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Long-Term Follow-Up After Catheter Ablation of Atrioventricular Nodal Reentrant Tachycardia in Children

D.Backhoff, S.Klehs, M.Müller, H.Schneider, T.Kriebel, T.Paul, U.Krause

Background: Catheter ablation for AV nodal reentrant tachycardia (AVNRT) in children and adult is the recommended treatment of choice with a reported acute success rate of 98% to 100%. The long term outcome for these children is unknown.
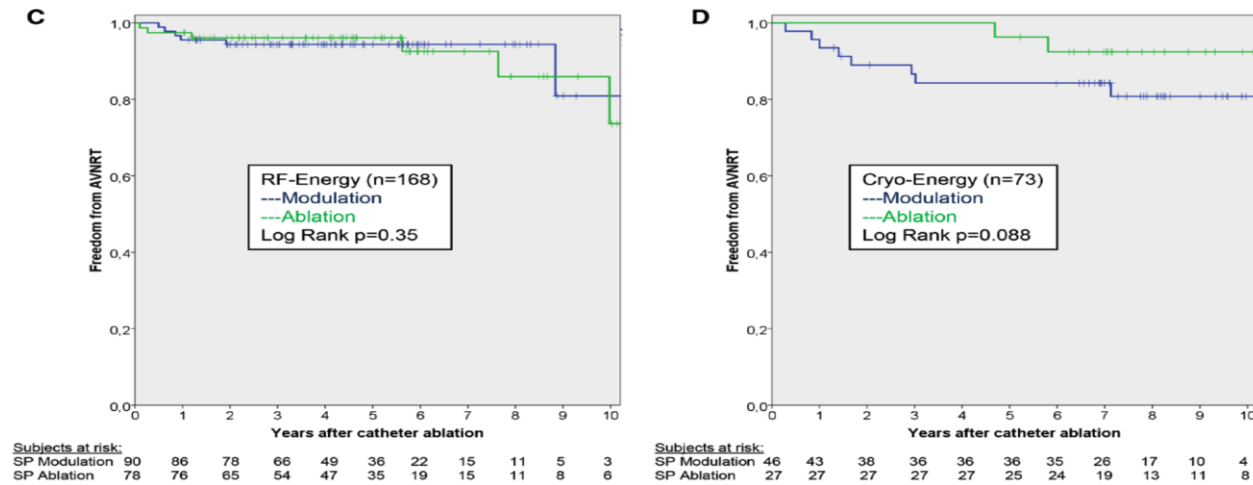
Objectives:
The focus of this study is to evaluate the long term course of pediatric patients after AVNRT ablation, specifically looking at the impact of the primary procedural end point (slow pathway (SP) ablation versus SP modulation) on long-term success, the incidence and timing of late AVNRT recurrence, as well as the incidence of late AV block or new tachyarrhythmias attributable to AVNRT ablation.

Methods: This is a single center retrospective observational study for children and adolescents undergoing AVNRT ablation from 2002 and 2014. Procedural end point of AVNRT ablation had been either SP ablation (no residual dual AV nodal physiology) or SP modulation (residual SP conduction allowing for a maximum of one atrial echo beat). Diagnosis of recurrence was established either by ECG documentation of typical SVT or—in patients with symptoms of AVNRT recurrence—presence of dual AV node physiology allowing for more than one atrial echo beat during repeat EPS.

Results:
• Data from 241 patients (after exclusion of patients who have permanent AV block or failed ablation) with a median follow-up of 5.9 were analyzed. For the whole study cohort, calculated freedom from AVNRT was 96% at 1 year, 94% at 3 years, 93% at 5 years, and 89% at 8 years post ablation.

Subjects at risk:											
SP Modulation	90	86	78	66	49	36	22	15	11	5	3
SP Ablation	78	76	65	54	47	35	19	15	11	8	6

Subjects at risk:											
SP Modulation	46	43	38	36	36	36	35	26	17	10	4
SP Ablation	27	27	27	27	27	25	24	19	13	11	8

• AVNRT recurrence occurred in 22 patients (9.1%); 41% of those recurred within the first year post ablation, whereas 27% occurred ≥ 5 years after the procedure.
• Although there was qualitative difference in long-term recurrence rates between patients with SP ablation versus SP modulation especially with cryoenergy (figure), the number of recurrence was too low for the analysis to have statistical power.
• None of the patients developed late AV block or new tachyarrhythmias attributable to AVNRT ablation.

Conclusion:
AVNRT ablation in pediatric patients was a safe and effective procedure with a cumulative long term success rate of 91%. Recurrences as late as after 10 years have been reported. Age, sex, body weight, and the choice of ablation energy did not appear to impact long-term freedom from AVNRT.

Reviewer's Comments:
This paper highlights the substantial rate of late recurrences even after 8-10 years of successful AVNRT ablation in children. While our understanding of the exact pathophysiology of AVNRT remains limited, changes in the geometry of Koch's triangle and the AV nodal physiology with age and growth could be potential contributing factors to AVNRT recurrence. Larger multicenter studies are needed to further identify risk factors for recurrence.

Hemodynamic Effects of Sustained Postoperative Cardiac Resynchronization Therapy in Infants After Repair of Congenital Heart Disease: Results of a Randomized Clinical Trial
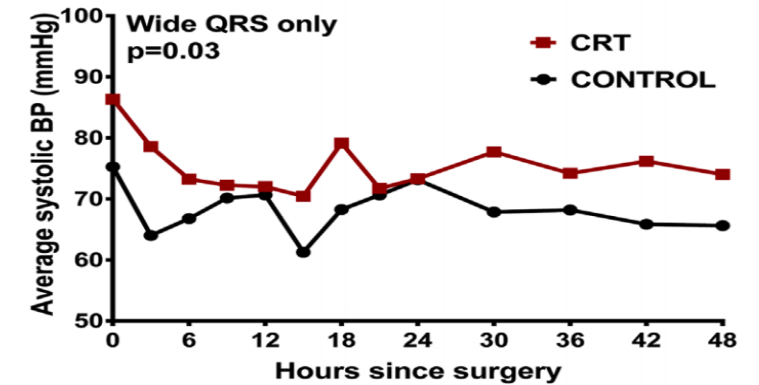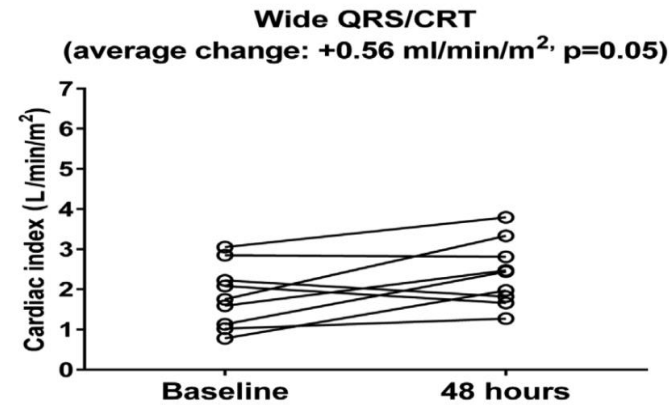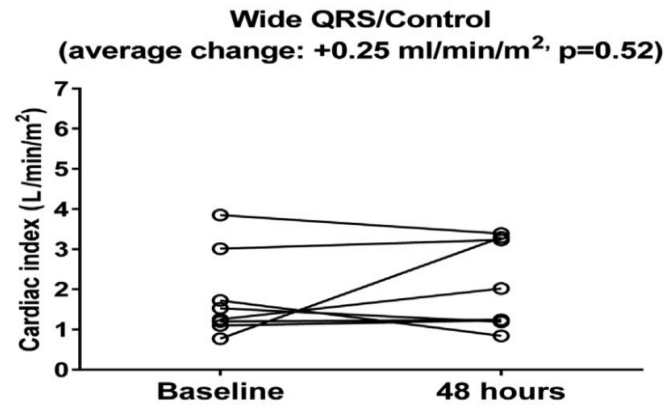
M.Friedberg, S.Schwartz, H.Zhang, C.Chiu-Man, C.Manlhiot, M.Ilina, G.Van Arsdell, J.Kirsh, B.McCrindle, E.Stephenson

Background: After repair of congenital heart disease (CHD), infants may be particularly susceptible to postoperative hemodynamic compromise and subsequently prolonged hospital stay. In previous adult and non-randomized pediatric studies, postoperative cardiac resynchronization therapy (CRT) has been shown to improve myocardial function and hemodynamics.

