CONGENITAL HEART DISEASE

RESEARCH ARTICLE

Diagnostic Electrophysiology Study Has Limited Value in Risk Stratification of Children and Young Adults with and without Congenital Heart Disease

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ABSTRACT. *The aim was to determine the utility of electrophysiology (EP) study in children and young adults to risk stratify for sudden cardiac death (SCD). A retrospective cohort study was performed to evaluate the usefulness of EP study in predicting a composite endpoint of SCD or appropriate implantable cardioverter-defibrillator (ICD) discharge in subjects with and without congenital heart disease (CHD). Over the 14-year study period (1995–2009), 169 subjects underwent EP study at a median age of 15.1 years (IQR 12.1–18.7) and median follow-up of 4.7 years (IQR 1.8–8.8). Eighty-five subjects had CHD and 84 subjects did not have CHD. In the With CHD group, 25 of 85 subjects (31%) had positive EP study defined as inducible hemodynamically significant ventricular tachycardia or ventricular fibrillation. An ICD was placed in 18 subjects, with five subjects having subsequent appropriate ICD discharge. Of the 60 out of 85 subjects (69%) with negative EP study, there were two ICDs implanted and no appropriate ICD discharges. Subjects with positive EP study had significantly improved freedom from composite outcome of SCD or ICD discharge (log rank $p = 0.002$). In the Without CHD group, 25 of 84 subjects (30%) had a positive EP study, and ICDs were implanted in 11 subjects, with one subsequent appropriate ICD discharge. Of the 59 of 84 (70%) subjects with negative EP study, eight had ICDs implanted with two appropriate ICD discharges. There was no significant difference in freedom from composite outcome in subjects with positive and negative EP study. There was no SCD in either group. In our cohort of patients, EP study had limited utility for risk stratification. However, a negative EP study in CHD subjects may suggest a low SCD risk.*

KEYWORDS. *congenital heart disease, implantable defibrillation therapy, intracardiac electrophysiology, sudden cardiac arrest, ventricular tachycardias.*

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Introduction

Sudden cardiac death (SCD) in the general pediatric population is relatively rare, with reported incidence of 2.3:100,000 patient-years.¹ However, children and adults with congenital heart disease (CHD) have a higher incidence of SCD, with a reported rate of 220:100,000 patient-years in some populations.² This higher incidence of SCD may be due to myriad causes, including intrinsic arrhythmia substrate from postoperative scarring and ongoing hemodynamic issues. With improving survival after CHD repair in the recent era,^{3,4} it is important to assess risk for this population and treat those at highest risk for SCD.

Previous studies have shown conflicting utility of the diagnostic electrophysiology (EP) study in patients with CHD. Alexander et al.⁵ showed an increased mortality risk in CHD patients with a positive EP study compared with those with a negative study, with a test sensitivity of 60% and specificity of 67% for mortality. Khairy et al.⁶ found that a positive EP study in patients with tetralogy of Fallot (TOF) had a sensitivity of 77.4% and specificity 79.5% for predicting future clinical ventricular tachycardia (VT) and SCD. However, others have shown limited use of EP study in surgically corrected TOF, with subjects who experience SCD having no inducible VT or ventricular fibrillation (VF) during prior EP study.⁷ Given the conflicting data, we sought to investigate the utility of EP study in predicting SCD in children and young adults with and without CHD in the recent surgical era.

Methods

Study design

An institutional review board-approved retrospective cohort review of consecutive subjects undergoing diagnostic EP study for SCD risk stratification at the Children's Hospital of Philadelphia between July 1, 1995, and April 1, 2009, was performed. Subjects were not included if they underwent EP study for reasons other than SCD risk stratification, such as investigation or interventional management of supraventricular tachycardia or VT. For subjects with multiple EP studies, only their first EP study at our institution was included.

