Late development of intra-atrial reentrant tachycardia in lateral tunnel Fontan patients and the preventive role of prophylactic cryoablation

Young Hye Ryu, MD,[a] Mi Kyoung Song, MD, PhD,[a] Sang-Yun Lee, MD, PhD,[a] Gi Beom Kim, MD, PhD,[a] Yong Jin Kim, MD, PhD,[b] and Eun-Jung Bae, MD, PhD[a]

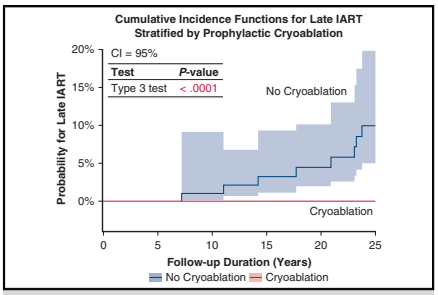
ABSTRACT

Objective: Intra-atrial reentrant tachycardia is an important late-onset complication in patients undergoing the Fontan procedure. However, the protective effects of prophylactic cryoablation against late-onset intra-atrial reentrant tachycardia are unclear. This study investigated the late development of intra-atrial reentrant tachycardia in patients undergoing the lateral tunnel Fontan procedure and the role of prophylactic cryoablation.

Methods: This was a single-center retrospective cohort study of patients who underwent the lateral tunnel Fontan procedure between 1988 and 2003. Univariate and multivariable competing risks regression models were used to determine the associations of prophylactic cryoablation and covariates with the outcomes of interest: late-onset intra-atrial reentrant tachycardia, all-cause mortality, and cardiovascular mortality.

Results: In total, 130 patients who underwent the lateral tunnel Fontan procedure, 30 of whom had undergone prophylactic cryoablation, were included in this study and followed up for a median of 23.6 years (interquartile range, 17.7-26.5). Intra-atrial reentrant tachycardia was identified in 14 patients (10.8%), none of whom underwent prophylactic cryoablation. The median Fontan-to-intra-atrial reentrant tachycardia time was 17.2 years (interquartile range, 11.1-23.1). Prophylactic cryoablation was protective against late-onset intra-atrial reentrant tachycardia ($P < .0001$) and cardiovascular mortality ($P < .0001$) in the type 3 test.

Conclusions: None of the patients who underwent prophylactic cryoablation developed late-onset intra-atrial reentrant tachycardia during a median follow-up time of 22.9 years. Our study demonstrated that prophylactic cryoablation was effective in preventing late-onset intra-atrial reentrant tachycardia and cardiovascular mortality in patients undergoing the lateral tunnel Fontan. (J Thorac Cardiovasc Surg 2023;■:1-10)



No patients with prophylactic cryoablation developed late IART for a median of 22.9 years.

CENTRAL MESSAGE

Prophylactic cryoablation was effective in preventing late-onset IART and cardiovascular mortality in patients who underwent the LT Fontan procedure.

PERSPECTIVE

IART is an important late-onset complication in patients undergoing the Fontan procedure. However, the protective effects of prophylactic cryoablation against late-onset IART are unclear. Our study revealed that prophylactic cryoablation in patients undergoing the LT Fontan procedure is feasible and effective in preventing late-onset IART and cardiovascular mortality.

See Commentary on page XXX.

CONG

Intra-atrial reentrant tachycardia (IART) is the most common type of tachyarrhythmia in patients undergoing the Fontan procedure and is directly associated with morbidity and mortality.[1-3] Atrial scarring from sutures during surgery and atrial remodeling after atrial dilatation predispose patients to atrial tachycardia. Sustained atrial tachyarrhythmia increases the risk of thrombosis and hemodynamic compromise and may lead to death.[2] The incidence of atrial tachyarrhythmia varies depending on the type of Fontan procedure and

From the [a]Department of Pediatrics, Seoul National University Children's Hospital, Seoul National University College of Medicine, Seoul, South Korea; and [b]Department of Thoracic and Cardiovascular Surgery, Sejong General Hospital, Bucheon, South Korea.

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Address for reprints: Eun-Jung Bae, MD, PhD, Department of Pediatrics, Seoul National University Children's Hospital, Pediatrics, Seoul National University College of Medicine, 101 Daehak-ro Jongno-gu, Seoul 03080, South Korea (E-mail: eunjbaek@snu.ac.kr).

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Abbreviations and Acronyms

BCPS = bidirectional cavopulmonary shunt
ECC = extracardiac conduit
EPS = electrophysiological study
IART = intra-atrial reentrant tachycardia
IQR = interquartile range
LT = lateral tunnel
VT = ventricular tachycardia

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follow-up duration.[2,4-10] Although early reports of the incidence of IART in patients undergoing the atriopulmonary Fontan reached 40%, recent advances in surgical techniques have reduced the rates to 10 to 20% in patients who underwent the lateral tunnel (LT) Fontan or extracardiac conduit (ECC) Fontan procedure.[6,11,12] Some centers prefer the ECC Fontan procedure to reduce the incidence of late-onset arrhythmia. However, contrary to expectations, reports on the incidence of arrhythmia between the 2 procedures are controversial; moreover, late stenosis associated with ECC is concerning.[13-17]

Modifications in surgical strategies have achieved a lower incidence of IART. However, more studies on IART preventive measures are needed. Because the surgical method involved the critical isthmus in LT Fontan, we hypothesized that prophylactic cryoablation between the right atriotomy line and the right atrioventricular valve would help prevent the formation of intra-atrial reentrant circuits that cause IART. Previous studies reported short-term results on prophylactic atrial incisions aimed at preventing IART. Although these studies demonstrated the feasibility and safety of interventional atrial incision, there was no significant decrease in the incidence of IART. Considering that intra-atrial circuits develop over a long period, long-term results are important to establish the effectiveness of prophylactic intervention. Thus, our study focused on investigating late-onset IART in patients undergoing the LT Fontan and the long-term protective effects of prophylactic cryoablation.