Objectives:
The objectives of this study were to investigate whether continuous CRT for 48 hours improves cardiac output and blood pressure in infants after biventricular repair of CHD and whether this effect is influenced by intraventricular dyssynchrony.

Methods: Infants less than 4 months of age undergoing biventricular surgical repair were randomized pre-operatively to either receive CRT (via an additional LV temporary pacing lead that was placed on the left lateral wall midway between the LV base and apex) or control group. The primary outcome was the change in cardiac index (CI) from baseline to 48 postoperative hours (or until extubation if earlier). CI was calculated using the Fick method with oxygen consumption measured by continuous respiratory mass spectroscopy.

Wide QRS/Control (average change: +0.25 ml/min/m^2, p=0.52)

Cardiac index (L/min/m^2) — Baseline vs 48 hours

Wide QRS/CRT (average change: +0.56 ml/min/m^2, p=0.05)

Cardiac index (L/min/m^2) — Baseline vs 48 hours

Wide QRS only p=0.03 — Average systolic BP (mmHg) vs Hours since surgery. CRT, CONTROL

Results:

- 42 infants were enrolled and randomized to either CRT (n=21) or controls (standard care and no CRT, n=21)
- For the study population as a whole, there was no change in CI or blood pressure between the two groups. However, when stratified by intrinsic QRS duration, there was a trend toward higher CI and blood pressure in the CRT patients with wide intrinsic QRS - >98th centile for age- compared to the control group (figure).
- These results were observed despite the fact that the average QRS duration did not show significant narrowing with pacing. This study was not powered to investigate other secondary clinical outcomes.
- There were no adverse events attributable to pacing.

Conclusion:

In infants undergoing biventricular repair of CHD, CRT improves systolic blood pressure and may improve CI in those with prolonged QRS duration for age.

Reviewer's Comments:

This pilot study concludes that CRT may be beneficial for postoperative hemodynamics in infants with a wide intrinsic QRS. Larger studies are needed to confirm these results and evaluate the effect of CRT on other clinical end points such as inotrope usage, ventilation times, and ICU length of stay. The cohort in this study was also quite heterogeneous, and other questions including the ideal location for LV lead placement and the patient population that may be best suited for this therapy require further investigation.

Assessing the Risks Associated with MRI in Patients with a Pacemaker or Defibrillator

Robert J. Russo, Heather S. Costa, Patricia D. Silva *et al.*

Background: The use of magnetic resonance imaging (MRI) poses potential safety concerns for patients with an implanted cardiac device (cardiac pacemaker or implantable cardioverter defibrillator [ICD]). There is a potential for magnetic field-induced cardiac lead heating, which could result in myocardial thermal injury and detrimental changes in pacing properties. Over the past 2 decades, "MRI conditional" devices have been designed to reduce such risks; however, there remains an estimated 2 million people in the US and 6 million worldwide with "non-MRI-conditional" devices, half of which are predicted to have a clinical indication for MRI during their lifetime.

Objectives:

1. The MagnaSafe Registry was established to determine the frequency of cardiac device-related clinical events and device setting changes among patients with non-MRI-conditional devices who undergo non-thoracic MRI at a magnetic field strength of 1.5 tesla
2. To define a simplified protocol for screening, monitoring, and device programming for such patients.

Methods:

- Patients in the registry were referred for clinically indicated non-thoracic MRI at a field strength of 1.5 tesla
- Devices were interrogated before and after MRI with a standardized protocol and reprogrammed before scanning
- Primary end points were death, generator or lead failure, induced arrhythmia, loss of capture, or electrical reset during scanning
- Secondary end points were changes in device settings

Table 2. Primary End Points.

End-Point Event	Pacemaker		ICD	
	Events/Cases	% (95% CI)	Events/Cases	% (95% CI)
Death during the MRI examination	0/1000	0 (0–0.4)	0/500	0 (0–0.8)
Generator failure requiring immediate replacement	0/1000	0 (0–0.4)	1/500*	0.2 (0.04–1.1)
Lead failure requiring immediate replacement†	0/1926	0 (0–0.2)	0/997	0 (0–0.4)
Loss of capture during the MRI examination‡	0/280	0 (0–1.4)	NA	NA
Observed atrial arrhythmia	5/1000	0.5 (0.2–1.2)	1/500	0.2 (0.04–1.1)
Observed ventricular arrhythmia	0/1000	0 (0–0.4)	0/500	0 (0–0.8)
Electrical reset§	6/1000	0.6 (0.3–1.3)	0/500	0 (0–0.8)

Table 4. Cases in Which a Secondary End-Point Event Occurred Immediately after MRI or by the Final Follow-up.*

End Point	Pacemaker		ICD	
	Immediate	Long-Term	Immediate	Long-Term
		number/total number (percent)		
Battery voltage decrease ≥0.04 V	3/802 (0.4)	0/802	24/333 (7.2)	14/333 (4.2)
Pacing lead threshold increase ≥0.5 V	13/1813 (0.7)	5/1813 (0.3)	8/951 (0.8)	3/951 (0.3)
P-wave amplitude decrease ≥50%	7/790 (0.9)	2/790 (0.3)	1/346 (0.3)	0/346
R-wave amplitude decrease ≥50%	0/844	0/844	1/496 (0.2)	0/496
Pacing lead impedance change ≥50 ohms	62/1902 (3.3)	26/1902 (1.4)	41/984 (4.2)	22/984 (2.2)
High-voltage lead impedance change ≥3 ohms	NA	NA	100/611 (16.4)	61/611 (10.0)

Results:
- MRI was done in 1000 cases in patients with a pacemaker and 500 cases in patients with an ICD.
- No deaths, lead failures, losses of capture, or ventricular arrhythmias occurred during MRI.
- One ICD generator could not be interrogated after MRI and required immediate replacement. Of note, the device was not appropriately programmed per protocol before the MRI.
- There were 6 cases of self-terminating Afib/flutter and 6 cases of partial electrical reset.
- Changes in lead impedance, pacing threshold, battery voltage, and P-wave and R-wave amplitude exceeded pre-specified thresholds in a small number of cases.
- Repeat MRI was not associated with increased risk of adverse events.

Conclusions:
- No patients with "non-MRI-conditional" cardiac devices who underwent non-thoracic MRI at 1.5 tesla, were appropriately screened, and had the cardiac device reprogrammed according to study protocol, had device or lead failure.

Implications for Pediatric EP:
- The study population was >18 years and applicability of these study results to pediatrics is yet unknown. All patients underwent non-thoracic MRIs and further studies in patients undergoing thoracic and cardiac MRIS, which would be particularly important in our ACHD patients, are warranted.

Mechanisms and predictors of recurrent tachycardia after catheter ablation for d-transposition of the great arteries after the Mustard or Senning operation

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Jamil A. Aboulhosn, MD,[†] Farnoosh Nik-Ahd, BA, BS,[*] Jeremy P. Moore, MD, MS, FHRS[*†]

Background: The Senning and Mustard operations for d-TGA are associated with SVT that increases in frequency over time. The most common mechanisms include cavotricuspid isthmus (CTI)-dependent intra-atrial reentrant tachycardia (IART), incisional or scar-related IART, focal atrial tachycardia, and less commonly AVNRT. SVT may recur in a significant number of cases post-ablation; however, little is known about the mechanism and predictors Sf recurrence.

Objectives: To describe the electrophysiological characteristics of recurrent tachycardia for patients with d-TGA s/p Senning/Mustard following an initially successful catheter ablation. The hypothesis was that the type and degree of recurrence would depend on the surgical technique used.

