

Sudden cardiac death and late arrhythmias after the Fontan operation

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Abstract

Objectives: We sought to examine the incidence and predictors of arrhythmias and sudden cardiac death (SCD) after Fontan operation.

Background: Arrhythmias and SCD have been reported following operations for congenital heart disease, but the incidence and risk factors have not been well defined in patients after a Fontan operation.

Methods: We reviewed records of all patients who had a Fontan operation from 1973 to 2012 ($n = 1052$) at our institution. A questionnaire was mailed to patients who were not known to be deceased at the initiation of the study. Late arrhythmias were classified as bradyarrhythmias or tachyarrhythmias requiring treatment >30 days after operation.

Results: We included 996/1052 (95%) patients with no arrhythmia diagnosis prior to Fontan. Overall 10-, 20-, and 30-year freedom from arrhythmias was 71%, 42%, and 24%, respectively. Of 864 patients who survived >30 days after Fontan, 304 (35%) had atrial flutter, 161 (19%) had atrial fibrillation, 108 (13%) had atrial tachycardia, 37 (4%) had reentrant supraventricular tachycardia, 40 (5%) had ventricular tachycardia, and 113 (13%) had sinus node dysfunction. Predictors of late arrhythmias included an atriopulmonary Fontan, age at operation (>16 years) or atrial arrhythmias postoperatively. During follow-up, 52/1052 (5%) patients had SCD, with 51 having documentation available; 8 patients died suddenly within 30 days and the remaining 43 had an average time to SCD of 6.9 ± 6.7 years (median was 3.8 years). Arrhythmias were documented in 28/43 (65%) patients prior to SCD. Predictors of SCD included atrioventricular valve replacement and post-bypass Fontan pressures >20 mm Hg; preoperative sinus rhythm was protective.

Conclusions: Arrhythmias and SCD are significant concerns among Fontan patients and specific risk factors may warrant closer follow-up and earlier consideration for therapy.

KEYWORDS

arrhythmias, Fontan, ICD, pacemaker, sudden cardiac death

1 | INTRODUCTION

The Fontan operation initially was described for patients with tricuspid atresia,^{1,2} but has become the operation of choice for most forms of functional single ventricle.³⁻⁷ The operation has undergone various technical modifications aimed at improving long term outcomes.^{8,9} However, the development of early and late arrhythmias remains a sig-

nificant issue after the Fontan operation. Many investigators have shown that this risk increases with longer duration of follow-up after the operation.¹⁰⁻¹³ Additionally, the risk of sudden cardiac death (SCD) in this patient population may be as high as 9% during late follow-up.¹⁴ In this study, we sought to examine the incidence and determinants of atrial and ventricular arrhythmias and SCD during early and late follow-up after the Fontan operation.

2 | METHODS

In this institutional review board approved single-center retrospective study, we reviewed the records of all patients ($n = 1052$) who had their initial Fontan operation at the Mayo Clinic from October 1973–June 2012. Information regarding demographic, anatomic, operative, postoperative variables, and Mayo follow-up was abstracted into a secure electronic database. As many of the patients had their follow-up care at other institutions, any available correspondence regarding echocardiography, cardiac catheterization, electrocardiography, Holter/event monitoring, laboratory, or surgical/procedural data was also entered into the database.

A medical questionnaire was mailed to all patients not known to be deceased at the initiation of the study. Nonresponders received second and third questionnaires and if these were not returned or completed, an attempt was made to contact the patients by telephone. The questionnaire included information regarding arrhythmia history, medications, implantation of a pacemaker, or an automated implantable cardioverter defibrillator (ICD) and the need for subsequent surgeries, electrophysiology studies, or ablation procedures.

Clinically significant arrhythmia was defined as need for antiarrhythmic drug therapy (excluding digoxin), pacemaker, ICD placement, or electrical/pharmacologic cardioversion. In this study, bradycardia was defined as heart rate <60 bpm or below the lower limit of normal for age when appropriate. Documentation of early postoperative bradycardia and tachycardia was obtained from review of progress notes and discharge summaries from the medical records. Patients with arrhythmias prior to the Fontan operation were excluded from univariate and multivariate analysis of late postoperative arrhythmias. Information about types of pacemakers and ICDs were obtained from operative reports, pacemaker/ICD interrogations, clinical notes, communication from local physicians, and patient surveys. A diagnosis of SCD was made based on clinical history and autopsy reports, after other discernable causes of death had had been excluded.

