpoint and validated with the use of appropriate stimulation maneuvers (10) during SR. Isolation of the superior vena cava or in case of a present persistent left superior vena cava was attempted only if spontaneous focal activity originated from those locations. Patients were classified as acute PVI nonresponders if any additional ablation strategy was required in addition to PVI.

ABLATION PROTOCOL DURING REPEAT ABLATION. Repeat ablation procedures were performed in patients with recurrence of any atrial tachyarrhythmia (including AF and AT). Initially—if present—PV conduction gaps in the wide area circumferential ablation line were targeted aiming for electrical reisolation of all PVs. Subsequently stimulation from the LAA and coronary sinus was performed including burst pacing. If AF was inducible, LA substrate modification by linear lesions was performed as described. Induced AT was carefully mapped and structures judged to be critical for the maintenance of the re-entry circuit or origins of focal AT were targeted for ablation. Following termination of the macro-re-entrant AT, ablation was continued until conduction block could be validated. A posterior "box lesion" and/or ablation of CFAE were performed in patients with repeat symptomatic episodes of AF, persistent PVI, and bidirectional block of the roofline and the connection toward the mitral annulus either lateral or anterior. For linear lesions, such ablation results were subsequently reconfirmed during a minimum waiting period of 30 min. The same approach was repeated for any induced AT. The endpoint of repeat ablation procedures was successful PVI and noninducibility of any sustained AF or AT episodes during final atrial stimulation.

POST-ABLATION STRATEGY AND FOLLOW-UP. Oral anticoagulation with phenprocoumon was started immediately after the procedure targeting an international normalized ratio of 2 to 3 or direct oral anticoagulant medication was maintained. In all patients, oral anticoagulation was continued for at least 3 months, and thereafter the decision for ongoing oral anticoagulation was made based on the patient's individual CHA_2DS_2-VASc (Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, Prior stroke or transient ischemic attack or thromboembolism, Vascular disease, Age 65 to 74 years, Sex category) score (5). Before discharge, 24-h echocardiographic monitoring and echocardiographic evaluation were performed. Discontinuation of antiarrhythmic drugs was recommended 3 months after ablation. A transthoracic echocardiogram, 12-lead electrocardiogram, and 24-h Holter recording were obtained 3, 6, and 12 months post-ablation and every 6 months thereafter. In addition, we performed regular telephonic interviews in 3- to 6-month intervals. Implantable pacemaker or defibrillators with atrial leads were used to access the AF burden. Outpatient clinical visits were immediately initiated by the referring cardiologist or by our institution in case of symptoms suggestive for recurrent arrhythmia. Recurrences were defined as any documented AF or AT episode >30 s following a 3-month blanking period. Patients without AF or AT recurrence were referred to as patients with stable SR throughout the entire follow-up period.

STATISTICAL ANALYSIS. Statistical analysis was performed using univariate and multivariate analyses. Descriptive statistics are reported as absolute or relative frequencies, mean ± SD, or median

TABLE 1 Characteristics of Patients at Baseline

	All Patients (n = 57)	Mild Lesion (n = 35)	Moderate Lesion (n = 10)	Severe Lesion (n = 12)
Age, yrs	51.1 ± 14.8	54.0 ± 14.3	43.7 ± 7.2	33.9 ± 14.9
Height, cm	175.0 ± 10.4	170.0 ± 10.3	181.0 ± 7.7	177.0 ± 7.1
Weight, kg	76.0 ± 17.6	75.0 ± 18.3	81.0 ± 17.7	70.0 ± 16.1
BMI, kg/m^2	24.7 ± 5.0	26.8 ± 5.3	23.8 ± 4.4	23.3 ± 4.5
Type of atrial fibrillation				
Paroxysmal	21 (37)	15 (43)	2 (20)	4 (33)
Persistent	36 (63)	20 (57)	8 (80)	8 (67)
Corrective surgery	30	21	9	0
Palliative surgery	6	1	0	5
Corrective intervention	5	4	0	1
Natural survivor	16	9	1	6
Duration of pressure overload, yrs	18.1 ± 15.8	18.1 ± 11.8	35.3 ± 19.3	5.3 ± 0.0
Duration of volume overload, yrs	26.1 ± 21.2	32.8 ± 22.0	6.7 ± 15.0	9.2 ± 21.6
History of cyanosis, yrs	9.2 ± 19.7	0	15.7 ± 0.0	7.3 ± 22.7
Major CHD diagnosis				
Secundum-type ASD				
Surgical closure	19	18	1	0
Interventional closure	3	3	0	0
Native	4	4	0	0
Congenitally corrected transposition of the great arteries	2	0	0	2
Double chambered right ventricle	1	0	1	0
Double inlet left ventricle	2	0	0	2
Complete double aortic arch	1	1	0	0
d-TGA*	1	0	0	1
Ebstein anomaly of the tricuspid valve	4	0	0	4
Coarctation	4	3	1	0
Complete AV septal defect	1	0	0	1
Pulmonary atresia with intact ventricular septum	1	0	0	1
Pulmonary atresia with VSD	1	0	0	1
Partial pulmonary venous drainage	1	0	1	0
Partial AV septal defect	2	0	2	0
Persistent ductus arteriosus	2	2	0	0
Shone complex	1	0	1	0
Persistent left superior caval vein	2†	2†	0	0
Situs inversus totalis	1	1	0	0
Tetralogy of Fallot	2	0	2	0
VSD	2	1	1	0
Arterial hypertension	23 (40.4)	17 (48.6)	5 (50.0)	1 (8.3)
Obesity	14 (24.6)	10 (28.6)	3 (30.0)	1 (8.3)
Diabetes mellitus	3 (5.3)	2 (5.7)	1 (10.0)	0
Bronchial asthma	3 (5.3)	2 (5.7)	1 (10.0)	0
Congestive heart failure	20 (35.1)	9 (25.7)	6 (60.0)	5 (41.7)
Pulmonary hypertension	5 (8.8)	4 (11.4)	0	1 (8.3)
History of stroke	8 (14.0)	5 (14.3)	1 (10.0)	2 (16.7)