Methods:
- Retrospective case study of patients with d-TGA s/p Senning or Mustard procedures who underwent a catheter ablation from 2004-2016.
- Clinical data collected included results of cardiac MRI/CT or cardiopulmonary exercise testing, antiarrhythmic use, history of pacemaker/ICD, and hemodynamic data obtained at the time of the catheter ablation.
- Characterization of the tachycardia was aided by electroanatomical mapping using either the EnSite system or CARTO in all cases.
- A transbaffle puncture was performed when mapping suggested origin of the tachycardia to be from the pulmonary venous atrium (PVA)
- Discrete linear surgical scars in the posterior and lateral PVA were classified into 1 of 2 possible categories on the bases of careful correlation with the surgical report. A posterior anastomosis was defined as a vertically arranged series of split potentials and/or scar voltages immediately adjacent to the right pulmonary veins after the Senning operation, while an atriotomy was defined as a similar pattern of signals located within the lateral morphologic RA, typically after the Mustard operation.
- Complete success was defined as elimination of all inducible tachycardias and partial success as elimination of >1 but not all inducible tachycardias. Recurrence was defined by clinical evidence of a sustained and organized SVT after a successful catheter ablation procedure.

Results:

- 28 patients underwent 38 procedures during the study period, the most common mechanism at the index procedure was CTI-IART.
- Over a median follow-up period of 1.6 years, 9 patients experienced recurrent tachycardia (32%), all of whom underwent repeat catheter ablation.
- Tachycardia recurrence was more common after the Senning vs the Mustard procedure (6 of 10 [60%] vs 3 of 18 [17%]; p=0.034).
- Substrates for recurrence were different from those at index procedure in 10 of 13 tachycardias (77%), with the most common location being the posterior anastomosis after the Senning (*modified left lateral view in such pt w/ IART).
- Complete control was achieved in 27 patients (96%).

Table 2 Characteristics of index vs repeat procedures

Characteristic	Index procedure (n = 28)	Repeat procedure (n = 9)	P
Age (y)	36.5 ± 7.4	33.3 ± 6.2	.376
Sex: male	18 (64)	6 (67)	1.000
Surgical repair			0.136
Senning	10 (36)	6 (67)	—
Mustard	18 (64)	3 (33)	—
Median number of tachycardia induced	1 (1–2)	1 (1–2.5)	.406
Median number of tachycardia ablated	1 (1–1)	1 (1–2)	.193
Mechanism			.261
CTI-dependent IART	16 (57)	3 (33)	—
Non–CTI-dependent IART	5 (18)	4 (44)	—
Focal AT	6 (21)	5 (56)	—
AVNRT	3 (11)	1 (11)	—
Isoproterenol used	7 (25)	6 (67)	.043
Isoproterenol yield*	6 (86)	2 (33)	.103
Irrigated energy	19 (68)	6 (67)	1.000
Force monitoring	4 (14)	2 (22)	.620
Multipolar mapping catheter	3 (11)	0 (0)	.562
Mapping system			0.078
EnSite	4 (14)	4 (44)	—
CARTO	24 (86)	5 (56)	—
Targeted atrium			.492
Pulmonary venous	13 (46)	6 (67)	—
Systemic venous	7 (25)	2 (22)	—
Both	8 (29)	1 (11)	—
Access to PVA			.545
Puncture	17 (81)	7 (100)	—
Baffle leak	4 (19)	0 (0)	—
Median number of ablation lesions	19 (13–32)	23 (8–41)	.807
Outcome			.395
Complete	25 (89)	7 (78)	—
Partial	2 (7)	2 (22)	—
Unsuccessful	1 (4)	0 (0)	—
Tachycardia recurrence	9 (32)	2 (22)	.695

* B
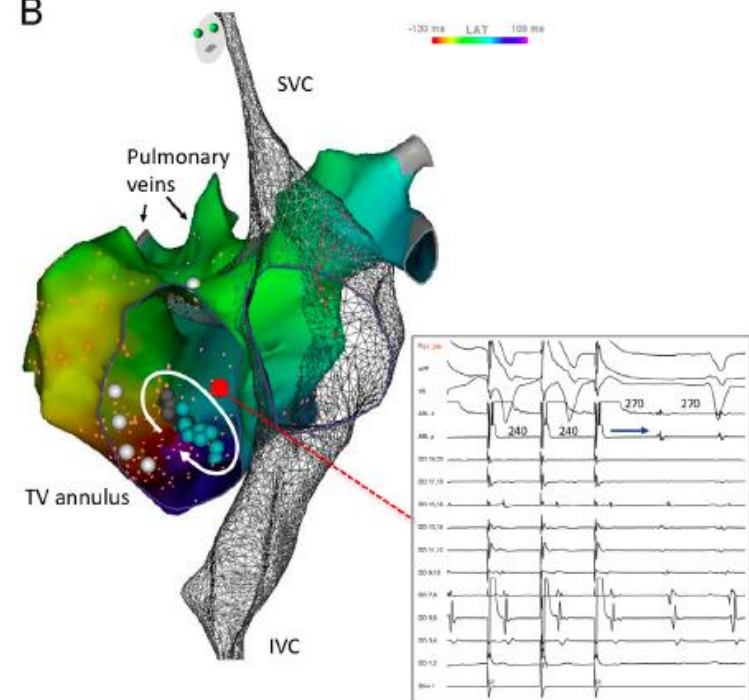
Conclusions:

- Recurrent SVT was relatively common following an initially successful catheter ablation, with the recurrent substrate differing from the initial substrate in the majority of cases.
- Recurrent SVT was more common after Senning procedures and often involved a posterior anastomosis.

Implications for ACHD EP:

- careful search for additional potential tachycardia substrates, centered primarily on the nature of the prior surgical technique, may be useful to avoid recurrent arrhythmias.

Transcription factor ETV1 is essential for rapid conduction in the heart

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Background:

Defects in the *fast conduction system* of the heart, including the pectinated atria myocardium (**PAM**) and the ventricular conduction system (**VCS**; comprising the His bundle, right and left bundle branches and Purkinje fiber cells), have been shown to result in a diverse array of arrhythmias including atrial fibrillation, ventricular tachyarrhythmias and heart block. Limited therapeutic options exist and underscores our relative lack of knowledge regarding the molecular regulators of the fast conduction system development, maturation and function.

Prior studies have demonstrated that the specialized properties of the fast conduction system is in part owed to enriched expression of key conduction genes including **Scn5a** (encoding a subunit of the cardiac sodium channel Nav1.5) and the high conductance gap junction protein Connexin 40 (**Cx40**). Additionally, while the transcription factor **Nkx2-5** has been previously shown to be required for VCS specification, certain genes including Scn5a remain unperturbed in expression in Nkx2-5 mutants arguing for the existence of other crucial regulators of VCS fate.
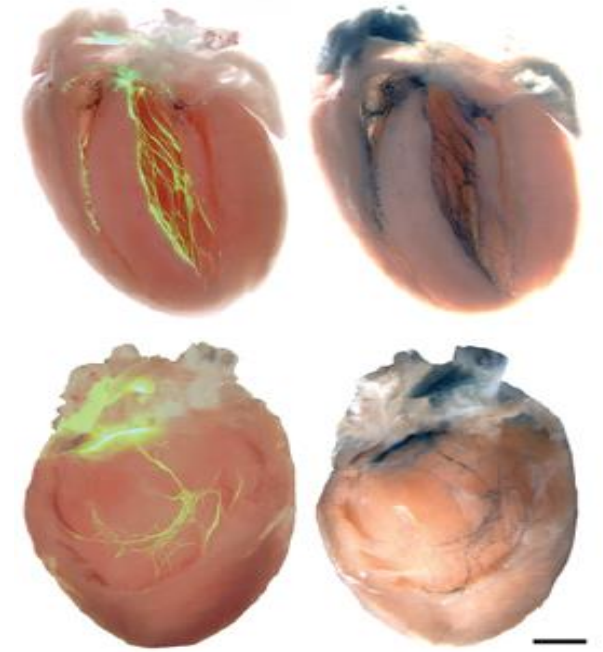
Figure 3b. ETV1 expression is enriched in fast conduction tissues of the adult murine heart. Contactin-2-enhanced green fluorescent protein (Cntn2-EGFP) (left, green) is a known specific marker of the conduction system. Etv1 lacZ/+ *knock-in* mice (right), express the lacZ reporter gene (blue) with overlapping expression in the VCS and PAM.