MATERIAL AND METHODS

Patient Selection and Data Collection

This was a single-center retrospective cohort study of patients with congenital heart disease who underwent the LT Fontan procedure at Seoul National University Children's Hospital between January 1988 and December 2003, which was the period when the LT Fontan was the preferred Fontan procedure at our center. After the development of the prophylactic arrhythmia surgery in August 1997, all consecutive patients undergoing the LT Fontan received prophylactic cryoablation. Patients with insufficient data or early mortality (death within 3 months after the Fontan procedure) were excluded from the study. Clinical records, surgical records, prescription records, electrocardiograms, 24-hour Holter monitor records, treadmill tests, cardiopulmonary exercise tests, echocardiograms, cardiac catheterization reports, electrophysiological study (EPS) reports, and imaging studies, including computed tomography and magnetic resonance imaging, were reviewed. For post-Fontan procedure surveillance, patients had 12-lead electrocardiograms every year and 24-hour Holter monitoring every 2 to 3 years. Electrophysiological studies were performed in patients with clinical symptoms or suspected arrhythmia. Data were collected until May 2022. In total, 138 patients underwent the LT Fontan procedure; 4 patients with insufficient medical records and 4 patients with early death were excluded. All excluded patients had undergone surgery without prophylactic cryoablation before June 1998.

This study was approved by the Institutional Review Board of the Seoul National University Hospital, which waived the requirement for individual consent because of the retrospective nature of the study (No.: 2208-185-1355; date of approval: September 9, 2022).

Definitions

Late-onset IART was defined as sustained macroreentrant atrial tachycardia, as shown by a 12-lead electrocardiogram, transesophageal electrogram, or 24-hour Holter monitoring more than 3 months after the Fontan procedure. Induced IART was defined as IART induced during an EPS. Sinus node dysfunction was defined as a sinus pause of 3 seconds or more with or without escape beats, predominant junctional rhythm, or sinus bradycardia 2 standard deviations lower than the normal range, according to the patient's age. Ventricular function was determined using echocardiography and magnetic resonance imaging data, including ejection fraction and tissue Doppler imaging. Arterial desaturation was defined as percutaneous oxygen saturation less than 89%. Patients possessing 2 well-formed ventricles of adequate size were categorized as having "2 well-formed ventricles" when divided according to single ventricle morphology.

Surgical Method of Prophylactic Cryoablation

Most patients in the prophylactic cryoablation group underwent a novel prophylactic arrhythmia surgery developed in August 1997, as shown in Figure 1. During the LT Fontan procedure, the right atriotomy line was extended to the coronary sinus. Cryoablation between the right atrioventricular valve and right atriotomy incision line was performed with a 10-mm probe at −60 to −80 °C for approximately 2 minutes. An intra-atrial baffle with a Gore-Tex patch using the sandwich technique was used to reduce the atrial suture line. A 16- to 18-mm Gore-Tex tube was cut in half and curved to form a cylinder-shaped Fontan pathway baffle. This was incorporated between the 2 atriotomy edges and sutured. The lateral aspect of the Fontan baffle was anterior to the crista terminalis. Two patients who underwent the LT Fontan procedure before August 1997 had received prophylactic cryoablation between the right atriotomy line and the right atrioventricular valve: 1 patient during atrioventricular valve replacement and 1 patient during pulmonary artery embolectomy.

Outcomes and Intervention

The primary outcome was late-onset IART. Secondary outcomes were all-cause mortality and cardiovascular mortality. This study focused on the effects of prophylactic cryoablation and risk analysis of other covariates associated with outcomes. The covariates included age at the time of Fontan procedure, sex, type of single ventricle, heterotaxia, and operations other than the Fontan procedure.

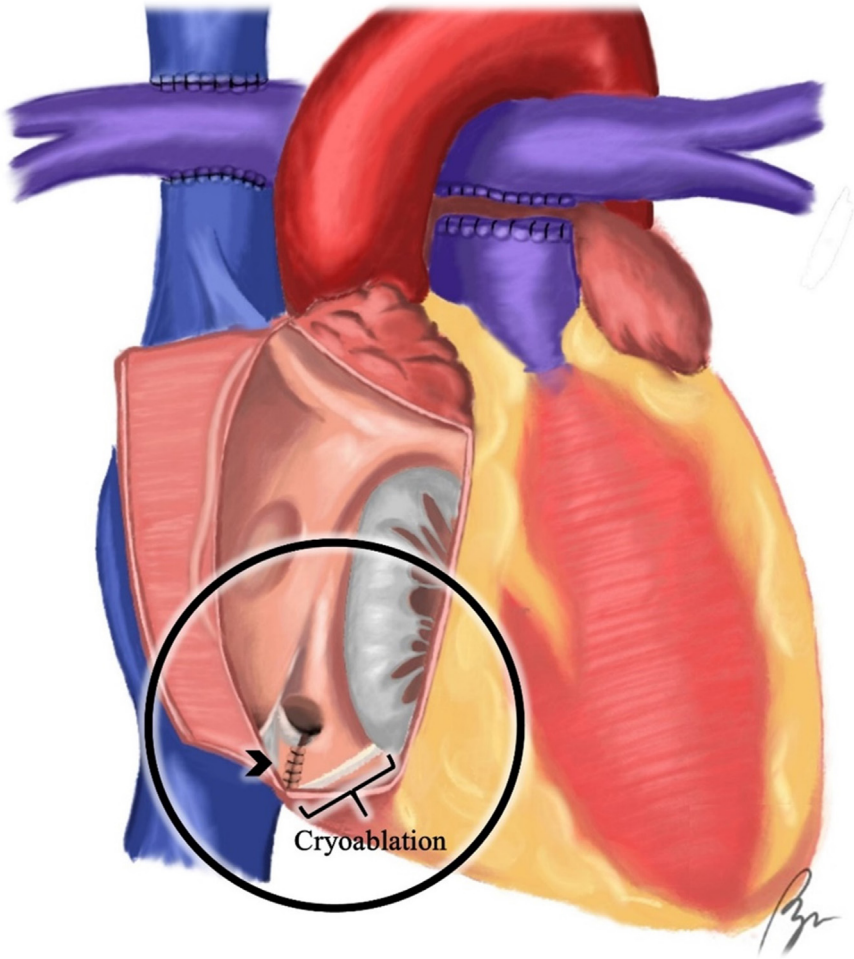


FIGURE 1. Prophylactic arrhythmia surgery method. Prophylactic arrhythmia surgery was performed by extending the right atriotomy line to the coronary sinus (*arrowhead*), performing cryoablation between the right AVV and the right atriotomy line (*curly bracket*), creating an intra-atrial baffle using the sandwich technique, and placing the lateral aspect of the Fontan baffle anterior to the crista terminalis. *AVV*, Atrioventricular valve.

