

To: **All members of the Pediatric EP Society (Updated May '03)**

Re: **TOF Sudden Cardiac Death Study**

Our society has attempted several collaborative studies on the topic of sudden cardiac death in patients with tetralogy of Fallot, but for various reasons, have produced limited data. In 1998, we set out to revisit this issue by designing a two phase project:

PHASE I- Retrospective case-control review of TOF patients with cardiac arrest, or documented VT, or appropriate ICD discharge, aimed at developing a scoring system based upon history and noninvasive tests that best identifies the high risk patient.

PHASE II- Prospective study of patients considered to be at high risk, focused on diagnostic V-stim, with assignment to treatment arm (probably ICD) if EPS positive, but if EPS negative, either beta blocker or no therapy.

We calculated the need for 50 cases and the corresponding 150 controls to meet statistical power requirements for PHASE I. Unfortunately, thus far we have only collected 41 cases, and the controls are incomplete for some of these.

At several recent Society meetings, we discussed options for rejuvenating the PHASE I project. To make participation easier, I have redesigned the data entry forms to be less detailed, and will accept cases without an absolute requirement for controls. Naturally, we would prefer to have cases & controls from the same institution, but if this is impossible, I can search the cardiology data base from my own department to fill in any blanks. Although this will dilute the power of the study to some degree, it will not represent a fatal flaw. I hope we can manage to pull PHASE I together this year. Thanks for your participation.

Edward P Walsh, MD

PHASE I
RETROSPECTIVE CASE-CONTROL STUDY OF LATE ARRHYTHMIAS
FOLLOWING TETRALOGY OF FALLOT REPAIR: A COLLABORATIVE
PROJECT OF THE PEDIATRIC EP SOCIETY

STUDY DESCRIPTION & DIRECTIONS

Purpose: Attempt to generate a clinical description of the patient at highest risk for late malignant arrhythmias following repair of tetralogy of Fallot (TOF), based on history, hemodynamic status, standard ECG, and *noninvasive* rhythm monitoring. If a strong predictive model is identified, these data may be used to select patients for future PHASE II prospective trials of EP testing and therapy focused on the population at greatest risk.

Background: There continues to be a concerning incidence of late morbidity & mortality related to sudden arrhythmic events in patients who have undergone surgery for TOF. These events appear primarily to involve ventricular tachyarrhythmias, but can also involve atrial tachycardias or AV conduction disturbances. Numerous prior studies, predominately from single centers, have attempted to identify clinical and laboratory features which might suggest causality and predict who is at risk. Such studies have led to a long but nonspecific list of risk factors, including:

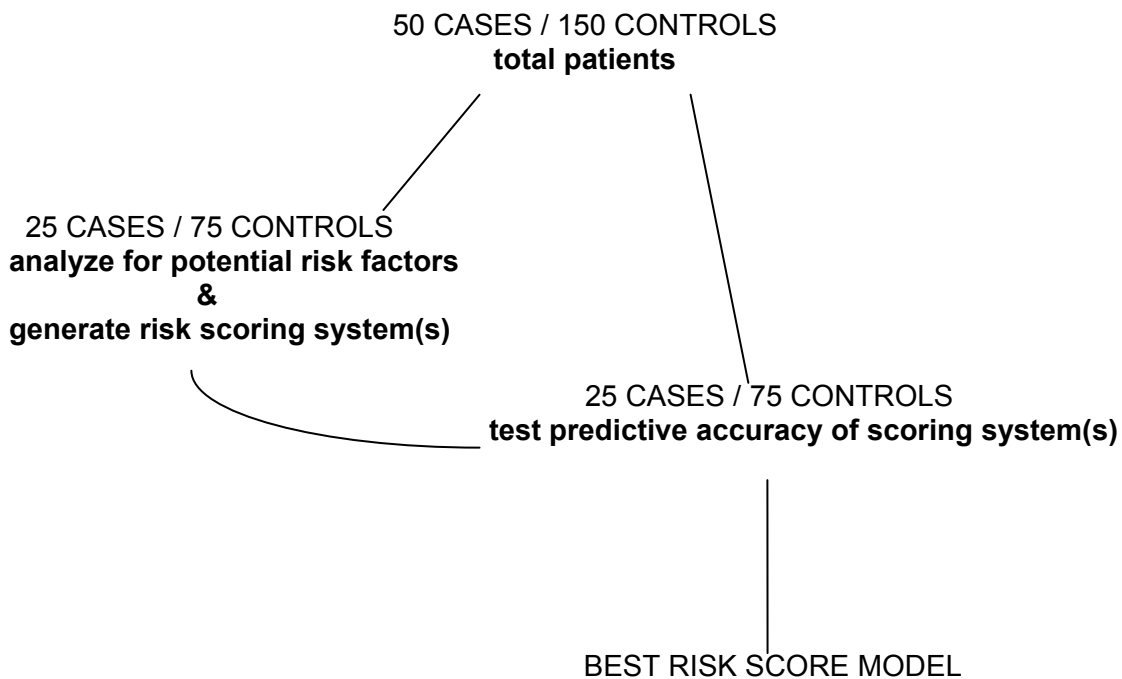
- history of syncope, or palpitations/dizziness
- spontaneous ventricular ectopy on ECG, Holter, or ETT
- induced tachycardias at invasive EP study
- residual hemodynamic problems (PR, PS, TR, residual VSD, etc.)
- late age at repair
- prior Waterston or Potts shunt
- older chronological age at follow-up
- bifascicular block (RBBB/LAH)
- prolonged QRS duration
- long QT or JT, wide QT or JT dispersion
- large RV size
- etc.