Results: In this study, *Shekhar et al.* used a multitude of approaches including signal transduction screens, transcriptional profiling, murine genetic models, cellular electrophysiology and human genetic analysis to implicate Etv1 as a regulator of the rapid conduction phenotype within the vertebrate heart.

Gene profiling of postnatal Purkinje cells and their embryonic predecessors, trabeculated cardiomyoctes, demonstrated enrichment of the transcription factor **Etv1** (*Fig 2a*) suggesting a role in their development. Prior studies have shown that Etv1 is a downstream target of the **Neuregulin** (NRG)/**ErbB/Ras-MAPK signaling**. Consistently, via a series of *in vitro* assays, neuregulin signaling was both necessary and sufficient to modify the expression of Etv1 and key rapid conduction genes in *ex vivo* cultured hearts (*Fig 1f*).

Etv1 knock out ('Etv1KO') mice exhibited conduction defects (*Fig 6*) and a roughly 50% reduction in Nkx2-5 mRNA (*Fig 7f*) and protein in fast conduction cell types. This was associated with VCS hypoplasia, phenocopying Nkx2-5 haploinsufficient mice (*Fig 8*). However, in comparison to Nkx2-5 haploinsufficient mice, Etv1KO mice demonstrated a reduced expression of Scn5a (*Fig 7f*). Consistently, patch clamp recordings of Etv1KO mouse Purkinje cells exhibited an abrogation of fast sodium channel biophysical properties, rendering their conduction properties similar to ventricular myocardium (*Fig 9a*). Finally, the authors demonstrated an association between a human ETV1 sequence variant with BBB in african americans and heart block in european americans.
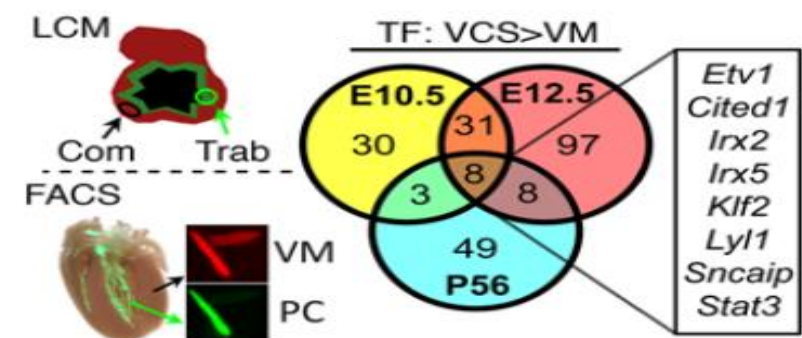

Figure 2a. Etv1 is one of the most enriched transcription factors in embryonic trabeculated myocytes and adult Purkinje fiber cells.
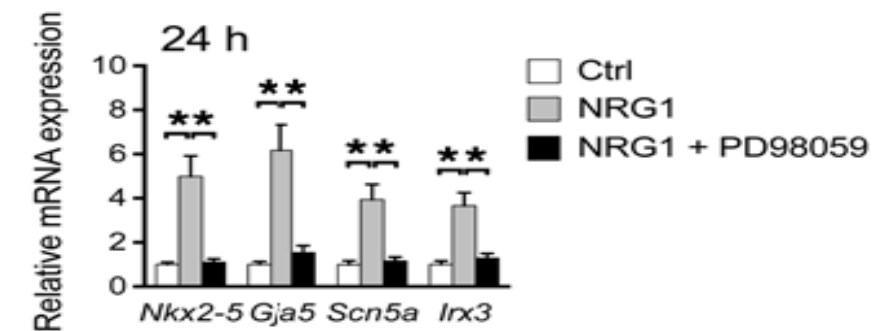

Figure 1f. Nrg1 induces expression of key rapid conduction genes, while the MAPK inhibitor PD98059 inhibits this expression.
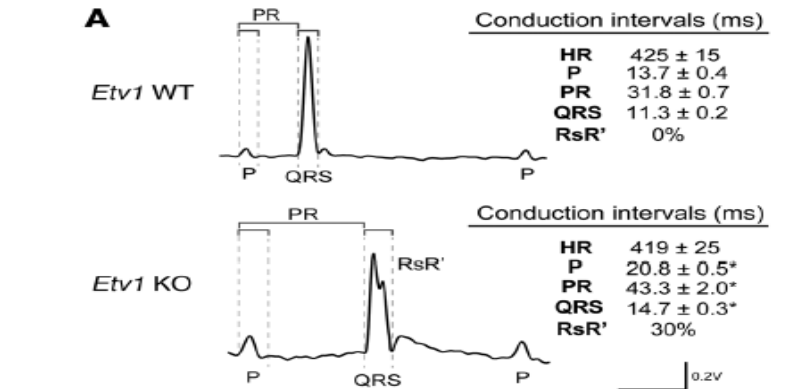

Figure 6. Etv1 mutant mice display conduction defects incl. prolonged P, PR and QRS intervals.

Conclusions and Implications:

In this study, *Shekhar et al.* implicate Etv1 as an important transcriptional regulator, necessary for the development of the rapid conduction system of the vertebrate heart, including the VCS, through mediating the expression of key conduction system genes including *Nkx2-5, Scn5a* and *Cx40*.

Future Directions:

Additional studies evaluating direct Etv1 gene targets using co-immunoprecipitation and, more globally, ChIP-CHIP assays will prove valuable in the future. Additionally, global gene changes in the setting of Etv1 loss of function using Cntn-EGFP; Etv1KO mice would help to expand upon its role as a putative master regulator of VCS development. Finally, both the gain- and loss-of-function experiments were "systemic" and there would be added value in utilizing CCS-specific conditional Etv1KO mice strains as well as a conduction-specific *in vivo* model of NRG1/Erb/MAPK signaling upregulation, emphasizing the need for continued efforts in our community to generate CCS-specific tools.
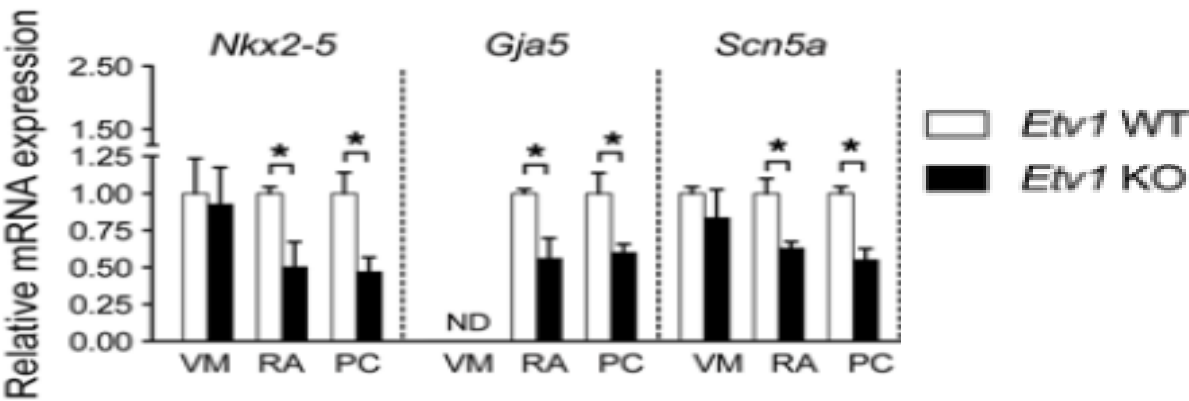