Statistical Analysis

Patient characteristics were summarized using medians and interquartile ranges (IQRs) for continuous variables and numbers and percentages for categorical variables. Baseline characteristics of patients with and without prophylactic cryoablation were compared using the nonparametric Mann–Whitney *U* test for continuous variables and Fisher exact test for categorical variables. By using the Fisher exact test, the prevalence of tachyarrhythmia was compared between patients with and without prophylactic cryoablation.

Univariate and multivariable competing risks regression models were used to determine the associations of prophylactic cryoablation and covariates with the outcomes of interest, with 95% CIs. Possible confounders such as age at the time of Fontan procedure, sex, single ventricle morphology, and heterotaxia were considered. Variables for multivariable models were selected with the stepwise method. Because death and incidence of IART are competing outcomes, the Fine-Gray proportional hazard model for competing risks was used.[18] Because of the long follow-up, patients were susceptible to encountering competing end states. The incorporation of these competing events into the analysis thus becomes crucial to correctly determine the absolute risk of a time-to-event outcome of interest. Consequently, instead of traditional survival analysis methods, a competing risks analysis was implemented in the present study. To calculate the hazard ratios, the cause-specific hazard was calculated. Cumulative incidence functions were determined. The proportional hazards assumption was checked using survival curves and the log minus log of the subdistribution hazard. The significance of the main effect on the Fine-Gray model procedure was assessed using the type 3 test. Statistical analyses were performed using SAS software (version 9.4; SAS Institute Inc).

RESULTS

Baseline Patient Characteristics

The demographic and clinical characteristics of the 130 participants are shown in Table 1. Thirty patients underwent prophylactic cryoablation of the right atrial critical isthmus: 28 patients during the Fontan procedure and 2 patients during therapeutic surgery after the Fontan operation. The median age at the time of Fontan procedure was 2.3 years (IQR, 1.6-3.4). Thirty-seven patients (28%) had heterotaxy syndrome (19.2% right isomerism and 9.2% left isomerism). Besides a history of a bidirectional cavopulmonary shunt (BCPS), atrioventricular valve repair, and atrial

TABLE 1. Baseline demographic and clinical characteristics

Demographics and clinical variables	All patients	No cryoablation	Cryoablation	*P* value
Total, N (%)	130 (100)	100 (76.92)	30 (23.08)	
Age at Fontan (y), median (IQR)	2.3 (1.6-3.4)	2.3 (1.6-3.4)	2.2 (1.6-3.8)	
Sex (male), N (%)	82 (63.1)	65 (65.0)	17 (56.7)	.518
Type of single ventricle, N (%)				.186
Right	76 (58.5)	61 (61.0)	15 (50.0)	
Left	39 (30.0)	26 (26.0)	13 (43.3)	
2 Well-formed	15 (11.5)	13 (13.0)	2 (6.7)	
Heterotaxia, N (%)				.317
None	93 (71.5)	68 (68.0)	25 (83.3)	
Right isomerism	25 (19.2)	21 (21.0)	4 (13.3)	
Left isomerism	12 (9.2)	11 (11.0)	1 (3.3)	
Initial diagnosis, N (%)				.326
Common inlet ventricle (unbalanced AVSD)	32 (24.6)	26 (26.0)	6 (20.0)	
Double inlet ventricle	35 (26.9)	25 (25.0)	10 (33.3)	
Tricuspid atresia	25 (19.2)	18 (18.0)	7 (23.3)	
Mitral atresia	21 (16.2)	19 (19.0)	2 (6.7)	
Complicated DORV	3 (2.3)	1 (1.0)	2 (6.7)	
Complicated TGA	5 (3.9)	4 (4.0)	1 (3.3)	
Pulmonary atresia with IVS	9 (6.9)	7 (7.0)	2 (6.7)	
Other operations, N (%)				
Previous BT shunt	47 (36.2)	35 (35.0)	12 (40.0)	.667
Previous PA banding	20 (15.4)	14 (14.0)	6 (20.0)	.403
Previous BCPS	**41 (31.5)**	**22 (22.0)**	**19 (63.3)**	**<.0001**
TAPVR repair	5 (3.9)	4 (4.0)	1 (3.3)	1
AVV repair	**4 (3.1)**	**1 (1.0)**	**3 (10.0)**	**.038**
Atrial septectomy	**56 (43.1)**	**37 (37.0)**	**19 (63.3)**	**.013**

Bold indicates statistically significant values. *N*, Number; *IQR*, interquartile range; *AVSD*, atrioventricular septal defect; *DORV*, double outlet right ventricle; *TGA*, transposition of the great arteries; *IVS*, intact ventricular septum; *BT*, Blalock-Taussig; *PA*, pulmonary artery; *BCPS*, bidirectional cavopulmonary shunt; *TAPVR*, total anomalous pulmonary venous return; *AVV*, atrioventricular valve.

septectomy, there was no significant difference in baseline characteristics between patients who underwent prophylactic cryoablation and patients who did not.

Long-Term Clinical Outcomes

The long-term clinical outcomes of all patients are summarized in Table 2. The median follow-up period for all patients was 23.6 years (IQR, 17.7-26.5). The median follow-up time was 22.9 years in patients who underwent cryoablation and 25.0 years in those who did not undergo cryoablation ($P = .051$). Of the 130 patients in this study, 53 (40.7%) had at least 1 tachyarrhythmic event that included IART, ventricular tachycardia (VT), sustained supraventricular tachycardia other than IART (atrioventricular reentrant tachycardia, atrioventricular node reentrant tachycardia, and junctional tachycardia), atrial fibrillation, nonsustained atrial tachycardia, and nonsustained VT. The most common tachyarrhythmia was nonsustained atrial tachycardia (n = 44, 33.9%), followed by supraventricular tachycardia other than IART (n = 23, 17.7%), IART (n = 14, 10.8%), nonsustained VT (n = 12, 9.2%), atrial fibrillation (n = 4, 3.1%), and VT (n = 1, 0.8%). Between the patients who underwent prophylactic cryoablation and the patients who did not, only IART incidence was significantly different ($P = .039$) (Table 2). Eighteen patients (13.9%) were diagnosed with sinus node dysfunction, and 19 patients (14.6%) underwent pacemaker implantation. Four patients (3.1%) had protein-losing enteropathy, 32 patients (24.6%) had ventricular dysfunction, 9 patients (6.9%) had moderate-to-severe atrioventricular valve regurgitation, 49 patients (37.7%) had desaturation with percutaneous oxygen saturation less than 89%, and 14 patients (10.8%) died.