Continued on the next page

(interquartile range), as appropriate. Inference results for group comparisons in means or distributions are obtained from 2-sample *t*, Wilcoxon, and Kruskal-Wallis tests and analysis of variance-type statistics in factorial designs (chi-square tests) depending on data scales. Furthermore, event-free survival was estimated using Kaplan-Meier calculations and compared between groups by log-rank tests. Multivariate prediction models for time to recurrences were assessed using stepwise Cox regression models. For each variable, the hazard ratios, the 95% confidence intervals (CIs), and the p values of the final model were computed using Wald-type statistics. A hazard ratio of <1 indicates a reduced likelihood of relapse for increasing values of the variable. Results were regarded as significant if the 2-sided p value was <0.05. All statistical results were obtained using R computing environment version 3.4.1 (R Foundation, Vienna, Austria).

RESULTS

PATIENT CHARACTERISTICS. From 2004 to 2017, a total of 57 consecutive ACHD (mean age 51.1 ± 14.8 years; range: 18.7 to 76.3 years) with drug-refractory AF underwent an initial attempt for catheter ablation of AF (PAF 37%, PERS 63%) at our institution. A median follow-up of 41 ± 36 months (range: 6 to 129 months) was available for the entire patient cohort. Obesity was present in 14 patients (24.6%, mean body mass index 24.7 ± 5 kg/m^2). All ACHD were classified according their level of CHD complexity into mild (n = 35, 61.4%), moderate (n = 10, 17.5%), and severe (n = 12, 21.1%). Two patients with left persistent superior caval vein (1 with situs solitus, 1 with situs inversus plus azygous continuity), 1 patient with situs inversus totalis alone, and 1 patient with double aortic arch have been classified as mild lesions. Of the 57 patients, 30 underwent corrective surgery and 6 palliative cardiac surgery, whereas 5 patients underwent catheter-mediated interventional treatment of their CHD. Sixteen patients were classified as natural survivors. The need for cardiopulmonary bypass during corrective cardiac surgery was reported in 66%. The individual lesions are summarized in Table 1. Congestive heart disease was present in 35% prior to the ablation. The median history of preoperative cyanosis was 9.2 ± 19.7 years (3 natural survivors suffered from lifelong cyanosis), volume overload 26.1 ± 21.2 years, and pressure overload 18.1 ± 15.8 years, respectively. Five patients died or underwent transplantation during the follow-up period (8.8%) due to hemodynamic consequences related to the CHD. None of the patients was lost to follow-up. The baseline characteristics of the entire study population are summarized in Table 1.