Figure 7f. Etv1 mutant mice demonstrate reduced expression of *Nkx2-5, Gja5 (Cx40),* and *Scn5a* in atrial (RA) and Purkinje cells (PC) but not in the ventricular myocardium (VC).
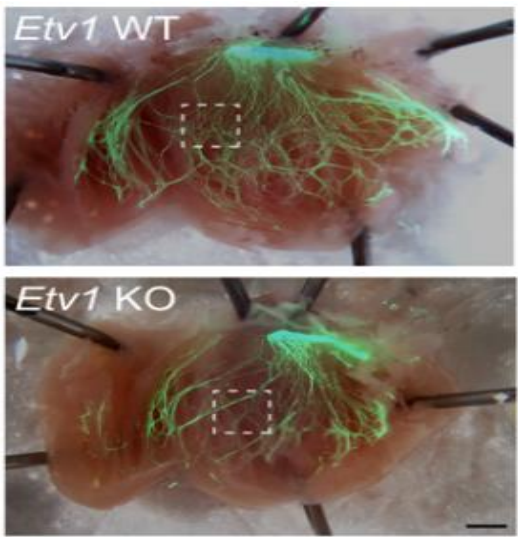

Figure 8a. Systemic Etv1 loss results in VCS hypoplasia. Etv1KO; Cntn2-EGFP murine heart with CCS labeled in green.
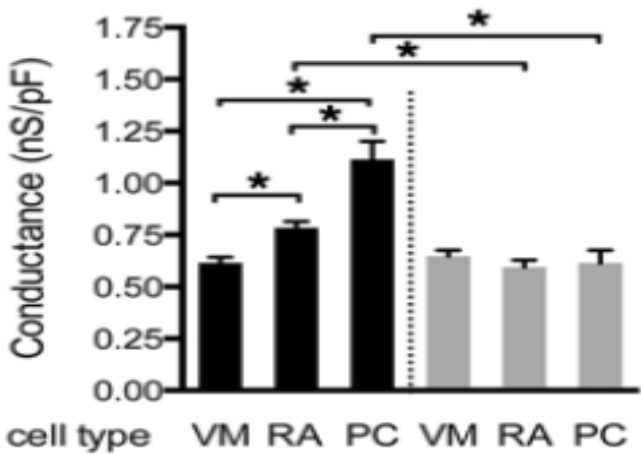

Figure 9a. Loss of Etv1 homogenizes sodium channel biophysical properties between ventricular, atrial and purkinje fiber cell types.

Development of the cardiac conduction system in Zebrafish

Kar-Lai Poon, Michael Liebling, Igor Kondrychyn, Thomas Brand, Vladimir Korzh

Background:

The zebrafish, *Danio rerio*, a tropical freshwater fish has been progressively utilized over the past 30+ years as a model system in developmental biology for its favorable characteristics including small size (3-5cm), short life cycle, transparency during development, high fertility, ease of performing unbiased mutagenesis screens, and *in vivo* assays including drug/small molecule delivery and optogenetics[1].

Zebrafish have a basic heart structure comprised of only two-chambers (*Fig 1*) as well as a simple cardiac conduction system (CCS) comprised of a SA node and AV node, both arranged in ring formations (SAR and AVR, respectively), offering the advantage of studying fundamental questions in pacemaker cell development. Additionally, and somewhat unexpectedly, zebrafish HRs (120-180bpm), tissue repolarization and ECG patterns more closely mimic human physiology than do their murine counterparts (HR 300-600bpm). Despite the power of this model system, few genes have been implicated in CCS development within zebrafish, setting the stage for additional work in defining markers and molecular regulators of pacemaker differentiation, maturation and function.
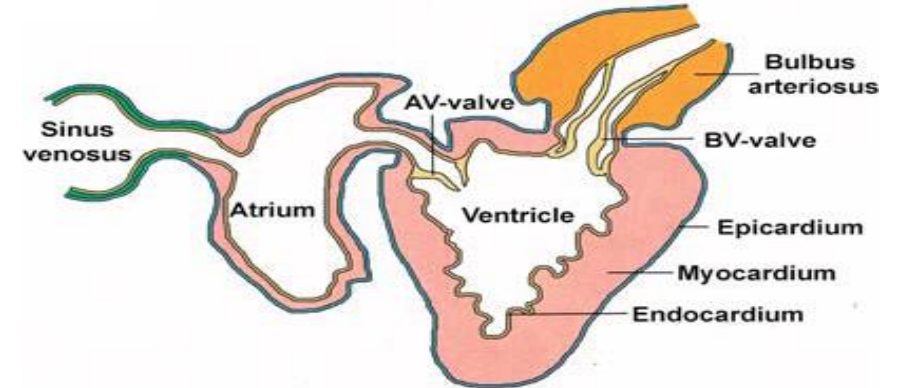

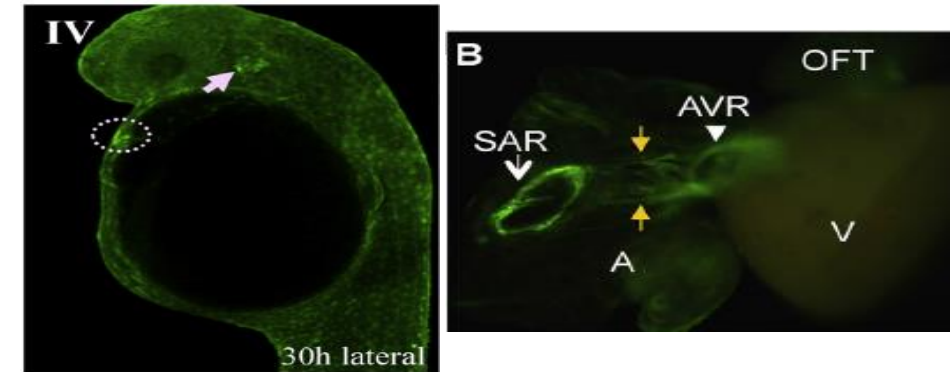**Figure 1.** The adult zebrafish heart.[1]

Figure 2. Left: Enhanced green fluorescent protein expression *in vivo* of th "SET33-mi59B" CCS
transgenic line (*Fig1-IV*). CCS circled. **Right:** High resolution image of EGFP expression specifically
within the ringed SAN (or SAR) and AVN (or AVR). Orange arrows denote internodal connections (*Fig 3b*).

[1]Poon and Brand. The Zebrafish model system in cardiovascular research: A tiny fish with mighty prospects. *Glob Card Sci Pract. 2013: 14.*

Results: In this study by *Poon et al.,* the authors evaluated two transgenic zebrafish lines previously created by their lab in an enhancer-trap screen in which the enhanced green-fluorescent protein (EGFP) gene is randomly inserted within the genome to identify novel cell-specific gene promoters and enhancers. They noted that two such lines (named SqET33-mi28 and SqET33-mi59B) expressed EGFP within a distribution consistent with the cardiac pacemaker cells (SAR and AVR) of the zebrafish (*Fig 2*).
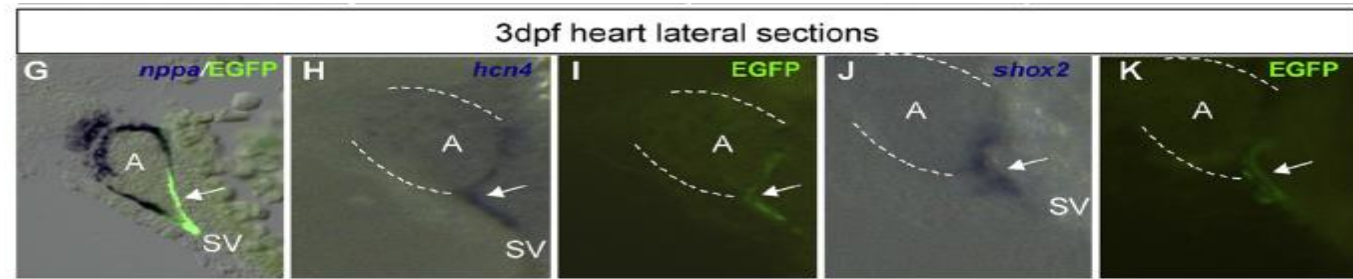

3dpf heart lateral sections

Figure 3. EGFP expression is specific to the CCS as shown by co-expression with known CCS components including *hcn4* and *shox2*. Note how EGFP is excluded from the *nppa* positive working myocardium (*Fig 2G-J*).
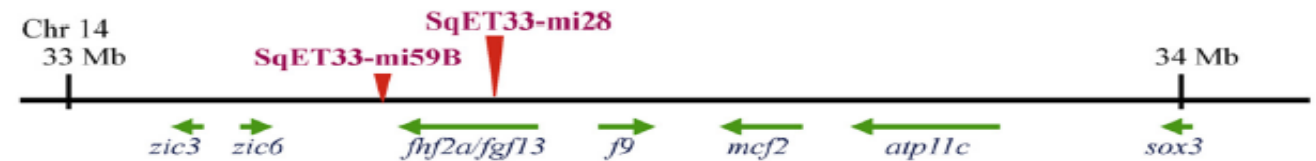

Figure 4. Mapping of the gene insertion points for both transgenic lines to a 1Kb on Chromosome 14 containing a cluster of 7 genes (*Fig 5a*).