Late-Onset Intra-Atrial Reentrant Tachycardia and Induced Intra-Atrial Reentrant Tachycardia

Fourteen patients (10.8%) developed late-onset IART at a median of 17.2 years (IQR, 11.1-23.1) after undergoing Fontan surgery. All patients were treated with antiarrhythmic medications. One patient underwent radiofrequency catheter ablation, and 2 patients underwent the

TABLE 2. Long-term clinical outcomes in lateral tunnel Fontan patients

Clinical variables	All patients	No cryoablation	Cryoablation	*P* value
Total, N (%)	130 (100)	100 (76.92)	30 (23.08)	
Follow-up time after Fontan (y), median (IQR)	23.6 (17.7-26.5)	25.0 (16.8-27.0)	22.9 (21.6-23.4)	.051
Tachyarrhythmia, N (%)	53 (40.7)	45 (45.0)	8 (26.7)	.091
IART	**14 (10.8)**	**14 (14.0)**	**0 (0.0)**	**.039**
SVT other than IART*	23 (17.7)	20 (20.0)	3 (10.0)	.402
AF	4 (3.1)	4 (4.0)	0 (0.0)	.573
VT	1 (0.8)	1 (1.0)	0 (0.0)	1
NSAT	44 (33.9)	38 (38.0)	6 (20.0)	.081
NSVT	12 (9.2)	10 (10.0)	2 (6.7)	.732
Sinus node dysfunction, N (%)	18 (13.9)	12 (12.0)	6 (20.0)	.364
Pacemaker implantation, N (%)	19 (14.6)	14 (14.0)	5 (16.7)	.77
Protein losing enteropathy, N (%)	4 (3.1)	4 (4.0)	0 (0.0)	.573
Ventricular dysfunction, N (%)	32 (24.6)	27 (27.0)	5 (16.7)	.416
Moderate-to-severe AVVR, N (%)	9 (6.9)	7 (7.0)	2 (6.7)	1
Desaturation (SpO_2 <89%), N (%)	49 (37.7)	40 (40.0)	9 (30.0)	.268
All-cause death, N (%)	14 (10.8)	11 (11.0)	3 (10.0)	1
Cardiovascular death, N (%)†	6 (4.6)	6 (6.0)	0 (0.0)	.335

Bold indicates statistically significant values. *N*, Number; *IQR*, interquartile range; *IART*, intra-atrial reentrant tachycardia; *SVT*, supraventricular tachycardia; *AF*, atrial fibrillation; *VT*, ventricular tachycardia; *NSAT*, nonsustained atrial tachycardia; *NSVT*, nonsustained ventricular tachycardia; *AVVR*, atrioventricular valve regurgitation; SpO_2, percutaneous oxygen saturation. *SVT other than IART includes paroxysmal supraventricular tachycardia, ectopic atrial tachycardia, and junctional tachycardia. †Cardiovascular death includes death due to heart failure, sudden cardiac death, and cardioembolic stroke.

Maze procedure. Four patients (28.6%) had left isomerism, 4 patients (28.6%) had right isomerism, and the remaining patients did not have heterotaxy syndrome (n = 6, 42.8%). The details of patient information are provided in Table E1. Patients had adequate control of IART, with a mean IART clinical severity score of 4.6 of a total of 12.[19] The median age of death of the 5 patients who had died at the last follow-up was 24.2 years (IQR, 20.9-26.7).

The competing risks regression model showed that age more than 4 years at the time of the Fontan procedure, 2 well-formed ventricles, and left isomerism were significantly associated with late-onset IART development in the univariate analysis, but only 2 well-formed ventricle morphology was significant in multivariable analysis (adjusted hazard ratio, 5.39) (Table 3). Cumulative incidence functions for late-onset IART stratified by prophylactic cryoablation revealed that none of the patients who underwent prophylactic cryoablation had a late-onset IART event (Figure 2, *A*). The type 3 test revealed that prophylactic cryoablation alone significantly prevented late-onset IART in multivariable analysis.

Forty-two patients who received the LT Fontan underwent EPS at a median of 7.6 years (IQR, 6.1-10.9) after the Fontan procedure, and IART was induced in 19 patients. Of the 19 patients with induced IART, 4 patients had a previous IART event and 1 patient developed clinical IART 5 years after the study. The predictability of late-onset clinical IART by induction study in the short term was 26.3% at a median follow-up of 23.6 years. In 1 patient with a previous IART event, IART was not induced in an EPS 10 years after the event. Of the patients with induced IART, 3 patients underwent prophylactic cryoablation.

Late All-Cause Mortality

During the median follow-up period of 23.6 years, 14 patients (10.8%) died. The median age at the time of death was 22.8 years. The main causes of death were heart failure (n = 4, 28.6%) and major bleeding (n = 5, 35.7%). Other causes were end-stage cancer (n = 1, 7%), septic shock (n = 1, 7%), sudden cardiac death (n = 1, 7%), cardioembolic stroke (n = 1, 7%), and postoperative hypoxic-ischemic brain damage (n = 1, 7%) (Table E2).

In the competing risks regression model, left isomerism was significantly associated with mortality in multivariable analysis (adjusted hazard ratio, 5.94) (Table 4). The type 3 test results revealed the type of single ventricle and left isomerism to be significantly associated with all-cause mortality.