CLINICAL OUTCOMES AFTER THE FIRST ABLATION PROCEDURE. PVI was achieved in all 57 patients. AT was present or inducible after PVI in 36 patients

(63.2%). Additional linear lesions to achieve electrical dissection were applied along the mitral isthmus (n = 24, 42.1%), along the LA roof (n = 23, 40.4%), across the cavotricuspid isthmus (n = 10, 17.5%), along the right atrial free wall (n = 6, 10.5%), and the LAA (2 patients, 3.5%). A posterior box lesion was placed in 3 patients (5.3%) and CFAE ablation was performed in 1 patient (1.8%) (Table 2). In 1 patient, coexisting atrioventricular nodal re-entrant tachycardia was revealed and slow pathway ablation was performed within the same procedure. Stable SR was achieved in all patients at the end of the procedure. After the median follow-up duration following the index procedure persistent SR was maintained in 15 patients (26.3%). Recurrent arrhythmias after the index procedure occurred in 32 patients and were PAF in 7 (21.9%), PERS in 21 (65.6%), and AT in 4 (12.5%) (Figure 1). The Kaplan-Meier estimate for arrhythmia-free survival following the index procedure was 63% (95% CI: 46% to 74%) for 1 year and 22% (95% CI: 11% to 37%) for 5 years, respectively. Arrhythmia recurred within the first year after ablation in 26 of 57 patients (45.6%); 42 patients (73.7%) had recurrences after 36 months and 50 patients (87.7%) had recurrences 5 years after initial ablation (Figure 2).

CLINICAL OUTCOMES AFTER REABLATION INCLUDING MULTIPLE PROCEDURES. Considering repeat or even multiple ablation procedures, 30 of 57 patients (52.6%) remained in stable SR after the median follow-up. The detailed summary of the individual ablation targets for each ablation procedure is demonstrated in Table 2. Recovered PV conduction was found in 21 of 32 patients (65%) at the first, 3 of 11 (27%) at the second, and in none at the third reablation procedure. Isolation of the LAA due to PVI and the need for additional ablation occurred in 2 patients during the first, 3 patients during the second, and 1 patient during the third procedure. These patients were carefully monitored for AF or AT recurrences and scheduled to receive an LAA occlusion device.

TABLE 1 Continued

	All Patients (n = 57)	Mild Lesion (n = 35)	Moderate Lesion (n = 10)	Severe Lesion (n = 12)
Sick sinus syndrome	8 (14.0)	4 (11.4)	2 (20.0)	2 (16.7)
AV block				
I–II	10 (17.5)	4 (11.4)	1 (10.0)	5 (41.7)
III	2 (3.5)	0	0	2 (16.7)
ICD implantation	2 (3.5)	0	0	2 (16.7)
Pacemaker implantation	13 (22.8)	3 (8.6)	4 (40.0)	6 (50.0)
Antiarrhythmic drug therapy				
Beta-blocker	42 (73.7)	26 (74.3)	7 (70.0)	9 (75.0)
Class IC antiarrhythmic drug	17 (29.8)	11 (31.4)	3 (30.0)	3 (25.0)
Amiodarone	6 (10.5)	5 (14.3)	3 (30.0)	1 (8.3)
Anticoagulation therapy				
DOAC	11 (19.3)	9 (25.7)	2 (20.0)	0
OAC	33 (57.9)	17 (48.6)	7 (70.0)	9 (75.0)
ASS	4 (7.0)	4 (11.4)	0	0

Values are mean ± SD, n (%), or n. *d-TGA after atrial switch repair. †One patient with left superior caval vein had coexistent situs inversus and azygous continuity.

ASD = atrial septal defect; ASS = aspirin; AV = atrioventricular; BMI = body mass index; CHD = congenital heart disease; DOAC = direct oral anticoagulation; d-TGA = D-transposition of the great arteries; ICD = implantable cardioverter-defibrillator; OAC = oral anticoagulation; VSD = ventricular septal defect.

Recurrent arrhythmias after the repeat ablation procedures are demonstrated in Figure 2. With respect to multiple ablation procedures, the Kaplan-Meier estimate for arrhythmia-free survival significantly improved with 99% (95% CI: 75% to 100%) for 1 year and 83% (95% CI: 56% to 92%) for 5 years ($p < 0.01$), respectively (Figure 2). This positive effect was observed across all subgroups irrespective of the underlying lesion ($p < 0.01$) or type of AF ($p < 0.01$). Arrhythmia recurred within the first year after ablation in 6 of 32 patients (18.75%); 14 patients (43.75%) had recurrences after 36 months and 17 patients (53.13%) had recurrences 5 years after the index procedure.