Variables used in the Cox regression analysis were analyzed as continuous variables initially. Discrete cutoffs were then selected based on hazard ratios. The measurements that were obtained (eg, pulmonary artery pressures, Fontan pressures, systemic ventricular end diastolic pressure, etc) were based on available preoperative cardiac catheterization data, direct intraoperative measurements (obtained routinely on a majority of the patients), and postoperative hospital course.

2.1 | Statistical analysis

All patients in the study had documentation of any known clinical arrhythmias and date of onset of their arrhythmia. Univariate and multivariate analysis for late clinical arrhythmia (ie, >30 days after the Fontan) was only carried out in those patients who survived 30 days after the Fontan operation and did not have a clinical arrhythmia prior to their Fontan. All deaths that occurred after the Fontan operation, regardless of cause, were considered in the survival analysis. Descriptive statistics for categorical variables were reported as frequency and percentage while continuous variables were reported as mean (stand-

ard deviation) or median (range) as appropriate. Kaplan-Meier curves were derived to calculate 10-, 20-, and 30-year freedom from late arrhythmia and SCD. Cox regression models were used to determine univariate and multivariate predictors of arrhythmia and SCD. The multivariable model considered significant univariate variables ($P < .05$) with model selection using the stepwise method. All statistical tests were two-sided with the alpha level set at .05 for statistical significance. SAS 9.3 (SAS Institute, Inc., Cary, NC) was used for the analysis.

3 | RESULTS

Between 1973 and 2012, 1052 patients had their initial Fontan operation at the Mayo Clinic. There were 996/1052 (95%) patients who did not have a diagnosis of an arrhythmia prior to their Fontan operation. Patient demographics of all patients having a Fontan operation and those without a preoperative arrhythmia are listed in **Table 1**. At last follow-up, 426/1052 patients (40%) were known to be dead. Mean age at the time of death in this cohort was 19.3 ± 14.7 years (median was 17.2 years). Of the 626 patients that were known to be alive, transplant free survival was verified in 427 (68%) patients with follow-up information within 5 years of the study termination date. Mean follow-up duration after the Fontan operation was 15.3 ± 9.3 years (median was 15.1 years; range was 34 days to 37 years). The mean age at the time of Fontan operation was 9.4 ± 7.5 years (median was 7 years; range 7 months to 53 years). Of the 723 follow-up questionnaires that were mailed out, 305 (42%) were returned completed.

3.1 | Early postoperative arrhythmia (<30 days after Fontan operation)

For the 1052 patients who had a Fontan operation, the incidence of early postoperative arrhythmias was as follows: 224 (21%) patients had

TABLE 1 Patient demographics

Characteristic	All Fontan patients ($n = 1052$) (%)	Patients without previous arrhythmia who survived >30 days ($n = 864$) (%)
Male	637 (61%)	518 (60%)
Type of Fontan operation		
Atriopulmonary connection	616 (59%)	495 (57%)
Intraatrial tunnel	262 (25%)	214 (25%)
Extracardiac conduit	120 (11%)	105 (12%)
Other type of Fontan	54 (5%)	50 (6%)
Preoperative anatomy		
Tricuspid atresia	273 (26%)	236 (27%)
Double inlet left ventricle	271 (26%)	227 (26%)
Heterotaxy	135 (13%)	94 (11%)
Pulmonary atresia/intact septum	35 (3%)	49 (6%)
Hypoplastic left heart syndrome	24 (2%)	20 (2%)
Other	314 (30%)	238 (28%)

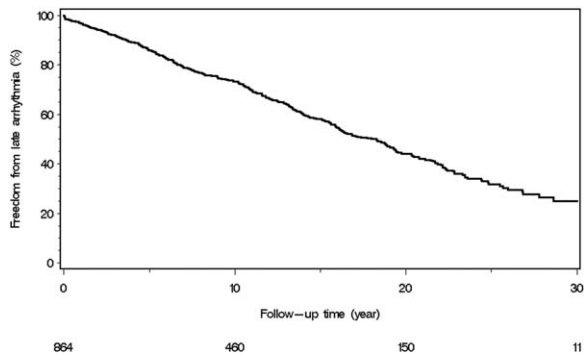


FIGURE 1 Freedom from late arrhythmias. Kaplan-Meier curve depicting freedom from late arrhythmias (>30 days) after the Fontan operation. Overall 10-, 20-, and 30-year freedom from new onset late arrhythmias after the Fontan operation was 71%, 42%, and 24%, respectively

atrial arrhythmias and 86 (8%) patients had ventricular arrhythmias. There were 97 (9%) patients who had transient third degree AV block following their Fontan operation, while only 31 (3%) patients required permanent pacemaker implantation for sinus node dysfunction or third degree AV block prior to hospital discharge.