They confirmed the expression specificity by whole mount *in situ hybridization* and immuno-fluorescence with other known markers native to the CCS including *hcn4* and *shox2* (*Fig 3*). The transgenic lines were also crossed into 2 known mutant backgrounds, implicating a role for endocardial signaling and/or hemodynamic stimulation in zebrafish pacemaker development. Finally, the authors determined the point of insertion of these transgenic lines within a cluster of genes (*Fig 4*) and confirmed that they reflected endogenous Fhf2 gene expression (*Fig 5*), previously implicated in murine CCS function.

Conclusions, Implications and Limitations: While perhaps lacking in depth of analysis, the article demonstrates the potential of zebrafish as a powerful genetic tool in our continued investigation into the development of the cardiac conduction system.

Not only do these strains provide a novel marker allowing for enhanced cell sorting and analysis of zebrafish pacemaker cells, they additionally allow for the ability to perform high throughput and unbiased forward mutagenesis screens to further define factors crucial to the development, maturation and function of pacemaker cells.
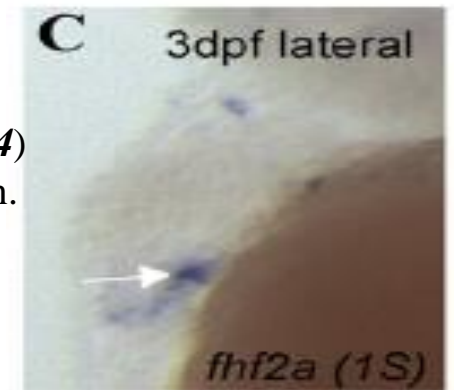
Figure 5. Of those cluster of genes, only fhf2a demonstrated CCS-specific expression, and thus recapitulated that seen in the EGFP transgenic lines (*Fig 5c*).

International Recommendations for Electrocardiographic Interpretation in Athletes

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Participation in intensive exercise (> 4 hours per week) is associated with electrical manifestations of enlarged cardiac chamber size and increased vagal tone

Normal ECG findings in athletes
These training-related ECG alterations are physiologic adaptations to regular exercise, considered normal variants in athletes, and do not require further evaluation in asymptomatic athletes with no significant family history.

Normal ECG finding	Definition
Increased QRS voltage	Isolated QRS voltage criteria for left (SV1 + RV5 or RV6 >3.5 mV) or right ventricular hypertrophy (RV1 + SV5 or SV6 >1.1 mV)
Incomplete RBBB	rSR' pattern in lead V_1 and a qRS pattern in lead V_6 with QRS duration <120 ms
Early repolarization	J-point elevation, ST-segment elevation, J waves, or terminal QRS slurring in the inferior and/or lateral leads
Black athlete repolarization variant	J-point elevation and convex ('domed') ST-segment elevation followed by T-wave inversion in leads V_1-V_4 in black athletes
Juvenile T-wave pattern	T-wave inversion V_1-V_3 in athletes age <16 yrs
Sinus bradycardia	≥30 beats/min
Sinus arrhythmia	Heart rate variation with respiration: rate increases during inspiration and decreases during expiration
Ectopic atrial rhythm	P waves are a different morphology compared with the sinus P-wave, such as negative P waves in the inferior leads ('low atrial rhythm')
Junctional escape rhythm	QRS rate is faster than the resting P-wave or sinus rate and typically <100 beats/min with narrow QRS complex unless the baseline QRS is conducted with aberrancy
1° AV block	PR interval 200-400 ms
Mobitz Type I (Wenckebach) 2° AV block	PR interval progressively lengthens until there is a non-conducted P-wave with no QRS complex; the first PR interval after the dropped beat is shorter than the last conducted PR interval

Early repolarization: present in up to 45% of Caucasian athletes and 63-91% of African-Carribbean athletes
-Currently there is no data to support a link between early repolarization and sudden cardiac death in athletes

African-American athletes commonly have J-point elevation, ST elevation and T-wave inversion in V1-V4
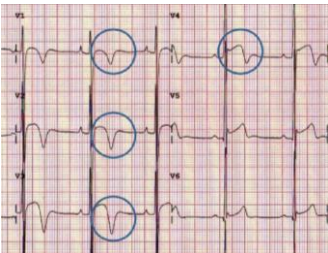
In isolation, borderline findings do not require further evaluation; but with multiple borderline findings, athlete should undergo further work-up

Borderline ECG findings in athletes
These ECG findings in isolation likely do not represent pathologic cardiovascular disease in athletes, but the presence of two or more borderline findings may warrant additional investigation until further data become available.

ECG abnormality	Definition
Left axis deviation	−30° to −90°
Left atrial enlargement	Prolonged P wave duration of >120 ms in leads I or II with negative portion of the P-wave ≥1 mm in depth and ≥40 ms in duration in lead V_1
Right axis deviation	>120°
Right atrial enlargement	P-wave ≥2.5 mm in II, III, or aVF
Complete right bundle branch block	rSR' pattern in lead V1 and a S wave wider than R wave in lead V_6 with QRS duration ≥120 ms

RBBB in present in 1% of population and incidence in young adult athletes is 0.5-2.5%
-Athletes with RBBB demonstrated larger right ventricular size, decreased RV function but with preserved fractional area change

T-wave inversion:
-inferior and lateral leads common in HCM
-right precordial leads in the absence of RBBB is common in ARVD

Anterior T-wave inversion with J-point elevation > 1 mm confined to leads V1-V4 has a low risk of cardiomyopathy
Anterior TWI without J-point elevation or with co-existent ST depression could signify a cardiomyopathy

Other ECG findings suggestive of ARVC: low limb-lead voltages, prolonged S-wave upstroke, PVCs with LBBB morphology, epsilon waves

Abnormal ECG findings in athletes
These ECG findings are unrelated to regular training or expected physiologic adaptation to exercise, may suggest the presence of pathologic cardiovascular disease, and require further diagnostic investigation.

| ECG abnormality	Definition
T wave inversion	≥1 mm in depth in two or more contiguous leads; excludes leads aVR, III, and V_1
• Anterior	• V_2-V_4 - excludes: black athletes with J-point elevation and convex ST-segment elevation followed by TWI in V_2-V_4; athletes age <16 with TWI in V_1-V_3; and biphasic T waves in only V_3
• Lateral	• I and AVL, V_5 and/or V_6 (only one lead of TWI required in V_5 or V_6)
• Inferolateral	• II and aVF, V_5-V_6, I and AVL
• Inferior	• II and aVF
ST-segment depression	≥0.5 mm in depth in two or more contiguous leads
Pathologic Q waves	Q/R ratio ≥0.25 or ≥40 ms in duration in two or more leads (excluding III and aVR)
Complete left bundle branch block	QRS ≥120 ms, predominantly negative QRS complex in lead V_1 (QS or rS), and upright notched or slurred R wave in leads I and V_6
Profound nonspecific intra-ventricular conduction delay	Any QRS duration ≥140 ms
Epsilon wave	Distinct low amplitude signal (small positive deflection or notch) between the end of the QRS complex and onset of the T-wave in leads V_1-V_3
Ventricular pre-excitation	PR interval <120 ms with a delta wave (slurred upstroke in the QRS complex) and wide QRS (≥120 ms)
Prolonged QT interval*	QTc ≥470 ms (male) QTc ≥480 ms (female) QTc ≥500 ms (marked QT prolongation)
Brugada Type 1 pattern	Coved pattern: initial ST-segment elevation ≥2 mm (high take-off) with downsloping ST-segment elevation followed by a negative symmetric T-wave in ≥ 1 leads in V_1-V_3
Profound sinus bradycardia	<30 beats/min or sinus pauses ≥3 s
Profound 1° AV block	≥400 ms
Mobitz Type II 2° AV block	Intermittently non-conducted P waves with a fixed PR interval
3° AV block	Complete heart block
Atrial tachyarrhythmias	Supraventricular tachycardia, atrial fibrillation, atrial flutter
PVC	≥2 PVCs per 10 s tracing
Ventricular arrhythmias	Couplets, triplets, and non-sustained ventricular tachycardia