Late Cardiovascular Mortality

Of the 14 patients who died, 6 (4.6%) died of cardiovascular conditions. Four patients died of heart failure, 1 patient died of sudden cardiac death, and 1 patient died of

TABLE 3. Competing risks regression models for late-onset intra-atrial reentrant tachycardia

Variables	Events	Incidence (per 1000 person-y)	Univariate HR (95% CI)	Univariate Type 3 test *P* value	Multivariable aHR (95% CI)	Multivariable Type 3 test *P* value
Prophylactic cryoablation				**<.0001**		**<.0001**
Not performed	14	6.39	1.00 (ref)		1.00 (ref)	
Performed	0	0.00	NA		NA	
Age at Fontan (y)				**.025**		.070
≤4	7	3.14	1.00 (ref)		1.00 (ref)	
>4	**7**	**11.69**	**4.32 (1.20-15.54)**		3.59 (0.90-14.34)	
Sex				.906		
Female	4	3.91	1.00 (ref)			
Male	10	5.53	1.09 (0.27-4.36)			
Type of single ventricle				**.004**		.056
Right	9	5.36	1.00 (ref)		1.00 (ref)	
Left	1	1.15	0.52 (0.06-4.62)		0.66 (0.08-5.50)	
2 Well-formed	**4**	**14.14**	**6.84 (1.83-25.56)**		**5.39 (1.02-28.50)**	
Heterotaxia				**.027**		.981
None or right isomerism	10	2.58	1.00 (ref)		1.00 (ref)	
Left isomerism	**4**	**15.54**	**4.31 (1.19-15.64)**		0.98 (0.17-5.70)	
Other operations						
Previous BT shunt	6	5.76	2.29 (0.62-8.49)	.216		
Previous PA banding	2	4.82	0.72 (0.10-5.49)	.752		
Previous BCPS	2	2.40	0.32 (0.04-2.46)	.272		
TAPVR repair	0	0.00	NA	**<.0001**		
AVV repair	0	0.00	NA	**<.0001**		
Atrial septectomy	3	2.37	0.37 (0.08-1.74)	.206		

Bold indicates statistically significant values. *HR*, Hazard ratio; *aHR*, adjusted hazard ratio; *NA*, not available; *BT*, Blalock-Taussig; *PA*, pulmonary artery; *BCPS*, bidirectional cavopulmonary shunt; *TAPVR*, total anomalous pulmonary venous return; *AVV*, atrioventricular valve; *IART*, intra-atrial reentrant tachycardia.

massive cardioembolic stroke (Table E2). The competing risks analysis revealed prophylactic cryoablation to be significantly protective against cardiovascular mortality in the type 3 test (Table 5). Cumulative incidence functions for cardiovascular mortality stratified by prophylactic cryoablation revealed that none of the patients who underwent

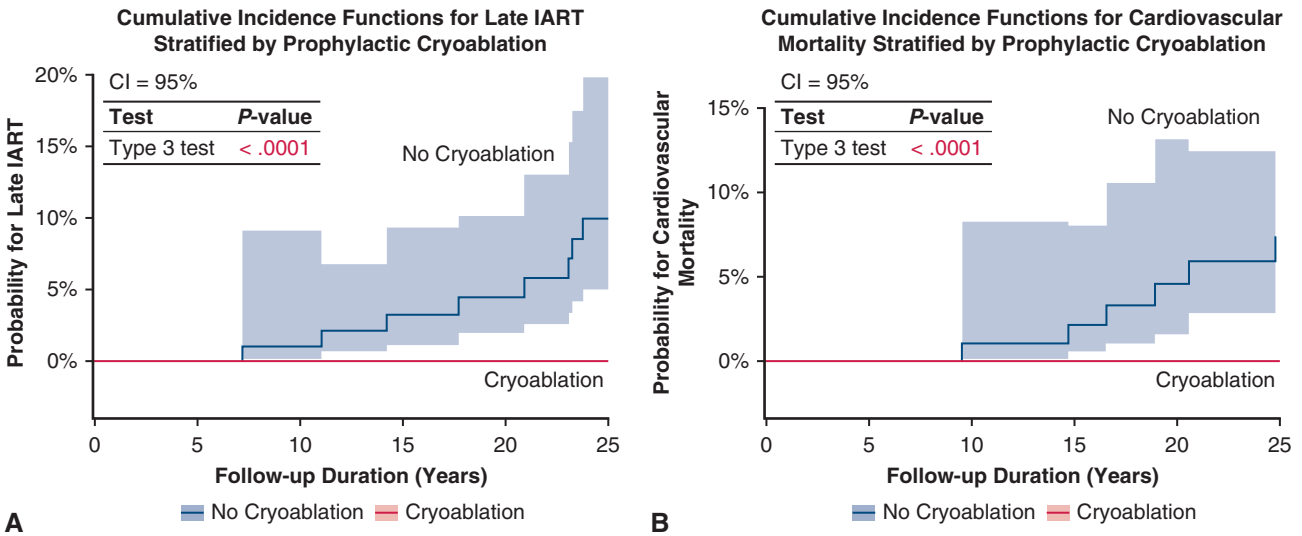


FIGURE 2. Cumulative incidence functions stratified by prophylactic cryoablation. A, Cumulative incidence functions for late-onset IART stratified by prophylactic cryoablation revealed that none of the patients who underwent prophylactic cryoablation had a late-onset IART event. B, Cumulative incidence functions for cardiovascular mortality stratified by prophylactic cryoablation revealed that prophylactic cryoablation was a significant protective factor. *IART*, Intra-atrial reentrant tachycardia.

TABLE 4. Competing risks regression models for all-cause mortality

Variables	Death events	Incidence (per 1000 person-y)	Univariate HR (95% CI)	Univariate Type 3 test *P* value	Multivariable aHR (95% CI)	Multivariable Type 3 test *P* value
Prophylactic cryoablation				.446		
Not performed	11	5.02	1.00 (ref)			
Performed	3	4.70	1.84 (0.39-8.76)			
Age at Fontan (y)				.397		
≤4	10	4.48	1.00 (ref)			
>4	4	6.68	1.77 (0.47-6.59)			
Sex				.561		
Female	5	4.88	1.00 (ref)			
Male	9	4.98	0.68 (0.19-2.47)			
Type of single ventricle				**<.0001**		**<.0001**
Right	11	6.55	1.00 (ref)		1.00 (ref)	
Left	3	3.46	0.58 (0.13-2.70)		0.67 (0.15-3.08)	
2 Well-formed	0	0.00	NA		NA	
Heterotaxia				**.027**		**.0009**
None or right isomerism	10	3.88	1.00 (ref)		1.00 (ref)	
Left isomerism	**4**	**15.54**	**4.59 (1.26-16.65)**		**5.94 (1.56-22.65)**	
Other operations						
Previous BT shunt	2	1.92	0.22 (0.03-1.76)	.154		
Previous PA banding	2	4.82	0.79 (0.10-6.24)	.821		
Previous BCPS	5	6.01	1.29 (0.33-5.15)	.715		
TAPVR repair	2	22.56	3.83 (0.43-34.20)	.230		
AVV repair	1	12.16	4.79 (0.52-44.54)	.168		
Atrial septectomy	3	2.37	0.46 (0.10-2.21)	.330		