3.2 | Late postoperative arrhythmia (>30 days after Fontan operation)

Of the 864 patients who survived at least 30 days after the Fontan operation and did not have a preoperative arrhythmia, there were 412 (48%) patients who were known to have developed a late arrhythmia. The mean age at diagnosis of arrhythmia was 20.0 ± 10.4 years (median was 18.0 years), and the mean duration from the Fontan operation to diagnosis of arrhythmia was 9.3 ± 7.1 years (median was 7.9 years). Overall 10-, 20-, and 30-year freedom from new onset late clinical arrhythmias after the Fontan operation was 71%, 42%, and 24%, respectively (Figure 1). Figure 2 demonstrates the long term freedom from arrhythmia by type of Fontan operation. The 20- and 30-year freedom from late arrhythmias for patients with an atriopulmonary type of Fontan was 37% and 21%, respectively. The breakdown of

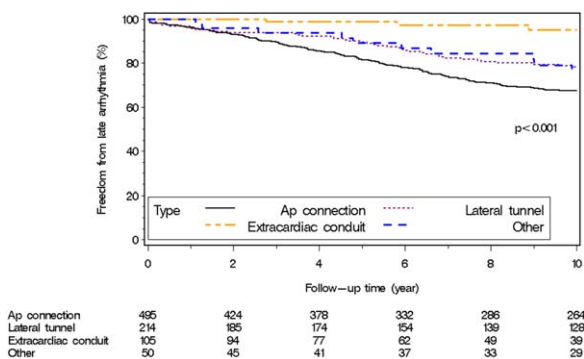


FIGURE 2 Freedom from late arrhythmias by type of Fontan operation. Kaplan-Meier curve depicting freedom from late arrhythmias (>30 days) by the type of Fontan operation

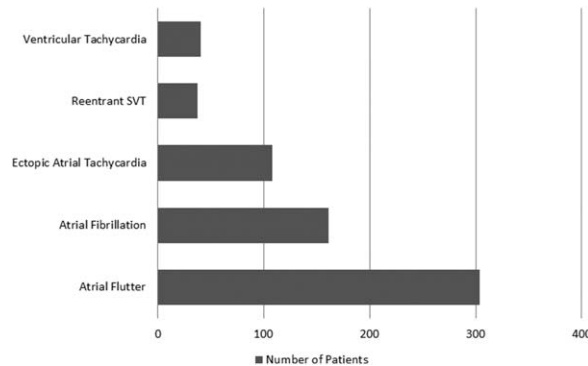


FIGURE 3 Incidence of late arrhythmias. Of 864 patients who survived >30 days after Fontan, 412 patients had late arrhythmias and the breakdown of arrhythmias was as follows: 304 (35%) had atrial flutter, 161 (19%) had atrial fibrillation, 108 (13%) had atrial tachycardia, 37 (4%) had reentrant supraventricular tachycardia (SVT), and 40 (5%) had ventricular tachycardia

arrhythmias is shown in Figure 3. Note that some patients had more than one arrhythmia type.

Freedom from late arrhythmia by era of operation and age at initial Fontan operation are shown in Table 2. Using univariate analysis, factors associated with increased risk of late arrhythmia included severe anatomic branch pulmonary artery stenosis or systemic ventricular end-diastolic pressure >12 mm Hg on preoperative catheterization, atrioventricular (AV) valve replacement during Fontan operation, postoperative low cardiac output, early atrial or ventricular arrhythmias and placement of a temporary pacemaker. Conversely, factors associated with a decreased risk of late arrhythmia included an interrupted inferior vena cava, surgical year after 1991, a bidirectional cavopulmonary anastomosis prior to Fontan and an extracardiac or intraatrial tunnel Fontan operation. In multivariate analysis, having an atriopulmonary type of Fontan or having atrial arrhythmias in the immediate postoperative period were associated with an increased overall risk of having late arrhythmias (Table 3). Additionally, when only preoperative and operative variables were used in multivariate analysis, age at initial Fontan operation >16 years was found to increase the risk of late arrhythmias.