Evaluation:

Lateral or inferolateral T-wave inversions:
-Echocardiogram
-Cardiac MRI with LGE if echo is non-diagnostic
-Exercise stress test and Holter for borderline patients
-Serial imaging follow-up
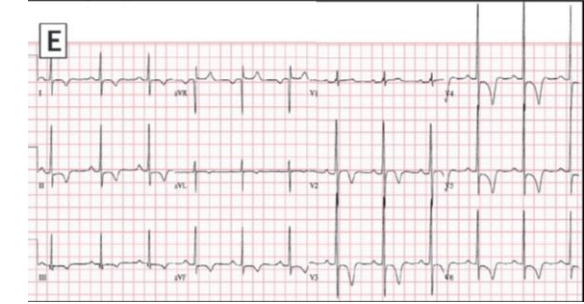
Anterior T-wave inversion with concern for ARVC:
-Echocardiogram, cardiac MRI, stress test, Holter and signal-averaged ECG
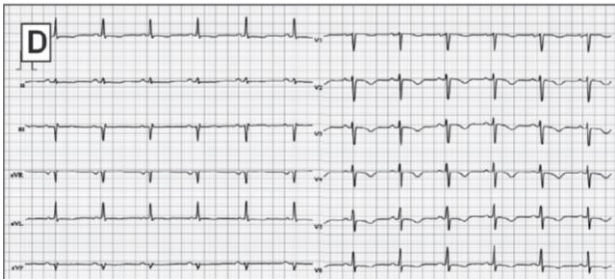
ST segment depression:
-Minimum of echocardiogram with cardiac MRI if non-diagnostic

Abnormal Q waves:
-Evaluate for presence of accessory pathway
-Presence in V1-V2 may be secondary to high-lead placement and repeat ECG is indicated
-Echocardiogram
-Cardiac MRI is there is high clinical suspicion
-Athletes > 30 yrs with CAD risk factors should get stress test

Complete LBBB (QRS > 120 msec):
-Found in less than 1 in 1,000 athletes
-Echocardiogram
-Cardiac MRI with perfusion study

Non-specific IV conduction delay (> 140 msec):
-Echocardiogram

Pre-excitation/WPW:
-At risk for SCD secondary to rapidly conducted atrial fibrillation
-Exercise stress test to evaluate for loss of pre-excitation
-Echocardiogram due to association with Ebstein's anomaly and cardiomyopathy
-Possible EP study if stress test is inconclusion: shortest pre-excited RR interval < 250 msec indicates a high-risk accessory pathway

Multiple PVCs:
-Echocardiogram
-Holter monitor and stress test
-Those with > 2,000 PVCs per day or PVCs that do not suppress with exercise may require cardiac MRI or electrophysiology study

Type I Brugada pattern:
-Evaluate regardless of symptoms
-Repeat ECG with high precordial leads with V1-V2 in 2nd/3rd intercostal space
-Consider accentuating factors: hyperkalemia, fever, lead placement, sodium channel blockers
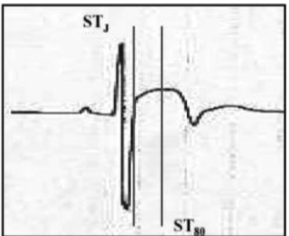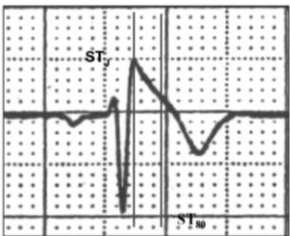
Long QT:
->470 msec in males, >480 msec in females warrants further work-up
Short QT only work-up with concerning clinical context
-Bazett's formula underestimates QTc at HR< 50 and overestimates at HR > 50
-Ideally measured in leads II and V5
-Utilize average QTc in sinus arrhythmia
-Low amplitude U waves should not be included
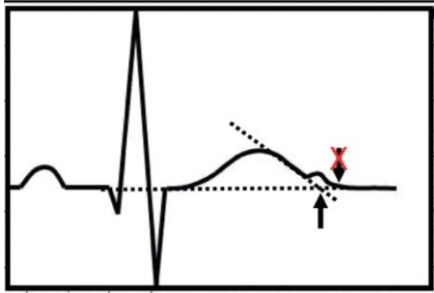
LQT work-up:
-History: syncope, seizures
-Family history: exertional syncope, "epilepsy", unexplained motor vehicle accident or drowning, sudden death < 50 years of age
-If histories are negative, repeat ECG another day

If repeat ECG is still abnormal (>500 msec):
-ECG of 1st degree relatives
-Referral to electrophysiologist
-Does not specifically recommend stress test

Sinus bradycardia or 1st degree AV block:
-Stress test to evaluate for increased HR and decreased PR interval
-Symptomatic patients may require echocardiogram or ambulatory ECG monitoring

2nd or 3rd degree AV block:
-Echocardiogram
-Ambulatory ECG monitoring and stress test
-Possible lab testing and cardiac MRI

Atrial tachyarrhythmias:
-Paroxysmal SVT: ECG during vagal maneuver to help determine mechanism of tachycardia
-Echocardiogram, ambulatory ECG monitor, exercise stress test
-Echocardiogram and/or cardiac MRI should be performed in cases of atrial fibrillation or atrial flutter

Ventricular arrhythmias:
-Echocardiogram
-Cardiac MRI
-Ambulatory ECG and exercise stress test

Reviewer comments:
- Guidelines written for adolescents and young adults, not young children
- Difference between normal variants of T-wave changes/inversion important to distinguish from pathologic changes
- In isolation borderline ECG findings do not necessitate further workup
- Even with criteria for "abnormal ECG" there will still be a large number of false positives and unnecessary workup
- Despite the improvement in screening guidelines, cost of additional workup will remain a limitation

Nationwide experience of catecholaminergic polymorphic ventricular tachycardia caused by RyR2 mutations

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Aims: To investigate penetrance, course of disease and extent of antiarrhythmic medication and ICD therapy in CPVT due to *RyR2* mutations in a Danish nationwide study

- CPVT can be caused by mutations in several genes: ryanodine receptor (RYR2: autosomal dominant), calsequestrin (CASQ2: autosomal recessive), calmodulin (CALM1-3) in addition to many others

RYR2
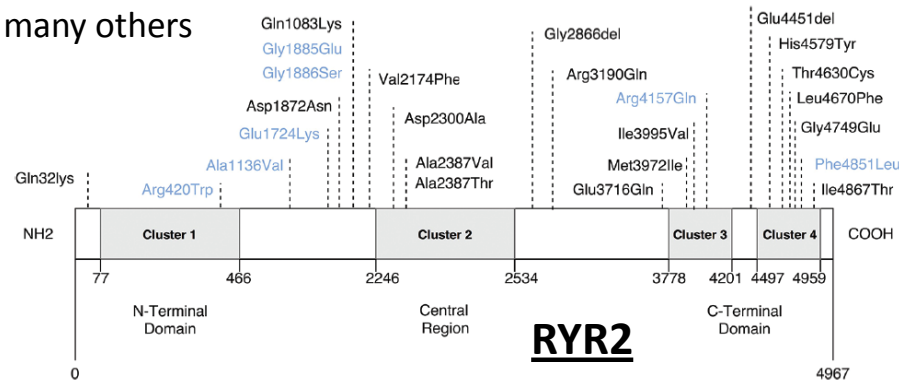
- Leads to diastolic leakage of CA++ from sarcoplasmic reticulum causing triggered activity and risk of sudden cardiac death (SCD) from ventricular arrhythmias
- Episodes higher risk during times of beta-agonism and increased catecholamines