Study procedures

Demographics, growth parameters, cardiac diagnoses, indication(s) for EP study, implantable cardioverter-defibrillator (ICD) placement, and length of follow-up were abstracted from the medical record. Follow-up data (collected up until October 1, 2012) were reviewed for subsequent SCD, appropriate ICD discharge, ICD complications, and death. The primary endpoint of the study was a composite outcome of SCD and, in subjects who had an ICD, an appropriate ICD discharge as a surrogate of SCD. EP study protocol included single, double, and triple programmed ventricular extra-stimuli introduced at two different drive train cycle lengths (600 and 400 ms) from the right ventricular apex and right ventricular outflow

tract with minimal extra-stimuli cycle length of 180 ms. The protocol was repeated at one drive train cycle length (400 or 450 ms) with isoproterenol administration if the baseline study was negative. A positive EP study was defined as inducible VF, sustained VT lasting greater than 30 s, or non-sustained VT that produced hemodynamic instability.

Statistical analysis

Standard descriptive statistics were determined. Continuous variables were expressed as median with inter-quartile range (IQR). Comparisons of means were performed through Wilcoxon rank sum tests. Comparison of risk of categorical outcomes was performed with Fisher's exact test. The primary analysis was difference in composite outcome between subjects with and without a positive EP study. Because of *a priori* concern that EP study would have different utility in subjects with and without congenital heart disease, subjects were separated into subgroups for analysis. To account for differential follow-up and drop-out, Kaplan-Meier curves for the composite outcome were plotted. Comparison of outcome between subjects based on EP study results was performed using the log-rank test. Test characteristics (i.e. sensitivity, specificity) and 95% confidence intervals were calculated. The study was a retrospective study with a fixed study population, and no formal power calculations were performed. Threshold for statistical significance was set at $p < 0.05$. All analyses were performed using Stata 12.1 SE (StataCorp, College Station, TX).

Results

Demographics and patient characteristics

One hundred and sixty-nine subjects underwent EP study for risk stratification for SCD during the study time period (**Table 1**). The median age at the time of EP study was 15 years (IQR 12–19) with eight subjects lost to follow up early after EP study with no subsequent clinic visit recorded. There were 85 subjects in the With CHD group and 84 subjects in the Without CHD group. Subjects with CHD were older at the time of EP study (median age 17.7 years (IQR 13.2–23.2) versus subjects without CHD (median age 14.4 years (IQR 11.3–16.1)), $p < 0.0001$) and had a longer follow-up time (7.0 years [IQR 3.4–10.6] versus 3.0 years (IQR 1.1–5.6), $p < 0.01$ respectively). There were 109 (64%) males with no significant gender differences in the two groups.

The number of EP studies performed for SCD risk stratification steadily declined over the study period (**Figure 1**), with 118 studies from 1995 to 2002, and only 51 studies from 2003 to 2009.

There were a variety of cardiac diagnoses in the two groups (**Figure 2**). About half of the group with CHD ($n = 44$) had some form of right heart obstruction; the majority had TOF ($n = 33$), with the remainder having pulmonary stenosis or double outlet right ventricle with pulmonary stenosis. There were 17 subjects with transposition of the great arteries (TGA) with an atrial

Table 1: Demographics and patient characteristics

	With CHD	Without CHD	All subjects
Total	85	84	169
Age (years)	17.7 (13.2–23.2)	14.4 (11.3–16.1)*	15.1 (12.1–18.7)
Male (n)	52 (61%)	57 (68%)	109 (64%)
Follow-up after EP study (years)	7.0 (3.4–10.6)	3.0 (1.1–5.6) [†]	4.7 (1.8–8.8)

CHD: congenital heart disease; EP: electrophysiology.

Data are given as counts (percentages) or median (interquartile range).

*Significant difference between the groups ($p < 0.0001$).

[†]Significant difference between the groups ($p < 0.01$).

switch operation. The Without CHD group was a heterogeneous group and included subjects with cardiomyopathy ($n = 17$), channelopathy ($n = 10$), and idiopathic VT ($n = 9$).

Indications for EP study

The majority (119, 70%) of both group subjects had more than one indication for EP study. The most common indications for EP study included non-sustained VT or premature ventricular contractions (PVCs) on Holter, palpitations, and syncope (**Figure 3**). More subjects in the CHD group had EP study performed for non-sustained VT or PVCs ($p < 0.001$) and palpitations ($p = 0.005$) compared with the Without CHD group. More subjects had EP study performed for syncope ($p < 0.001$) and family history of SCD ($p = 0.001$) in the Without CHD group compared with the other group as shown in **Figure 3**.