Perhaps the single biggest obstacle to judging the predictive value of these items has been the relatively low incidence of sudden death in the TOF population, which limits statistical power even for centers with large surgical volumes. A collaborative approach is clearly required. It is the goal of the Pediatric EP Society to revive a multicenter study of arrhythmias in postoperative TOF patients, beginning with this retrospective PHASE I project that attempts to better define the patient at highest risk.

Study Design: This analysis will be conducted in a case-control format. Centers will identify CASE patients who have suffered documented or suspected malignant arrhythmias, whether or not they survived, and review the patient's records for details of

surgical history, hemodynamic status, medications, ECG, and any available forms of noninvasive rhythm monitoring. It is *not* a requirement that the patient had an EP study, although EP data will be analyzed if provided. The center will then attempt to find 3 CONTROL patients for each CASE, matched primarily for era of surgery, and review similar historical and laboratory data. Copies of recent 12-lead ECG's must be available for all CASE and CONTROL patients. In order to have sufficient statistical power, we calculate the need for a minimum of 50 cases and their corresponding 150 controls, but we would be happy to have more. If you cannot identify suitable CONTROL patients from your center, you may still submit CASE data, and attempts will be made to fill the gap from the data base at Boston Children's Hospital.

The CASES and their corresponding CONTROLS will be divided into 2 groups for analysis (diagram). One group will be used to compare CASES and CONTROLS by univariate and multivariate analysis, in attempts to find the best isolated risk factors, or some combination of risk factors, for serious arrhythmic events. These risk factors will then be worked into one or more risk scoring systems, which can be tested on the remaining CASES and CONTROLS to test the predictive accuracy of various models.



Study Organization: Data will be coordinated at Boston Children's Hospital, with the help of statisticians from the Harvard School of Public Health who have consulted on study design. The data base will be retained after completion of this retrospective study, and will then be made available for the use of any contributing member who wishes to review it for other EP Society projects in the future.

INCLUSION CRITERIA

- 1) **CASE** or **CONTROL** patients can have any of the following diagnosis:
 - standard TOF
 - TOF with pulmonary atresia (if you prefer, pulmonary atresia with VSD)
 - TOF with discontinuous L pulmonary artery
 - TOF with aberrant LAD from the R coronary artery
 - DORV with subaortic VSD who have undergone TOF-like repair (no sub AS)
 - D-TGA/VSD/PS following Rastelli operation (no sub AS)

- 2) **CASE** or **CONTROL** patients must have undergone at least one attempt at complete intracardiac repair, involving VSD closure and relief of RV outflow tract obstruction (by either patch, conduit, or muscle resection). Patients without prior surgery, or those simply palliated by shunts, are excluded.