TABLE 2 Kaplan-Meier estimates of freedom from late arrhythmia after the Fontan operation

Variable	10-year	20-year	30-year
Operative era			
1973–1990	70%	41%	23%
1991–2000	82%	51%	–
2001–2012	89%	–	–
Age at Fontan			
Less than 2 years	72%	46%	–
2–4 years	88%	55%	36%
5–16 years	72%	43%	28%
>16 years	63%	36%	11%

TABLE 3 Cox regression model for predictors of late arrhythmia after the Fontan operation

Variable	Univariate hazard ratio (HR)	P-value	Multivariate hazard ratio (HR)	P-value
Operative factors				
Fontan–atriopulmonary connection	1.73	<.001	1.74	<.001
Postoperative factors				
Postoperative atrial arrhythmia	1.91	<.001	1.93	<.001

3.3 | Sinus node dysfunction and pacemaker implantation

During long-term follow-up (18.2 ± 8.8 years), 113/864 (13%) patients were diagnosed with sinus node dysfunction and 212/864 (25%) patients had late pacemaker placement (>30 days after Fontan operation). Indications for late pacemaker placement were as follows (sometimes >1 indication in the same patient): late tachyarrhythmia (84%), sinus node dysfunction (48%), and third degree AV block (22%). In patients requiring temporary pacing for sinus node/AV node dysfunction immediately after Fontan, long-term freedom from pacemaker implantation was 73%, 59%, and 41% at 10, 20, and 30 years. In comparison, in patients not requiring temporary pacing after the Fontan, long-term freedom from pacemaker implantation was 90%, 74%, and 50%, respectively.

3.4 | Sudden cardiac death

The overall incidence of SCD in this cohort was 5% (52/1052). Of these 52 patients, documented date of death was confirmed in 51 (98%). Eight of the 51 patients died suddenly within 30 days after their Fontan operation. Of the patients who survived >30 days after the Fontan operation, 43/864 (5%) had late SCD at mean age of 20.5 ± 10.1 years (median was 18.0 years) and a mean of 6.9 ± 6.7 years (median was 3.8 years) after the Fontan operation. SCD represented 10% (43/426) of late Fontan deaths. Incidence of SCD at 10, 20, and 30 years after the Fontan operation was 4.6%, 6.2%, and 7.1%, respectively (Figure 4). In multivariate analysis, it was noted that AV valve replacement at the time of Fontan and post-bypass Fontan pres-

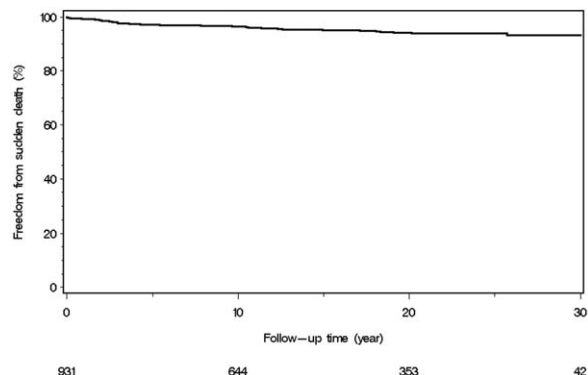


FIGURE 4 Freedom from sudden death. Kaplan-Meier curve depicting freedom from sudden cardiac death (SCD) after the Fontan operation. Overall 10-, 20-, and 30-year freedom from SCD after the Fontan operation was 97%, 95%, and 94%, respectively

sure >20 mm Hg were associated with an increased risk of SCD while preoperative sinus rhythm was protective (Table 4).

Of the 43 patients with late SCD, 28 (65%) patients had a previous diagnosis of a clinical arrhythmia at some point following the Fontan operation (some patients with more than 1 type of arrhythmia). The arrhythmias included 14 (50%) with atrial flutter, 8 (29%) with atrial fibrillation, 5 (18%) with reentrant SVT, 9 (32%) with ectopic atrial tachycardia, and 5 (18%) patients with ventricular tachycardia. All five patients with ventricular tachycardia died prior to 1995 (3/5 patients also had concomitant atrial arrhythmias) and specific information regarding their ventricular tachycardia was unavailable.