PROCEDURAL DATA AND COMPLICATIONS. Total procedure duration was 235 ± 87 min, total fluoroscopy time was 33.7 ± 21.7 min, and fluoroscopy dose was 670 ± 2,774 cGy · cm^2. There was only 1 major

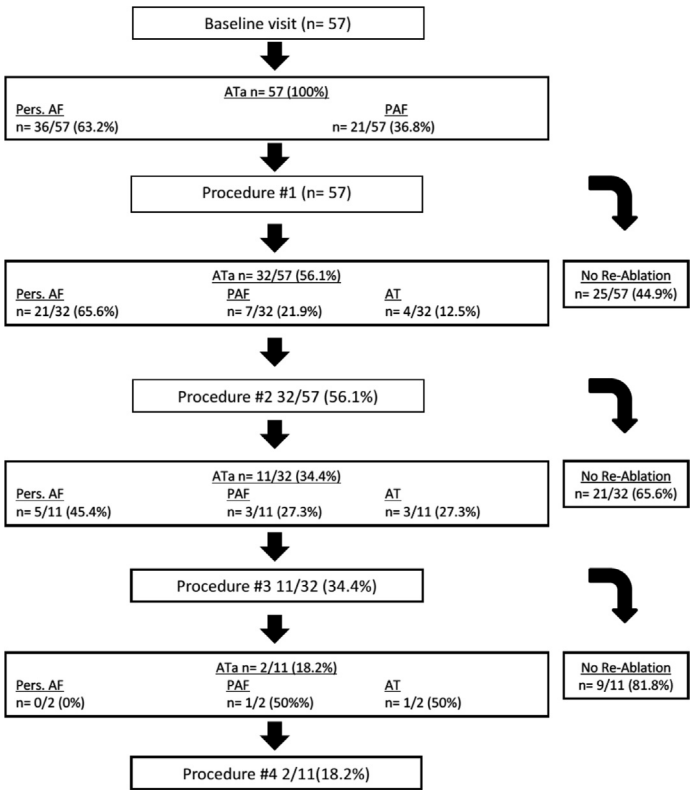
TABLE 2 Summary of Ablation Procedures

		PVI and Additional Ablation								
				Left Atrium					Right Atrium	
Procedure	N	PVI Only	MI Line	Roof Line	Posterior Wall Isolation	LAA Isolation	CTI	Linear/Focal	CFAE (Biatrial)	Others
First	57	21 (36.8)	24 (42.1)	23 (40.4)	3 (5.3)	2 (3.5)	10 (17.5)	6 (10.5)	1 (1.8)	1 (1.8)
Second	32	7 (21.9)	20 (62.5)	15 (46.9)	9 (28.1)	3 (9.4)	9 (28.1)	3 (9.4)	0	1 (3.1)
Third	11	2 (18.2)	7 (63.6)	2 (18.2)	7 (63.6)	1 (9.1)	3 (27.3)	2 (18.2)	0	1 (9.1)
Fourth	2	0	2 (100)	1 (50.0)	1 (50.0)	0	0	1 (50.0)	0	0

Values are n (%) unless otherwise indicated.

CFAE = complex fractionated atrial electrogram; CTI = cavotricuspid isthmus; LAA = left atrial appendage; MI = mitral isthmus; PVI = pulmonary vein isolation.

FIGURE 1 Arrhythmia Outcome



The flowchart demonstrates arrhythmia outcome. AT = atrial tachycardia; ATa = atrial tachyarrhythmia; PAF = paroxysmal atrial fibrillation; Pers AF = persistent atrial fibrillation.

complication (1.8%) related to the first ablation procedure requiring intervention (pericardial tamponade). Minor complications were reported in 12 of 57 procedures (21.1%) including mild or moderate groin hematoma (10.5%) and others (10.5%). No major complication was observed related to the reablation procedures. After reablation, we observed pericardial effusion (n = 1), groin hematoma (n = 2), and pleural effusions (n = 1), none requiring intervention.

PREDICTORS FOR ARRHYTHMIA RECURRENCE. After the first procedure, univariate predictors of arrhythmia recurrence were an elevated body mass index of >30 kg/m^2 (p = 0.045), PERS as initial arrhythmia (p = 0.047), fluoroscopy dose (p = 0.033), history of pre-operative cyanosis (p = 0.026), and history of previous oral anticoagulation (warfarin or direct oral anticoagulants; p = 0.002). None of these parameters remained significant when performing multivariate analysis.

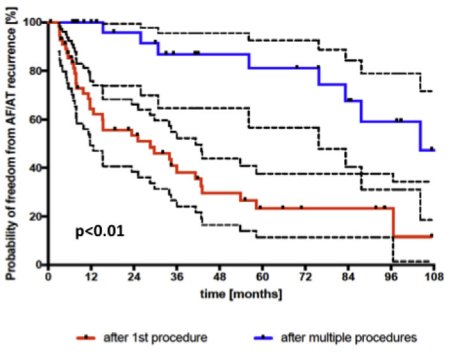
DISCUSSION

MAJOR FINDINGS. This is the first and largest study reporting impact, safety, and mid- to long-term success of AF ablation in ACHD transferring ablation strategies established in patients without cardiac anomalies. This analysis has 3 major findings. First, ablation strategies for AF can be safely and effectively transferred from patients with anatomically normal hearts to ACHD. Second, ongoing disease, challenging anatomy in concert with heterogeneous acquired arrhythmogenic substrates may account for the trend toward the increased need of reablation. Third, AF ablation in ACHD leads to remarkable mid- to long-term results. AF ablation in ACHD should be reserved to highly specialized and dedicated teams with experience in all aspects of ACHD treatment.