- 3) **CASE** patients may have suffered any of the following **EVENTS**
 - sudden death without identifiable non-cardiac cause
 - cardiac arrest suspected or documented to be due to any arrhythmia, (including VT, VF, atrial flutter, AV block, drug proarrhythmia, etc.), whether or not the patient was successfully resuscitated
 - documented spontaneous sustained VT, even if hemodynamically stable
 - documented appropriate ICD discharge

- 4) The 3 **CONTROL** patients must have had their intracardiac repair within about 5 years of the corresponding **CASE**, but need not be matched for chronological age, precise anatomy, surgical center, nor any other variable.

- 5) Certain items are required for both a **CASE** or **CONTROL**:
 - 12-lead ECG within 2 years of **EVENT** or last follow-up (provide copy)
 - Holter or exercise test within 5 years of **EVENT** or last follow-up
 - Echo or cath within 5 years of **EVENT** or last follow-up
 - Chest X-ray within 5 years of **EVENT** or last follow-up

- 6) Identify all your patients by initials on the data sheet. Fill in a "case/control set number" in the upper right corner of the first page, and be sure to circle whether a patient is a case or control. For example, the first patient you review from your center would be SET#1, which will include CASE #1 and CONTROL patients #1A, #1B, and #1C. Review check list on first page for eligibility.

- 7) We have obtained IRB approval from the Committee on Clinical investigation at Boston Children's Hospital for this retrospective study. If your own institution has a firm policy on retrospective data analysis that requires you to submit your own application, please do so.

- 3) Please mail completed forms (with ECG's attached) to:

Ed Walsh
Dept of Cardiology, Children's Hospital
300 Longwood Ave
Boston MA 02115

TOF STUDY (DATA FORM)

CENTER: _____

PATIENT INITIALS: _____

PHYSICIAN: _____

CASE / CONTROL SET # _____

check one: CASE
 CONTROL A
 CONTROL B
 CONTROL C

Patient's date of birth : ___ / ___ / ___

Date of last cardiac follow-up ___ / ___ / ___

Date of serious EVENT (CASE patient) ___ / ___ / ___

INCLUSION CHECK LIST

<u>CASE patient</u>	<u>CONTROL patient</u>
<input type="checkbox"/> EVENT* within last 15 years	<input type="checkbox"/> Repair within 5 years of corresponding CASE
<input type="checkbox"/> Diagnosis of TOF*	<input type="checkbox"/> Diagnosis of TOF*
<input type="checkbox"/> ECG within 2 years of EVENT (provide copy)	<input type="checkbox"/> Most recent cardiac F/U visit 1998 or thereafter
<input type="checkbox"/> Holter or ETT within 5 years of EVENT	<input type="checkbox"/> ECG within 2 years of most recent F/U (provide copy)
<input type="checkbox"/> Echo or cath within 5 years of EVENT	<input type="checkbox"/> Holter or ETT within 5 yrs of most recent F/U
<input type="checkbox"/> CXR within 5 years of EVENT	<input type="checkbox"/> Echo or cath within 5 years of most recent F/U
	<input type="checkbox"/> CXR within 5 years of most recent F/U

* see Study Description & Directions sheets for definitions

Anatomic Diagnosis:

- tetralogy of Fallot
 - tetralogy/pulm atresia
 - DORV with TOF-type repair (no sub AS)
 - TGA/VSD s/p Rastelli (no sub AS)
 - other _____
-

Cardiac Surgical History

Op #1 Type _____
Date ____/____/____

Op #2 Type _____
Date ____/____/____

Op #3 Type _____
Date ____/____/____

Op #4 Type _____
Date ____/____/____

Functional/Symptom Status

NYHA class _____

near time of EVENT, or at
last follow-up for CONTROLS

- R-side congestive symptoms? no yes
 - Exercise intolerance? no yes
 - Palpitations? no yes
 - Dizziness? no yes
 - Syncope? no yes
-

Medications & Devices none

near time of EVENT, or at
last follow-up for CONTROLS

(check any that apply)

- digoxin
- diuretics
- potassium
- ACE inhib
- coumadin
- other (_____)
- IA (specify _____)
- IB (specify _____)
- IC (specify _____)
- beta-blk
- Sotalol
- Amiodarone
- Verapamil
- Atrial pacemaker
- Ventricular pacemaker
- Dual chamber pacemaker
- ICD