Bold indicates statistically significant values. *HR*, Hazard ratio; *aHR*, adjusted hazard ratio; *NA*, not available; *BT*, Blalock-Taussig; *PA*, pulmonary artery; *BCPS*, bidirectional cavopulmonary shunt; *TAPVR*, total anomalous pulmonary venous return; *AVV*, atrioventricular valve.

prophylactic cryoablation had died of a cardiovascular cause (Figure 2, *B*).

DISCUSSION

This study aimed to investigate late-onset IART in patients who underwent the LT Fontan and evaluate the long-term effects of prophylactic cryoablation. During a median follow-up of 22.9 years (IQR, 21.6-23.4) and a total of 638.4 person-years, none of the patients who underwent prophylactic cryoablation developed late-onset IART. Prophylactic cryoablation has been proven to be safe and effective in preventing late-onset IART and cardiovascular mortality in patients undergoing the LT Fontan. To the best of our knowledge, this is the first long-term study on the effects of interventional prophylactic cryoablation in preventing late-onset IART.

Late-onset IART has a significant impact on the morbidity and mortality of patients who undergo the Fontan procedure.[1,2,4] Although management is crucial, the complex morphology of the underlying congenital heart disease and anatomic changes after a series of operations make transcatheter ablation of the intra-atrial circuit difficult with a high chance of failure. Baffle puncture is necessary in many cases; however, factors such as altered anatomy, different alignments, and baffle calcification may make the puncture unfeasible or dangerous. For these reasons, a few centers have proposed surgical interventions during the Fontan procedure to prevent the development of intra-atrial circuits.[20,21] The cavotricuspid isthmus-dependent intra-atrial circuit is the main cause of late-onset IART in patients undergoing LT and ECC Fontan.[22] Previous studies have designed a simple method to interrupt the potential pathway of an intra-atrial circuit by creating a linear incision and applying cryoablation between the tricuspid annulus and the suture line of the LT, based on canine Fontan models.[20,21,23] Although proven safe, only short- and mid-term follow-up results have been reported. For other types of arrhythmia, there is no simple and effective prophylactic procedure that can be performed during the Fontan operation.

In 2004, Collins and colleagues[20] reported short-term results of a modified Fontan procedure for IART prophylaxis. The study was a prospective, randomized, double-blind study involving 42 patients with a mean follow-up period of 2.4 years. The study demonstrated the feasibility and safety of interventional atrial incision. In 2016, Law and colleagues[21] published midterm results on the effects of a strategic incision to prevent IART in the right atrium. The

TABLE 5. Competing risks regression models for cardiovascular mortality

Variables	Death events	Incidence (per 1000 person-y)	Univariate HR (95% CI)	Univariate Type 3 test *P* value	Multivariable aHR (95% CI)	Multivariable Type 3 test *P* value
Prophylactic cryoablation				**<.0001**		**<.0001**
Not performed	6	2.74	1.00 (ref)		1.00 (ref)	
Performed	0	0.00	NA		NA	
Age at Fontan (y)				.511		
≤4	4	1.79	1.00 (ref)			
>4	2	3.34	1.76 (0.33-9.39)			
Sex				.894		
Female	2	1.95	1.00 (ref)			
Male	4	2.21	1.12 (0.21-5.91)			
Type of single ventricle				**<.0001**		.231
Right	5	2.98	1.00 (ref)		1.00 (ref)	
Left	1	1.15	0.40 (0.05-3.58)		0.36 (0.07-1.90)	
2 Well-formed	0		NA		NA	
Heterotaxia				.588		
None or right isomerism	5	1.94	1.00 (ref)			
Left isomerism	1	3.88	1.82 (0.21-16.00)			
Other operations						
Previous BT shunt	1	0.96	0.34 (0.04-2.86)	.322		
Previous PA banding	1	2.41	1.18 (0.14-9.94)	.877		
Previous BCPS	3	3.61	2.46 (0.53-11.53)	.253		
TAPVR repair	1	11.28	5.73 (0.61-53.66)	.126		
AVV repair	0	0.00	NA	**<.0001**		
Atrial septectomy	1	0.79	0.26 (0.03-2.09)	.203		

Bold indicates statistically significant values. *HR*, Hazard ratio; *aHR*, adjusted hazard ratio; *NA*, not available; *BT*, Blalock-Taussig; *PA*, pulmonary artery; *BCPS*, bidirectional cavopulmonary shunt; *TAPVR*, total anomalous pulmonary venous return; *AVV*, atrioventricular valve.

study was also a randomized controlled clinical trial of 134 participants, with follow-up results for 114 patients after a median of 8.2 years. The results showed no statistically significant difference in the incidence of IART between the 2 groups possibly because of the indeterminate duration of follow-up.

Our center previously published the midterm results of a novel prophylactic arrhythmia surgery at the initial LT Fontan procedure developed in August 1997.[24] The prophylactic method was slightly different from that used in previous studies, which used incisions only from the atriotomy site to the right atrioventricular valve. Under the impression that injury to the crista terminalis precipitated the abnormal conduction, the lateral aspect of the Fontan baffle was placed anterior to the crista terminalis. In addition, a sandwich technique using a Gore-Tex patch was used to reduce the extensive atrial suture line. The present study reports the long-term significance of prophylactic cryoablation in patients undergoing the LT Fontan with a median follow-up of 23.6 years, which, to the best of our knowledge, is the longest reported follow-up result. We believe this study may serve as a reference for preventive interventions in Fontan procedures.