ABLATION STRATEGIES FOR AF IN ACHD. ACHD display a heterogeneous population presenting with symptomatic AF at comparably younger age, especially when complex CHD is present. Some suffer from post-surgical or post-interventional residuals resulting in a wide range of mild to severe hemodynamic consequences. Arrhythmia load in ACHD is generally high with and without a history of surgical intervention (1). In this context, surgical interventions (11), pre-existing anatomical abnormalities (1), atrial scarring and fibrosis (12), heterogeneity in depolarization, repolarization and refractory periods, effects on cardiac chamber distension, and excitability (11) may count relevant for the initiation and maintenance of AF in ACHD. The Pediatric and Congenital Electrophysiology Society and Heart Rhythm Society consensus document states that catheter ablation for AF might be considered after failure of trials of cardioversion with rhythm control and in the context of adequate antithrombotic therapy. The ablation approaches could probably be adapted from standard strategies in non-ACHD patients (1). Philip et al. (13) reported attractive results focusing on PVI for the treatment of AF in ACHD as compared with patients without structural heart disease in a propensity-matched study including 36 patients suffering from CHD. The investigators demonstrated that maintenance of SR after PVI in ACHD appeared similar to those with structural normal hearts (13). In contrast to our cohort, the number of patients was relatively low, ablation protocols and strategies varied, and patients suffered predominantly from mild cardiac lesions. Thus, all patients in our study underwent AF ablation following a sequential ablation approach with the endpoints we have already mentioned. In **Figure 2**, the limited success rate of a single procedure is

demonstrated (1 year: 63%; 5 years: 22%). But the ablation success rate has been improved significantly after performing multiple ablation procedures (1 year: 99%, 5 years: 83%; $p < 0.01$) (**Figure 2**). This effect was observed irrespective of CHD complexity, type of AF, or instant of ablation. Freedom from arrhythmia recurrence in our heterogeneous and younger ACHD cohort compares favorably with the success rates in older patients without CHD suffering from chronic forms of AF (8,13–19). Using arrhythmia termination as an additional endpoint, our data led to adequate long-term results as previously reported (3,20). One may speculate that the trend toward a higher reablation rate in this study can be explained by multiple factors affecting ablation success and lesions' consistency including the on-going disease and heterogeneous pre-conditions. In this context, Teuwen et al. (21) demonstrated that episodes of AF and AT frequently coexist in ACHD and that a progression from PAF to long-standing PERS or permanent AF occurs frequently and relatively fast after the initial episode of AF. Therefore, the investigators state that an aggressive therapy and close follow-up of ACHD suffering from AT and AF is justified (21). Early ablation for AT and AF may potentially avoid degeneration from stable ATs to AF or prevent from progression to chronic forms. Based on our findings, a combined approach seems reasonable combining PVI with additional linear lesion sets as well as homogenization of atrial scar and fibrotic tissue (**Figures 3 and 4**).

FIGURE 2 Procedure Outcomes

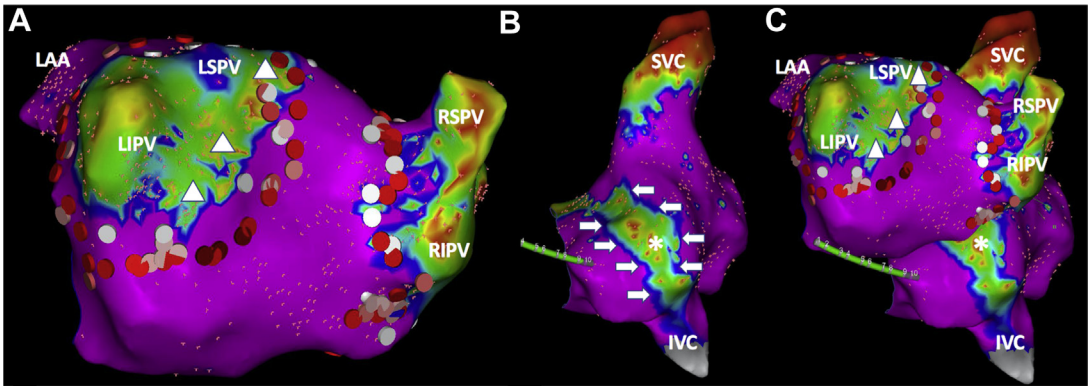


	months									
	0	12	24	36	48	60	72	84	96	108
1st	57	31	23	15	11	7	5	5	3	1
multiple	32	26	23	18	16	15	14	10	8	4

Single and multiple procedure outcomes. Kaplan-Meier event-free survival curve (including 95% confidence interval as **dashed lines**) after the first procedure **(red line)** and after multiple ablation procedures **(blue line).** AF = atrial fibrillation; AT = atrial tachycardia.