3.5 | ICD placement

None of the 52 patients with SCD had undergone placement of an ICD following the Fontan operation. There were 14 patients who did not die suddenly that had an ICD placed at a mean duration of 17.1 ± 7.3 years (median was 17.0 years) after the Fontan operation (mean age was 31.8 ± 14.7 years, median was 30.5 years). None of these patients underwent placement of ICD for primary prevention of SCD. Indications and dates of ICD placement were available for 12/14 patients (all occurred >30 days after Fontan) and these are summarized in Table 5. There were no appropriate shocks in this group of patients, but two patients sustained inappropriate shocks (secondary to 1 episode of intraatrial reentry tachycardia and 3 episodes of atrial tachycardia).

4 | DISCUSSION

These findings detailing early and late follow-up in a large cohort of patients after the Fontan operation confirm that arrhythmia and SCD remain a significant concern. In addition, this data allows for the identification of risk factors contributing to the development of late arrhythmia and SCD.

4.1 | Early postoperative arrhythmia (<30 days after Fontan operation)

The incidence of early postoperative tachyarrhythmia (<30 days after the Fontan operation) in this study is higher than the reported incidence in other studies.^{15,16} This finding is not surprising considering that most of the patients in our study were relatively older at the time of their initial Fontan operation (mean age 9.4 ± 7.5 years, median 7 years) and had a longer follow-up period. Previous investigators have

TABLE 4 Cox regression model for predictors of sudden cardiac death after the Fontan operation

Variable	Univariate hazard ratio (HR)	P-value	Multivariate hazard ratio (HR)	P-value
Preoperative factors				
Sinus rhythm on ECG	0.25	<.001	0.3	.009
Operative factors				
Postoperative Fontan pressure >20 mm Hg	2.96	.01	2.94	.007
AV valve replacement at time of Fontan	10.15	<.001	6.13	.004

AV, atrioventricular.

established that the incidence of postoperative arrhythmias after the Fontan operation is higher in those undergoing the Fontan operation at an older age.^{12,13,16} In addition we noted that the frequency of permanent pacemaker placement for sinus node dysfunction or third degree AV block prior to hospital discharge after the Fontan operation was approximately 3%, which is similar to the reported incidence by other investigators.^{8,15,17} The number is higher than the expected frequency in the current Fontan era due to additional risk factors in this cohort such as earlier surgical techniques (along with longer bypass times), older age at the time of initial Fontan and a higher proportion of heterotaxy patients. A majority of the patients requiring temporary pacing in the immediate postoperative period did not require placement of a permanent pacemaker prior to hospital discharge but did have a higher chance of requiring a pacemaker long term.

4.2 | Late postoperative arrhythmia (>30 days after Fontan operation)

In patients who survived at least 30 days after the Fontan operation and did not have a preoperative arrhythmia, almost half of the patients were diagnosed with a late clinical arrhythmia. This number may be an underestimate as a proportion of the patients in this study did not have complete follow-up data available after their Fontan operation. Depending on the length of follow-up, the reported incidence of late arrhythmias has been anywhere from 6%-50%.^{8,11-13,15,18} In our study, the overall duration of follow-up was shorter for the extracardiac conduit (mean was 7.5 ± 5.9 years) and lateral tunnel groups (mean was

12.3 ± 9.1 years) in comparison to patients with atriopulmonary connections (mean was 14.9 ± 12.0 years). It is, therefore, conceivable that the true incidence of arrhythmia in the extracardiac cohort is underestimated. Many reports detail an overwhelming predominance of reentrant atrial tachycardia in this group, yet these findings herald a surprisingly high incidence of atrial fibrillation and ectopic atrial tachycardia. These novel and intriguing data are important for clinicians who manage the population of aging patients after Fontan.

When we examined the factors associated with increased risk of late arrhythmia using univariate or multivariate analysis, many of them were associated with poor short or long term hemodynamics after the Fontan operation. Interestingly, a bidirectional cavopulmonary anastomosis prior to the Fontan operation was associated with a lower risk of late arrhythmias on univariate analysis, however, this factor did not bear out on multivariate analysis. This may be explained by the fact that these patients represented a small portion of the overall cohort, or that the protective effect was due to an influence of a later surgical era or the type of Fontan operation (most patients with a bidirectional cavopulmonary anastomosis had an associated lateral tunnel or extracardiac Fontan).