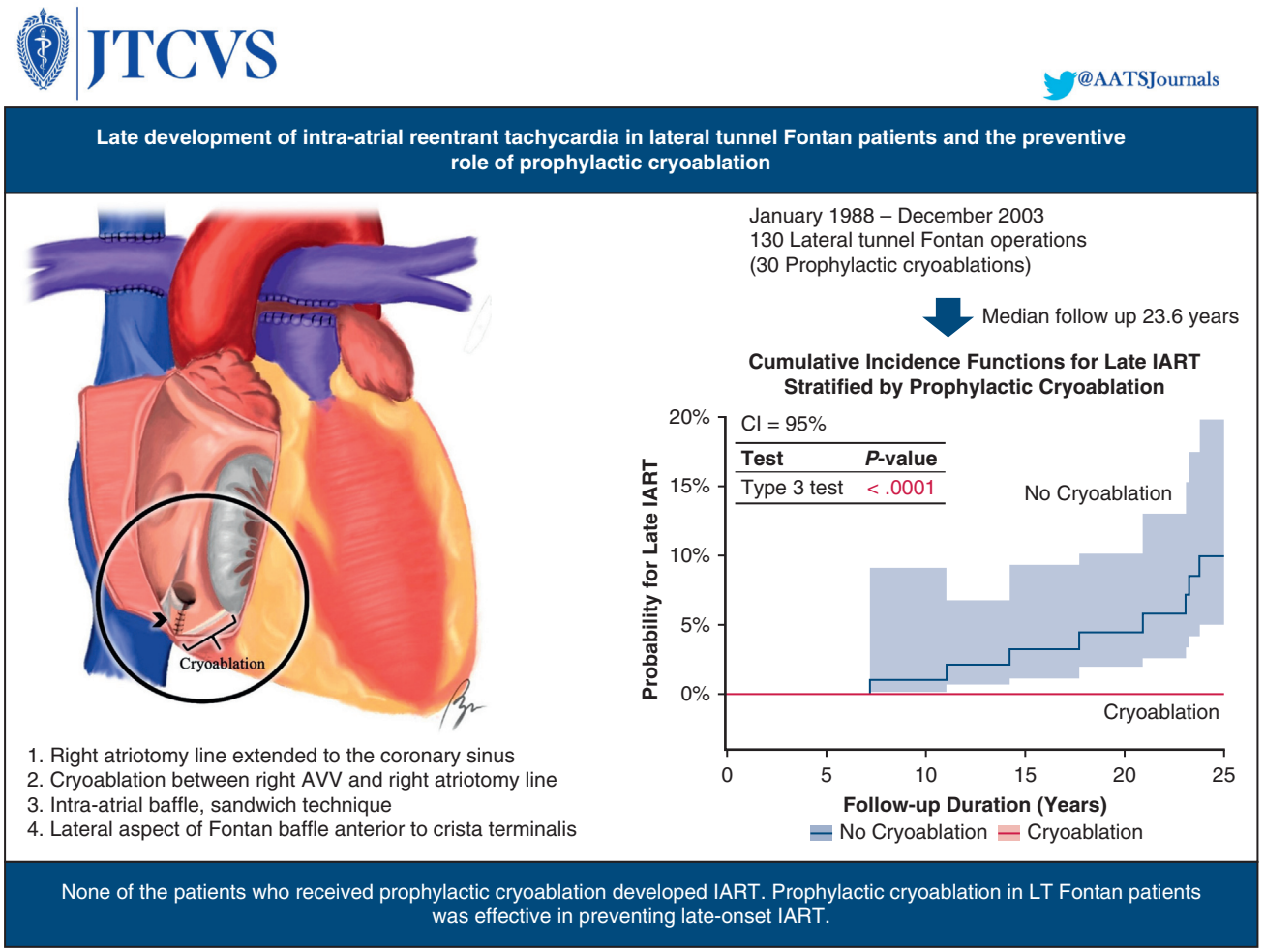
The competing risks analysis revealed that having a morphology of 2 well-formed ventricles was significantly associated with late-onset IART development. Although significant only in univariate analysis, age greater than 4 years at the time of the Fontan procedure and left isomerism were associated with late-onset IART. Efforts made to perform the Fontan procedure at an appropriate age may help prevent late-onset IART. In addition, prophylactic cryoablation may be more important in left isomerism because of the unfeasible anatomy for catheter intervention due to inferior vena cava interruption.

The Fontan procedure has evolved over the years, with most institutions performing the LT or ECC Fontan procedure. Although many studies have compared the outcomes of both surgeries, debates on the optimal Fontan procedure remain inconclusive because of controversial results.[15] Many centers prefer the ECC Fontan procedure because of its likelihood of reducing the incidence of arrhythmia; however, recent reports of arrhythmia occurrence were not significantly different between the 2 techniques. In addition, it is more difficult to treat arrhythmia in patients undergoing the ECC Fontan with challenging transvenous catheter access.[25] Moreover, with reports of late complications in patients undergoing the ECC Fontan, such as conduit stenosis, the LT Fontan procedure is

a potential alternative.[16,17] With interventional prophylactic cryoablation to prevent late-onset IART, the LT Fontan may be preferred from an arrhythmia perspective.

Study Limitations

This study was limited by its single-center retrospective design. The relatively small number of patients who underwent cryoablation may have contributed to the limitation of this study. However, because this study was conducted at a single center, 109 (83.8%) LT Fontan procedures and all prophylactic arrhythmia surgeries were performed by 1 surgeon, which reduced the errors and confounding effects of the influence of the operator. Furthermore, prophylactic arrhythmia surgery was introduced in 1997, resulting in different time periods between the group that underwent prophylactic cryoablation and the group that did not. Specifically, the Fontan procedure dates of the prophylactic cryoablation group ranged from 1997 to 2003, whereas the dates of the no-prophylactic cryoablation group ranged from 1988 to 2003. This temporal difference introduces a period effect that can potentially confound the analysis. Factors such as surgical experience and advancements in postoperative care, which can affect patient outcomes and mortality rates, are associated with this era effect. To mitigate this issue, one strategy used was the exclusion of early mortality within 3 months after surgery. Additionally, another manifestation of this era effect is the more frequent use of the BCPS in the prophylactic cryoablation group. Patients who did not undergo BCPS may have had an extended period of volume overload, potentially increasing the risk of arrhythmia. Although the previous use of BCPS could have introduced confounding variables, the competing risks regression models showed that BCPS did not impact IART occurrence.