TYPE OF RECURRENT ARRHYTHMIA. Ablation procedures in ACHD are often complex and require pre-interventional planning and techniques for volume imaging of the heart. Integration into 3-dimensional electroanatomic mapping offers several advantages including reduction of fluoroscopy and better success rates (22–24). Novel high-resolution electroanatomic mapping systems show promise for improved understanding of atrial tissue characteristics as well as electrical propagation (25,26). This technology becomes increasingly important for heterogeneous and scarred regions of the atria as well as for challenging arrhythmia substrates that might be affected by previous intervention, ablation, or surgery (**Figure 3**). Laţcu et al. (26) demonstrated that the critical isthmus of re-entrant scar-related AT showed much lower electrogram amplitudes with a significantly slower conduction velocity than the surrounding parts of the circuit and ablation of the areas of slow conduction resulted in a high acute success. One may also speculate that these technical advancements allow for improved discrimination of fibrotic low-voltage zones and healthy excitable tissue. In **Figure 1**, the proportion of patients with AT scheduled for reablation is shown to increase with each procedure and to decrease for PAF and PERS. In addition, **Table 2** indicates that the number of PVI-responder decreases, whereas the number of linear lesions and ablation of non-PV trigger increases or remains more or less consistent (with exception of the LA roof line) for the first, second, and third procedures. This could be explained by the fact that PV reconnection becomes more unlikely with every single ablation attempt. Instead, creation of extensive ablation-induced scar within the atria, creation of incomplete lines of conduction block, or scarring as well as side effects of previous intervention or surgery may serve as a substrate for AT micro and macro re-entrant circuits (**Figure 4**). This observation is an analog to the previous series (20) and can be transferred from patients without cardiac anomalies to ACHD. Coexistence of AT and AF in ACHD has been described previously (21,27) and AT was present or inducible in the majority of patients after PVI (**Table 2, Figure 1**). Previous data demonstrated that the development of atrial arrhythmias was related to a higher number of surgical procedures (1,21,27) as cardiac surgery results in atrial incisions and insertion of prosthetic materials (**Figure 3**) and furthermore persisting pressure and volume overload may give rise to extensive atrial