In this study, we demonstrated that atrial arrhythmias in the immediate postoperative period were associated with an increased overall risk of having late arrhythmias. Other authors have shown that postoperative atrial arrhythmias are associated with an increased risk of late bradyarrhythmias and tachyarrhythmias.^{12,19} These studies have postulated that factors such as disruption of nodal conduction tissues or damage to the sinus node artery resulting in loss of sinus node function produce an additive effect along with continued atrial distention, poor ventricular function and elevated central venous pressures in the development of late atrial tachyarrhythmias.^{20,21}

TABLE 5 Indications for Implantable Cardiac Defibrillators after the Fontan operation

Indication	N = 12
Resuscitated arrest	3
Ventricular fibrillation in the postoperative period	2
Syncope with concurrent documented ventricular tachycardia	2
Poor ventricular function with non-sustained ventricular tachycardia	2
Non-sustained ventricular fibrillation on pacemaker interrogation	1
Inducible ventricular tachycardia with hemodynamic compromise on EP study	1
Palpitations associated with syncope	1

4.3 | Sinus node dysfunction and pacemaker implantation

For the 25% of patients who had late pacemaker placement the predominant indications for pacemaker placement were late arrhythmias and sinus node dysfunction. This may be different in the current era, with the improved outcomes of transcatheter ablation procedures and Fontan conversion or revision (with or without concomitant maze operation).²² We also noted that in patients requiring temporary pacing for sinus node/AV node dysfunction, there was an increased long-term incidence of pacemaker implantation compared to patients that did not require temporary pacing after their operation. This suggests that perhaps those patients requiring

temporary pacing after the Fontan operation may represent an “at risk cohort” that may require closer monitoring during long term follow-up.

4.4 | Sudden cardiac death

There are very few studies of the incidence of SCD after the Fontan operation. While Khairy et al. have previously published a 9% incidence of sudden death after the Fontan operation,¹⁴ the only associated risk factor was a high incidence of previous atrial arrhythmias. Using multivariate analysis, we noted that AV valve replacement at time of Fontan and post-bypass Fontan pressure >20 mm Hg were associated with an increased risk of SCD while preoperative sinus rhythm was protective. While specific information prior to death was not always available for the patients that had late SCD, it was observed in this study that two-third of the patients had a previous diagnosis of a clinical arrhythmia. It still remains to be determined whether these patients were directly at a risk of clinically malignant arrhythmia because of their previous history, or if their arrhythmia was simply a clinical marker of their poor hemodynamic status.

4.5 | ICD placement

While there is an increased risk of SCD after the Fontan operation, at the present time there is no clear indication for universal placement of an ICD for primary prevention of SCD in this group of patients, except perhaps in the case of poor single ventricle function. Many have suggested using an LVEF cutoff of <30%-35% as an indication for ICD placement for primary prevention of SCD for adult patients with ischemic and non-ischemic heart disease.²³ However, direct extrapolation of this cutoff to Fontan patients with indeterminate ventricular morphology or systemic right ventricles is challenging. In addition, there are other factors to consider when considering ICD placement in Fontan patients. Transvenous access can be difficult or impossible, and the presence of an intracardiac shunt may provide prohibitive risk from a thromboembolic point of view. Subcutaneous ICDs may circumvent some of these issues, yet one is obliged to remain cognizant of the high incidence of atrial arrhythmias and the risk of inappropriate ICD shocks. Further studies are needed to determine the occurrence of appropriate ICD shocks in this patient population and the decision to proceed with ICD placement in this group needs to be approached with caution given that we are still attempting to identify the specific risk factors for SCD.

4.6 | Limitations

This is a single center cohort from a large tertiary referral center over an almost four decade time frame, with the inherent limitations related to follow-up and survey response rates. Attempts were made to overcome this limitation by obtaining detailed and specific follow-up information on patients whenever possible, and the data was censored using the last known date of follow-up.

5 | CONCLUSIONS

Despite the changing paradigm of Fontan operations, it is evident as more patients with a Fontan palliation live into adulthood that there is an increasing risk of long-term arrhythmia and sudden cardiac death. Understanding these risk factors will enable us to provide better surveillance and treatment for long term arrhythmias and institute possible life-saving measures for those at risk for SCD. In contrast to patients with acquired heart disease, it appears systemic ventricular function cannot be relied on to aid in risk stratification for primary prevention, and further collaborative studies are necessary to confirm or negate these provocative findings.

DISCLOSURE

BCC is a consultant for Medtronic. The other authors have no conflicts of interest to disclose. None of the disclosures pertain to this study and none of the companies provided financial support for this study.

AUTHOR CONTRIBUTIONS

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