EP study and subsequent SCD

The EP study outcomes are shown in **Figure 4**.

With CHD group. Twenty-five of 85 (29%) subjects had a positive EP study. Of these, 18/25 (72%) had an ICD implanted. During follow-up, 5/18 (20%) had an appropriate ICD discharge. Among the 60 subjects with a negative EP study, there were only two ICDs implanted (3%). None of the subjects with a negative EP study had a subsequent appropriate ICD discharge or SCD during

follow-up. There was a significant difference in freedom from SCD or appropriate ICD therapy among CHD patients with positive and negative EP studies (log rank $p = 0.002$) (**Figure 5a**). At 5 years after EP study, freedom from composite outcome was 82% in the 19 patients followed with positive EP study and 100% in the 36 subjects still followed with negative EP study. The sensitivity of EP study for predicting the composite outcome was 100% (97.5% one-sided CI 52–100) and the specificity was 75% (95% CI 63–83).

Without CHD group. Twenty-five of 84 (29%) subjects had a positive EP study. Of these, 11/25 subjects (44%) had ICDs implanted. During follow-up, one subject had an appropriate ICD discharge, and there were no SCDs. Among the 59 subjects with a negative EP study, eight ICDs were implanted (14%). During follow-up, two subjects had appropriate ICD discharges, and there were no SCDs. There was no significant difference in freedom from composite outcome in these subjects with positive and negative EP study (log rank $p = 0.99$) (**Figure 5b**). At 5 years after EP study, freedom from composite outcome was 96% in the 15 subjects still followed with negative EP study and 95% in the 10 subjects with positive EP study. The sensitivity of EP study for predicting the combined outcome event for subjects without CHD was 33% (95% CI 6–79) and the specificity was 70% (95% CI 60–79).

We performed multivariate analysis of the common denominators in the two groups and found that TOF, ventricular dysfunction, prolonged QRS, age at EP study, or gender were not risk factors for appropriate ICD shock or SCD. However, we believe this study does not have the power for such analysis given the heterogeneous patient population and small number of outcome events.

Mortality

Although there was no SCD during the follow-up period in either group, there were three deaths in the CHD group and two deaths in the non-CHD group. In the CHD group, one subject died during a hospital admission for heart failure, and one died from acute abdominal crisis secondary to a jejunal volvulus. There was one death in each group from complications of rejection after orthotopic heart transplant. In the group without CHD, one subject required placement of a left ventricular assist device for severe ventricular dysfunction and died from sepsis and multisystem organ failure.

Figure 1: Decline in number of electrophysiology studies performed per year over the study period for risk stratification of sudden cardiac death.

Figure 2: Cardiac diagnoses of subjects with and without congenital heart disease.

Correlation between arrhythmia during EP study and electrograms during appropriate ICD discharge

As summarized in **Table 2**, the clinical arrhythmias (as interpreted by ICD electrograms) during an appropriated ICD shock correlated with the EP study-induced arrhythmia in four out of subjects with CHD. The clinical arrhythmias were different from the EP study induced arrhythmia in all three subjects without CHD who had an appropriate ICD shock (**Table 2**).

ICD complications

Among the 39 ICDs implanted, four (10%) had acute complications. In the CHD group, one subject had acute Mustard baffle obstruction. In the Without CHD group, there was one subject each with infection, subclavian rupture, and lead migration. During follow-up, there were six lead fractures (15%). In addition, there were eight subjects with surgery for device recall and 11 (28%) who had inappropriate ICD discharges needing ICD re-programming. There was a higher complication rate in the without CHD group (29%) than in the with CHD group (19%) ($p=0.04$).