FIGURE 3 Example of a First Ablation Procedure

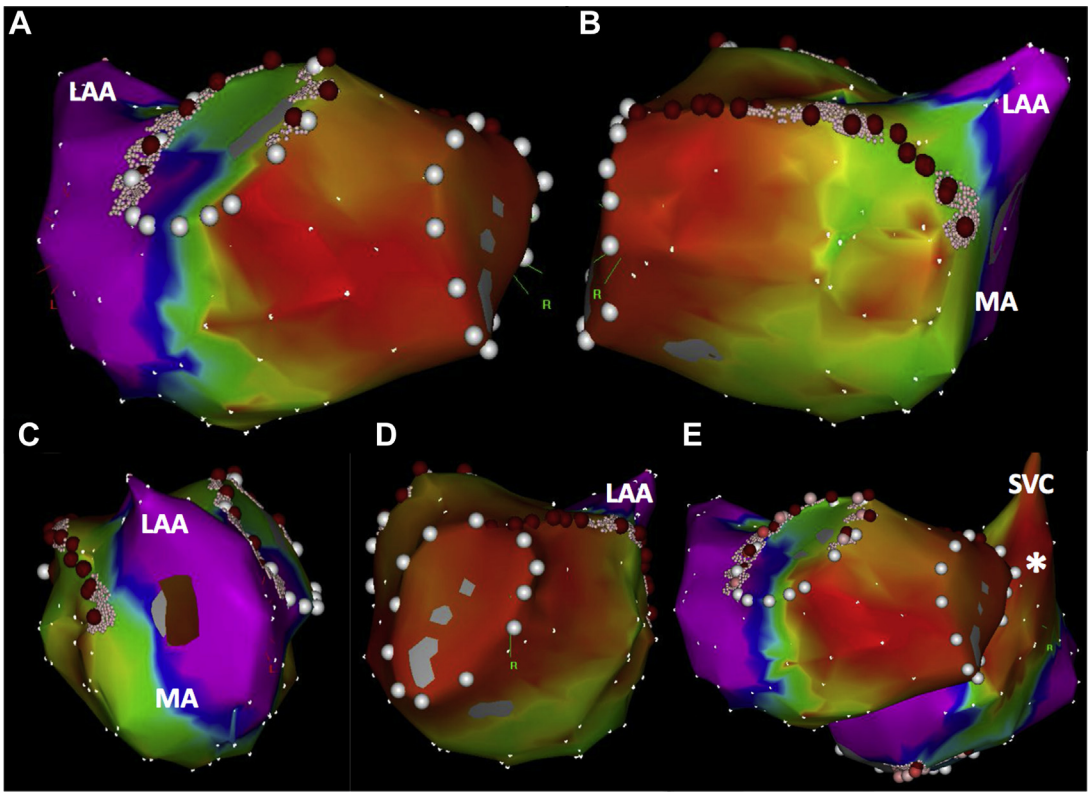


Patient-specific example of a first ablation procedure in a 63-year-old woman with a secundum type atrial septal defect after surgical patch closure suffering from persistent atrial fibrillation. Three-dimensional reconstruction of the left atrium and right atrium using high-density and fast anatomical mapping. **(A)** Posterior-anterior view of the left atrium demonstrating wide area circumferential ablation **(red dots)** including ostial low-voltage area **(triangles)** close to the left inferior pulmonary vein (LIPV) and the transition zone between the left superior pulmonary vein (LSPV) and the left atrial roof. **(B)** Posterior-anterior view of the right atrium with high-density visualization of the interatrial patch **(asterisk)** including atrial suture lines **(arrows)**. **(C)** Biatrial electroanatomical visualization of the ablation lines and the interatrial patch **(asterisk)**. IVC = inferior vena cava; LAA = left atrial appendage; RIPV = right inferior pulmonary vein; RSPV = right superior pulmonary vein; SVC = superior vena cava.

scarring (28-30). These pre-conditions will promote development of macro re-entrant tachycardia. In addition, coincident focal AT frequently arise in patients with CHD as low voltage areas result in diminishing electric coupling, thereby facilitating ectopic activity (21). This may explain why PVI and additional ablation of AT was highly effective in our cohort even when requiring reablation (**Figure 4**). Successful AF ablation in ACHD might be considered as a therapeutic cornerstone, as it will slow down the progression of the underlying CHD and the resulting symptoms of congestive heart failure.

PREDICTORS OF ARRHYTHMIA RECURRENCE. Owing to the efforts and successes in pediatric cardiac surgery, pediatric cardiac interventions, and intensive care medicine, the number of ACHD is constantly increasing. The presence or development of AF is one of the consequences to be "paid" for this pleasant process and our data demonstrate that AF ablation in ACHD is safe and effective. There is still a lack of evidence about pre-conditions and comorbidities that might predict the success of AF ablation. Recently, Ávila et al. (31) described the "natural" history, CHD-specific time intervals, and risk factors associated with AT in an ACHD cohort. Teuwen et al. (21) reported that AT frequently degenerates into AF with a mean age at onset of approximately 30 years in ACHD. In this context, 29.8% of our cohort underwent previous intervention for right-sided AT before the diagnosis of AF and AT was present or at least inducible in the majority of our patients (**Table 2, Figure 1**). In addition, some CHD lesions were found to be associated with the presence of AF (32). Furthermore, atrial dilatation (33,34) and hemodynamic parameter (34,35) have been demonstrated to increase the risk for AF or AT recurrence. As an example, the role of severe but temporal pressure and volume overload to develop or maintain LA enlargement as well as structural remodeling has been evaluated in highly trained endurance athletes suffering from AF (34). In contrast to ACHD, these athletes have long episodes of rest and do not have a permanent atrial volume load due to an underlying CHD lesion. A typical example is the atrial septal defect, which is often unrecognized and therefore treated late by corrective surgery or intervention with preceding decades of permanent volume overload (**Figure 3**). Arrhythmia recurrence was increased in patients with an elevated body mass index of >30 kg/m^2 ($p = 0.047$), PERS as initial arrhythmia ($p = 0.047$), fluoroscopy dose ($p = 0.033$), history of preoperative cyanosis ($p = 0.026$), and history of previous oral anticoagulation therapy ($p = 0.002$). The discrimination of risk factors for AF in ACHD may also allow for improved counseling, more targeted screening, and earlier detection. One may speculate that our data indicate to perform catheter AF ablation in ACHD at a relatively early stage of disease progression and irrespective of the underlying lesion, as freedom from