Methods:
- Danish national hereditary heart disease web database identified:
  - Probands with pathogenic RYR2 mutation and clinical CPVT
  - Relatives with RYR2 mutation
- Relatives were broken into symptomatic and asymptomatic

- Symptomatic relatives had ≥1 of the following:
  - SCD or aborted SCD
  - Unexplained syncope or syncope related to ventricular tachycardia (VT)
  - Appropriate ICD shock
  - Polymorphic VT, bidirectional VT or PVCs with bidirectional morphology on Holter
  - Positive exercise stress test
  - Symptomatic multifocal atrial tachycardia (MAT)
- ICD settings
  - Monitor zone (200-240 bpm), therapy zone > 240 bpm + ATP
  - Appropriate shock: polymorphic/bidirectional VT, VF
  - Inappropriate shock: SVT, noise or over-sensing
  - Electrical storm: > 3 shocks in 24 hour period

Patient clinical characteristics

	Total (n=51)	Probands (n=23)	Symptomatic relatives (n=18)	Asymptomatic relatives (n=10)
Median age (IQR), years*	32 (14–45)	16 (10–33)	43 (28–55)	22 (18–49)
Female gender, n (%)	35 (68)	15 (65)	14 (78)	6 (60)
Median follow-up (IQR), months†	57(32–139)	85 (24–170)	49 (32–135)	56 (43–69)
Resting QTc, ms, mean (SD)	407 (32)	413 (35)	412 (30)	390 (26)
Primary symptom, n (%)				
SCD	8 (16)	5 (22)	3 (17)	0 (0)
ASCD	13 (25)	11 (48)	2 (12)	0 (0)
Syncope	9 (18)	4 (17)	5 (27)	0 (0)
Palpitations	4 (8)	0 (0)	4 (22)	0 (0)
Dyspnoea	2 (4)	2 (9)	0 (0)	0 (0)
Chest pain	1 (2)	1 (4)	0 (0)	0 (0)
Cascade screening	14 (27)	0 (0)	4 (22)	10 (100)
Exercise test results, n (%)				
Polymorph or bidirectional VT	4 (7)	2 (9)	2 (12)	0 (0)
PVCs (bidirectional)	7 (14)	4 (17)	3 (16)	0 (0)
Bigeminy or monofocal PVCs	12 (24)	6 (26)	6 (33)	0 (0)
Normal test	10 (20)	1 (4)	3 (16)	6 (60)
Not tested (age, SCD, other)	18 (35)	10 (44)	4 (23)	4 (40)
ICD	28 (55)	16 (70)	11 (61)	1 (10)
SVT	6 (11)	3 (12)	3 (17)	0 (0)
Radiofrequency ablation of SVT	5 (83)	3 (100)	2 (66)	0 (0)
Number of ablation procedures	13	7	6	0

Results:
- 20/23 (87%) of probands had SCD, aborted SCD or syncope as the first presenting symptom
- No patients died during follow-up of arrhythmia related events and no relatives had fatal/near-fatal events
- 89% of patients with syncopal events were exercise or emotionally induced
- 11/51 (22%) had classic CPVT during exercise
- 25 RYR mutations identified:
  - 7 known, 18 novel
  - 23 missense, 2 deletions
- 51 patients identified with RYR2 mutation
  - Penetrance estimated at 76%: 39/51 with clinical CPVT

ICD therapy:
- 8 patients received total of 21 appropriate shocks (5 probands, 3 relatives)
- 2 had refused anti-arrhythmic therapy
- 1 proband & 1 relative had electrical storm, remainder of appropriate shocks converted to sinus rhythm
- 4/28 (14%) received total of 18 inappropriate shocks
  - 39% lead malfunction, 61% SVT
- Most common lead complications: dislodgement and malfunction
- 5 patients developed MAT
  - 60% were controlled with flecainide
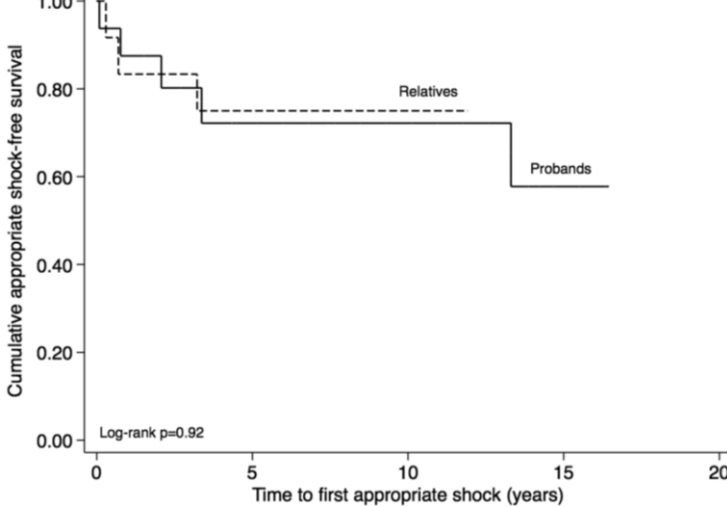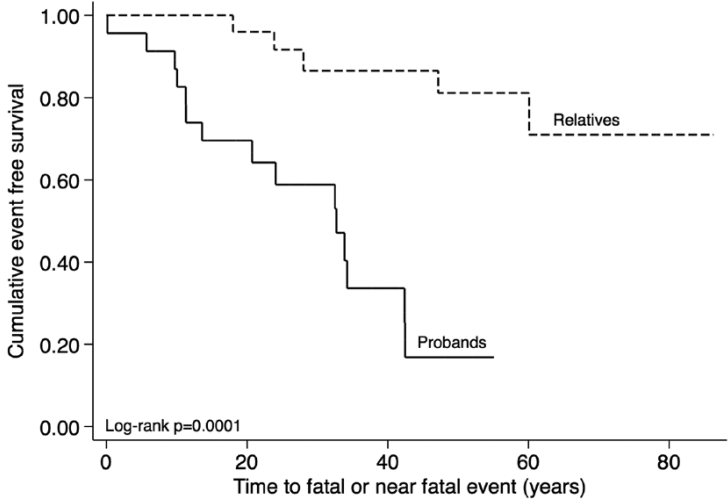 - 1 required AV nodal ablation

Table 3 Characteristics and follow-up data for Danish CPVT patients with an implantable cardioverter defibrillator

	Probands	Relatives
Patients with ICD	16	12
Median follow-up with ICD (IQR), months	87 (52–168)	48 (42–81)
ICD, primary prevention	1 (6)	6 (50)
ICD, secondary prevention	15 (94)	6 (50)
ICD events:		
Appropriate shocks, patients (>240 bpm)	5 (31)	3 (25)
Total No of shocks, (n)	21	9
Inappropriate shocks, patients	2 (11)	2 (17)
Total No of shocks (n)	13	5
-ICD lead malfunction (n)	6	1
-MAT (n)	7	0
-Atrial fibrillation (n)	0	4

- 8 patients were SCD victims (5 proband, 3 relatives)
- 28/43 (65%) had transvenous ICD (3/4 single-chamber)
- Remainder of patients did not meet ICD indications but were treated with beta-blocker or BB + flecainide

Conclusions:
- In RYR2+ CPVT patients, there is a high incidence of syncope or SCD as presenting symptom
- Probands were significantly younger (16 versus 43 years) and had more severe disease
- Anti-arrhythmic and ICD therapy is effective: no deaths in proband group or fatal/near fatal events in relatives during follow-up
- Only 6/28 patients with ICD received appropriate shocks on medical therapy
- SVT is a significant cause of inappropriate shock therapy

Reviewer comments:
- Highlights the high-risk for CPVT to present with life-threatening arrhythmia
- High efficacy of medications and ICD in cohort
- Discovered 18 novel RYR2 mutations
- 76% penetrance; mutation does not equal clinical disease and may lead to unnecessary interventions
- High rate of lead complications/inappropriate shocks