Discussion

EP study for risk stratification of patients with operated CHD

This study represents an evaluation of EP study to predict SCD in at-risk children and young adults with and without CHD during the recent surgical era. The primary finding of this study was the observation that a negative EP study in subjects with CHD risk stratifies one to be relatively low risk. In subjects with CHD, a positive EP study was associated with a significant difference in freedom from composite outcome of SCD and appropriate ICD discharge. Similar to prior studies,^{5,6} we observed a high sensitivity of EP study in predicting SCD and appropriate ICD discharge. Although there was no SCD in this study, the surrogate marker of appropriate ICD discharge occurred only in subjects with a positive EP study, suggesting that negative EP studies risk stratify subjects into a lower risk group. One previous study has shown no such correlation as all five of their subjects with SCD had a prior negative EP study.⁷ The authors explained this as being secondary to a less aggressive EP stimulation protocol. It also important to keep in mind that this risk stratification is not life-long since changes to

Figure 3: Indications for electrophysiology study in subjects with and without congenital heart disease.

Figure 4: Flowchart of electrophysiology study results, implantable cardioverter-defibrillator implantation, and composite outcome events of sudden cardiac death or appropriate implantable cardioverter-defibrillator discharge in all study subjects.

the hemodynamics (such as worsening ventricular function) may alter the arrhythmia potential during follow-up and increase risk of SCD.

There has been a declining use of EP study for prediction of SCD, perhaps due to increasing use of non-invasive markers for SCD risk stratification.^{5,8-12} This declining trend was observed in our cohort as well. Indeed, relevant clinical data, such as symptoms (i.e. unexplained syncope), arrhythmias on Holter monitor, and residual hemodynamic lesions need to be considered. Long-term outcome studies have suggested an increased risk of SCD in patients with late age of repair, heart failure, and residual hemodynamic lesions after repair of TOF,^{7,11,13-16} TGA with atrial switch^{9,16} and arterial switch operations,¹⁷⁻¹⁹ and aortic stenosis.²⁰ Our study confirms that a diagnostic EP study has limited use in risk stratification. Small individual numbers precludes subgroup analysis for lesion specific risk stratification.

EP study for risk stratification of subjects without CHD

EP study did not accurately risk-stratify subjects without CHD, as there was no significant difference in time to SCD or appropriate ICD therapy in subjects with positive and negative EP study. EP study has a low sensitivity

and specificity for predicting the composite outcome. Most importantly there were broad confidence intervals to these test characteristics because of the limited number of study subjects and rarity of outcome event of SCD. Many of the children and young adults who underwent EP study in this study were in the era when the utility of the study was unclear. Subsequent studies have shown low utility of EP study in long QT syndrome²¹ and questionable value in arrhythmogenic right ventricular cardiomyopathy.^{22,23} Other disorders, such as cardiomyopathy, have established non-invasive criteria such as low ventricular ejection fraction for risk stratification and ICD placement.²⁴⁻²⁶ There are mixed results of the ability of EP study to risk stratify patients with hypertrophic cardiomyopathy,^{27,28} but accepted current guidelines now stratify patients on established clinical criteria without the use of EP study.²⁹⁻³¹

Overall indications for EP study

The indications for EP study in pediatrics for SCD risk stratification alone are limited. In our cohort the most common indications included non-sustained VT or PVCs and symptoms such as syncope and palpitations. In four out of five subjects with CHD, a positive EP study and the clinical arrhythmias documented by ICD electrogram

Figure 5: Kaplan–Meier survival curves for freedom from composite outcome of sudden cardiac death or appropriate implantable cardioverter-defibrillator discharge by electrophysiology study result for subjects (a) with congenital heart disease (CHD) (log rank $p = 0.002$) and (b) without CHD (log rank $p = 0.99$).

were similar. It is also possible that CHD patients experience several types of arrhythmia, contradicting the notion that CHD patients predominantly experience monomorphic VT originating from suture lines, and that polymorphic VT is only a spurious finding during aggressive EP study.^{32,33–35} Indeed, Khairy et al.⁶ noted that polymorphic VT increased the sensitivity and only mildly decreased the specificity of EP study in predicting SCD of CHD patients. One important indication for considering an EP study is to determine the nature of an

arrhythmia in a symptomatic patient for optimal ICD programming. Enabling anti-tachycardia pacing zones may help avoid ICD discharges, especially in patients with monomorphic VT that can be pace terminated. On the other hand, in subjects without CHD, the arrhythmias induced during the EP study often differed from that on ICD electrogram at appropriate discharge.