FIGURE 4 Example of a Reablation Procedure



Patient-specific example of a reablation procedure in a 34-year-old man with post-surgical complex congenital heart disease suffering from recurrent atrial fibrillation after initial pulmonary vein isolation. The 3-dimensional reconstruction demonstrates widespread low-voltage areas predominantly in the **(A)** posterior (posterior-anterior view) and **(B)** anterior left atrial wall (right anterior oblique view), as well as biatrial dilatation (left atrial volume: 197 ml; right atrial volume: 168 ml) due to long-lasting preoperative volume and pressure overload. **(A-E)** Reisolation **(red dots)** of the left-sided pulmonary veins was performed after previous identification of the right- and left-sided pulmonary vein ostia **(white dots).** Afterward, left atrial tachycardia was induced and successfully ablated performing an anterior line connecting the low-voltage areas with the mitral annulus (MA) and the right superior pulmonary vein: **(B)** right anterior oblique view, **(C)** left anterior oblique view, **(D)** right lateral view. **(E)** In addition, typical atrial flutter was induced and successfully treated with right-sided ablation of the cavotricuspid isthmus. Right atrial incision for heart-lung machine support during corrective surgery is visualized in the right atrium based on a circumscribed low-voltage area. *SVC. Abbreviations as in Figure 3.

AF/AT recurrence was achieved in a high proportion of patients across all types of ACHD lesions (Figure 1).

SAFETY AND COMPLICATIONS PERFORMING AF ABLATION IN ACHD. Previous studies reported major complications in patients undergoing catheter ablation for AF in up to 5% in a population with an average age of 60 years (36,37) and Saguner et al. (38) reported an incidence of 4.9% in a relatively young cohort. In our cohort, the procedure-related rate for major complications was 1.8% for the index procedure and 1% when considering all ablation procedures. AF ablation in ACHD is safe when performed at a tertiary referral electrophysiology center incorporating cardiologists with profound expert knowledge in ACHD and when ablations are performed by experienced and skilled investigators with long-term experience in both AF ablation and ablation of complex atrial arrhythmias. An increased rate of post-ablation PV stenosis as reported previously in younger patients (38) has not been observed. However, when performing AF ablation in younger patients, special attention should be given to perform ablation well outside of the PV to prevent PV stenosis. Focusing on the long-term follow-up, there is also evidence that our approach to adopt the regimen for oral anticoagulation from non-ACHD patients is feasible and safe. In patients with LAA isolation due to extensive ablation, the risk for thromboembolic complications is elevated and the rate of

reconnection and the related function is not clear (39,40). Therefore, these patients require intensified monitoring and implantation of a LAA closure device should be considered.

STUDY LIMITATIONS. Although this is currently the largest study reporting the long-term outcome of AF ablation in ACHD, patient numbers were relatively low over the long observation period. In addition, ACHD represent a very heterogeneous cohort due to multiple different structural lesions and few patients with the most severe lesions. However, it has to be considered that most severe lesions are certainly still rare in adulthood. A follow-up based on Holter monitoring and clinical evaluation may underestimate the real incidence of AF recurrence, particularly as AF regression and symptom improvement after ablation bear the potential for under-recognition of symptomatic AF episodes.

CONCLUSIONS

AF ablation strategies established in patients with structural normal hearts can be transferred to the inhomogeneous ACHD population with comparable safety and efficacy. Different types of congenital cardiac malformations with variant residue and sequelae are giving rise to heterogeneous arrhythmogenic pre-conditions, which may account for the trend toward a higher reablation rate. AF ablation in ACHD can achieve remarkable mid- to long-term results but should be reserved to dedicated centers with profound specialization in ACHD.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: AF is an emerging arrhythmia in ACHD. Evidence is lacking regarding individual risk stratification, ablation strategies, and long-term follow-up after AF ablation in ACHD. Predominantly, operators have transferred ablation approaches, including PVI, connecting linear lesion sets to the left-sided mitral isthmus, and cavotricuspid isthmus ablation, and no reliable data currently exist for substrate-based ablation approaches. Therefore, this study aimed to evaluate the impact, safety, and efficacy of AF ablation in ACHD transferring AF ablation strategies from patients without cardiac anomalies to ACHD.

TRANSLATIONAL OUTLOOK: AF ablation strategies established in patients with structurally normal hearts can be transferred to the inhomogeneous ACHD population and can achieve remarkable mid- to long-term results. Different types of congenital cardiac malformations with variant heterogeneous and individual arrhythmogenic pre-conditions may account for the trend toward a higher reablation rate. AF ablation in ACHD might be considered as a therapeutic cornerstone and bears the potential to slow down the progression of the underlying CHD and the resulting symptoms.

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