*AVV, atrioventricular valve; CI, confidence interval; IART, intra-atrial reentrant tachycardia; LT Fontan, lateral tunnel Fontan

FIGURE 3. This was a retrospective single-center cohort study of 130 patients who underwent the LT Fontan procedure between 1988 and 2003. Of these patients, 30 underwent prophylactic cryoablation. None of the patients who underwent prophylactic cryoablation developed late-onset IART during the median follow-up time of 22.9 years. Prophylactic cryoablation in patients undergoing the LT Fontan was effective in preventing late-onset IART. *AVV*, Atrioventricular valve; *IART*, intra-atrial reentrant tachycardia; *LT*, lateral tunnel.

CONCLUSIONS

None of the patients who underwent prophylactic cryoablation developed late-onset IART during a median follow-up of 22.9 years and a total of 638.4 person-years (Figure 3). Although further follow-up and data collection are required, our study demonstrated that prophylactic cryoablation in patients undergoing the LT Fontan was effective in preventing late-onset IART and cardiovascular mortality.

Conflict of Interest Statement

The authors reported no conflicts of interest.

The *Journal* policy requires editors and reviewers to disclose conflicts of interest and to decline handling or reviewing manuscripts for which they may have a conflict of interest. The editors and reviewers of this article have no conflicts of interest.

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Key Words: atrial flutter, cardiovascular mortality, intra-atrial reentrant tachycardia, lateral tunnel Fontan operation, mortality, prophylactic cryoablation

TABLE E1. Lateral tunnel Fontan patients with late-onset intra-atrial reentrant tachycardia

Patient no.	Age at Fontan (y)	Sex	Initial diagnosis	Type of ventricle	Isomerism	Fontan-to-IART time (y)	Treatment	Antiarrhythmic medication	IART clinical severity score	Death
1	2.1	M	Common inlet ventricle	Right	Right	16.6	Maze operation, medication	Digoxin, Sotalol	5	Died (AoD 20.9 y)
2	2.6	M	Common inlet ventricle	Right	None	4.9	Medication	Digoxin, Sotalol, Carvedilol	7	Died (AoD 26.7 y)
3	2.9	F	Double inlet ventricle	Right	None	19	Medication	Digoxin, Propranolol	4	Died (AoD 24.2 y)
4	10.1	M	Mitral atresia	Right	Left	14.7	Medication	Digoxin	4	Died (AoD 28.2 y)
5	6.7	M	Mitral atresia	Right	Right	10.3	Medication	Digoxin, Carvedilol	5	Died (AoD 20.8 y)
6	13.9	M	Common inlet ventricle	Right	Right	17.7	Medication	Digoxin, Sotalol, Carvedilol	6	
7	4.2	F	Complicated TGA	2	Left	25.3	Maze operation, medication	Sotalol	5	
8	4.1	F	Complicated DORV	2	None	20.9	RFCA, medication	Digoxin, Sotalol	5	
9	2.8	M	Common inlet ventricle	2	Right	7.2	Medication	Digoxin, Sotalol	5	
10	2.8	M	Mitral atresia	Right	None	11.1	Medication	Digoxin, Sotalol	5	
11	4.2	F	Tricuspid atresia	Left	None	23.2	Medication	Digoxin, Sotalol	5	
12	1.3	M	Complicated DORV	2	Left	23.8	Medication	Digoxin	3	
13	6.1	M	Mitral atresia	Right	Left	14.2	Medication	Carvedilol	3	
14	1.3	M	Double inlet ventricle	Right	None	23.1	Medication	none	2	
						Median 17.2 (IQR, 11.1-23.1)			Mean 4.6/12	Median 24.2 (IQR, 20.9-26.7)

IART, Intra-atrial reentrant tachycardia; *M*, male; *AoD*, age of death; *F*, female; *TGA*, transposition of great arteries; *DORV*, double outlet right ventricle; *RFCA*, radiofrequency catheter ablation; *IQR*, interquartile range.

TABLE E2. Mortality among lateral tunnel Fontan patients

Patient no.	Sex	Initial diagnosis	Type of ventricle	Isomerism	Age at Fontan (y)	IART event (cryoablation)	Age of death (y)	Cause of death
1	M	Common inlet ventricle	Right	Right	2.1	Yes (no)	20.9	Heart failure
2	M	Common inlet ventricle	Right	None	2.8	No (no)	29.6	Heart failure
3	F	Double inlet ventricle	Right	None	2.9	Yes (no)	24.2	Heart failure
4	M	Mitral atresia	Right	Left	10.1	Yes (no)	28.2	Heart failure
5	F	Common inlet ventricle	Right	Left	1.6	None (no)	11.2	Major bleeding: pulmonary hemorrhage
6	M	Common inlet ventricle	Right	None	2.6	Yes (no)	26.7	Major bleeding: variceal bleeding Sepsis: vancomycin-resistant enterococcus faecium
7	M	Mitral atresia	Right	None	1.5	None (no)	21.5	Major bleeding: GI bleeding
8	F	Tricuspid atresia	Left	None	1.8	None (yes)	17.2	Major bleeding: GI bleeding End-stage cancer: HCC
9	M	Common inlet ventricle	Right	Left	11.3	None (yes)	38.7	Major bleeding: intracranial hemorrhage (coagulopathy)
10	F	Common inlet ventricle	Right	Right	5.5	None (no)	26.2	Cardioembolic stroke
11	M	Common inlet ventricle	Left	Left	3.3	None (no)	18.9	End-stage cancer: pheochromocytoma
12	M	Mitral atresia	Right	Right	6.7	Yes (no)	20.8	Sepsis: pneumococcus
13	F	Mitral atresia	Right	None	3.4	None (yes)	9.2	Postoperative hypoxic ischemic brain damage
14	M	Tricuspid atresia	Left	None	1.6	None (no)	26.9	Sudden cardiac death
							Median 22.8 (IQR, 19.4-26.9)	

IART, Intra-atrial reentrant tachycardia; *M*, male; *F*, female; *GI*, gastrointestinal; *HCC*, hepatocellular carcinoma; *IQR*, interquartile range.