It is important to emphasize that our study evaluated the utility of EP study to risk stratify patients for SCD, and did not consider the underlying rationale to perform EP study.

Decision to implant ICD and its consequences

The decision to implant a primary prevention ICD in children and young adults with and without CHD is often challenging. Although clinical parameters such as ventricular function and symptoms such as unexplained syncope and evidence of sustained or non-sustained ventricular arrhythmias are helpful in risk stratification, an EP study may be helpful in this decision-making process. A negative EP study in some specific clinical situations may be reassuring. The number of acute ICD complications in this series was 10%, but a much higher percentage of our subjects experienced unfavorable events during follow up, including lead fracture rate (13%), device recall (21%), and inappropriate ICD discharge (28%). These numbers are similar to previously reported rates of ICD complications in children and congenital heart disease patients.^{36,37} Additionally, there is growing evidence of the decreased quality of life experienced by pediatric patients with ICD that must be considered.³⁸ This highlights the unique challenge of risk stratification and primary prevention strategies for pediatric patients with risk of SCD

Study limitations

There were several study limitations:

1. Most importantly, the outcome event (SCD) was rare, and the CHD and pediatric population studied relatively small, which made multivariable analyses to account for potential confounders and effect modifiers not feasible. The smaller subgroup analysis of conditions such as TOF was also not feasible for the same reason.
2. Secondly, the decision to perform EP study was made by clinical providers, which could have caused a bias

Table 2: Correlation between arrhythmia during EP study and stored electrograms during appropriate ICD discharge in subjects with and without CHD

	Diagnosis	EP study induced rhythm	ICD electrogram
A. With CHD	Truncus arteriosus	Monomorphic VT	Monomorphic VT
	TGA	Monomorphic VT	Polymorphic VT
	Aortic stenosis, coarctation	Polymorphic VT	Polymorphic VT
	TGA	Polymorphic VT	VF
	TOF	VF	Polymorphic VT
B. Without CHD	Prior aborted SCD	Negative	VF
	Hypertrophic cardiomyopathy	Negative	VF
	Idiopathic VT	Polymorphic VT	Monomorphic VT

CHD: congenital heart disease; EP: electrophysiology; ICD: implantable cardioverter-defibrillator SCD: sudden cardiac death; TGA: transposition of the great arteries; TOF: tetralogy of Fallot; VT: ventricular tachycardia.

toward including subjects with increased risk of SCD (patients with a high pretest probability of positive EP study given their indications prompting EP study). Alternatively, it also may have biased the study toward including subjects with decreased risk of SCD (patients without a definitive indication for ICD placement who required risk stratification). VT/VF induction during EP study could have been a non-specific finding. This would influence EP study positive and negative predictive values but would not affect sensitivity and specificity.

3. This was a retrospective single-center cohort study, which may limit its generalizability to centers with different patient populations and different study indicators. The group that underwent EP study may reflect the population in which there is uncertainty in the SCD risk. Another limitation was the considerable loss to follow up. We attempted to account for this through the use of survival analysis, yet the differential loss to follow up among subjects with positive and negative EP studies could lead to bias.
4. Our primary outcome was a combined outcome of SCD and the surrogate marker for SCD of appropriate ICD discharge. Previous studies have shown that using appropriate ICD discharge may overestimate the incidence of SCD,³⁹ resulting in a potential misclassification bias.
5. Finally, the current study addresses the test characteristics of EP study but not its relative efficacy against other strategies. Nor does it address the marginal benefit relative to those strategies as part of an integrated risk stratification program.

Conclusion

EP study has limited utility in risk stratification of children and young adults with CHD and assessing their need for ICD implantation. There may be specific situations in which an EP study provides further information that can be considered alongside clinical non-invasive risk factors, such as residual hemodynamically significant lesions and cardiac function. The results must be interpreted with caution. A negative EP study may be somewhat reassuring in CHD patients given the high sensitivity shown in this and prior studies, but this appears to be dependent on the EP study protocol used. The utility of EP study in pediatric and young adult subjects without CHD was not demonstrated in this study.

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