Are there clear reasons to question drug compliance? no yes

Are there clear reasons to suspect pacemaker or ICD malfunction? no yes

Serum potassium near time of EVENT or at last follow-up: low normal high unknown

Electrocardiogram Date of ECG ___/___/___

nearest to EVENT, or
most recent for CONTROLS

(NB: COPY OF TRACE SHOULD BE ATTACHED AND SENT ALONG WITH DATA FORM FOR EACH CASE & CONTROL. ECG'S WILL BE READ IN A BLINDED FASHION AT THE COORDINATING CENTER)

Chest X-Ray Date of film ___/___/___

nearest to EVENT, or
most recent for
CONTROLS

Cardiomegaly (circle one):	none	mild	moderate	severe
Pulmonary venous markings:	normal	congested		
Pulmonary arterial flow:	normal	decreased	increased	
Flow symmetry:	normal	L>R	R>L	

Echocardiogram Date of Echo ___/___/___

nearest to EVENT, or
most recent
for CONTROLS

RVOT obstruction (circle one):	none	mild	moderate	severe
Pulmonary regurg:	none	mild	moderate	severe
Tricuspid regurg	none	mild	moderate	severe
RV size:	normal	mild-mod enlarg		severe enlarge
RV function:	normal	good	fair	poor
Residual VSD:	none	small	moderate	large
Residual ASD:	none	small	moderate	large
LV function:	normal	good	fair	poor
Branch PA's:	OK	R-obstruct	L-obstruct	R&L-obstruct
Estimate of RV pressure:	normal	<1/2 syst	>1/2 syst	

Other observations: _____

Cardiac Cath Date of cath ___/___/___

nearest to EVENT, or
most recent for CONTROLS

SVC	___%	RA	___ mmHg (mean)
RA	___%	RV	___/___ mmHg
RV	___%	MPA	___/___ mmHg
PA	___%	LPA	___/___ mmHg
LV	___%	RPA	___/___ mmHg
AO	___%	PCW	___ mmHg (mean)
		LV	___/___ mmHg

Angio & other observations

Holter Monitoring

Date of Holter ___ / ___ / ___

nearest to EVENT, or
most recent for CONTROLS

Check all abnormalities that apply for **Holter on above date**:

- SA node dysfunction
- non-physiologic AV block
- atrial flutter or fib (maximum vent response rate: ___BPM)
- other SVT
- Ventricular arrhythmias (check highest grade below)
 - isolated uniform
 - isolated multiform
 - couplets
 - VT (max # Beats ___ fastest rate ___)
 - monomorphic
 - polymorphic

Exercise Test

Date of test ___ / ___ / ___

Nearest to EVENT, or
most recent for CONTROLS

Check all abnormalities that apply for **test on above date**:

- SA node dysfunction
- non-physiologic AV block
- atrial flutter or fib (maximum vent response rate: ___BPM)
- other SVT
- Ventricular arrhythmias (check highest grade below)
 - isolated uniform
 - isolated multiform
 - couplets
 - VT (max # Beats ___ fastest rate ___)
 - monomorphic
 - polymorphic

EP Studies

- | | |
|----------|--|
| Study #1 | Date ___ / ___ / ___
Findings: _____
Action: _____ |
| Study #2 | Date ___ / ___ / ___
Findings: _____
Action: _____ |
| Study #3 | Date ___ / ___ / ___
Findings: _____
Action: _____ |
| Study #4 | Date ___ / ___ / ___
Findings: _____
Action: _____ |

Serious EVENT for CASE patients

- a) type of EVENT (check one) unexpected, unwitnessed sudden deathpresumed arrhythmic event. No non-cardiac etiology found
 witnessed arrest with unsuccessful resuscitation (documented or suspected initial rhythm: _____)
 witnessed arrest with successful resuscitation (documented or suspected initial rhythm: _____)
 spontaneous sustained VT without cardiac arrest
 appropriate ICD discharge for spontaneous VT/VF

c) description of EVENT: _____

d) outcome: _____

e) was autopsy done? (circle one): not applicable yes no (if yes, please provide details on back)