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# CPVT: The Only Thing that Scares me in the Inherited Arrhythmia Clinic

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<https://heartsinrhythm.ca>



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# Conflict of Interest

- none



<https://heartsinrhythm.ca>



HRS – Heart  
Rhythm Society



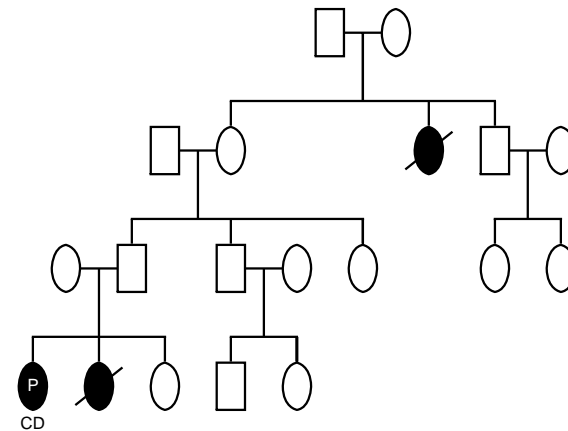
CCS – Canadian  
Cardiovascular Society

I am an open access person – for slides, e mail  
[akrahn@mail.ubc.ca](mailto:akrahn@mail.ubc.ca)  
(I will repeat that at the end)

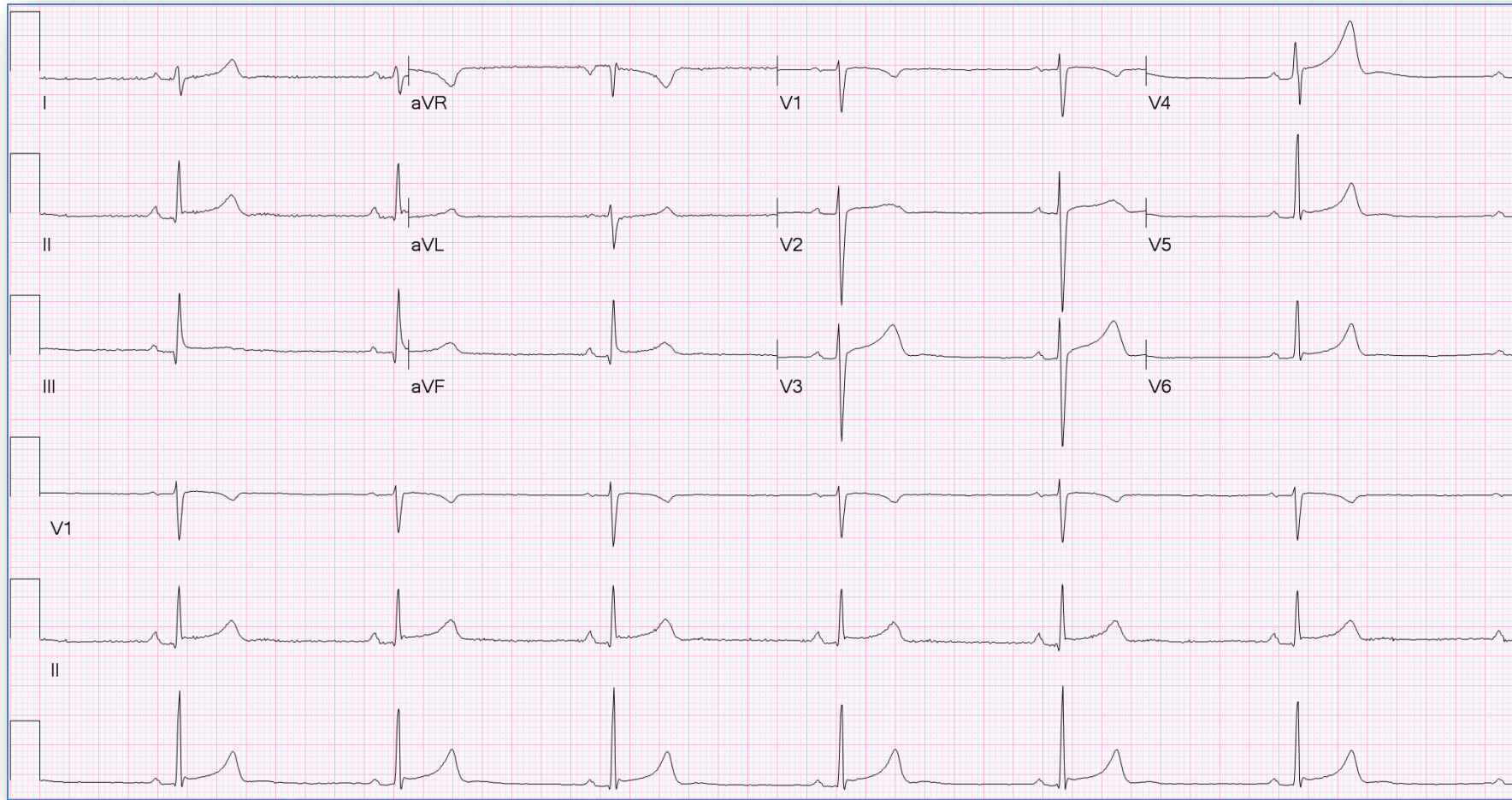


# Case Presentation

- 21 year old female Triathlete
- Palpitations while swimming, lightheaded
- Gets out of pool and has syncope
- Awakens after 10 seconds, heart pounding
- Gets up, LOC again
- No previous events
- Sister with SIDS at 2 months
- Dutch heritage

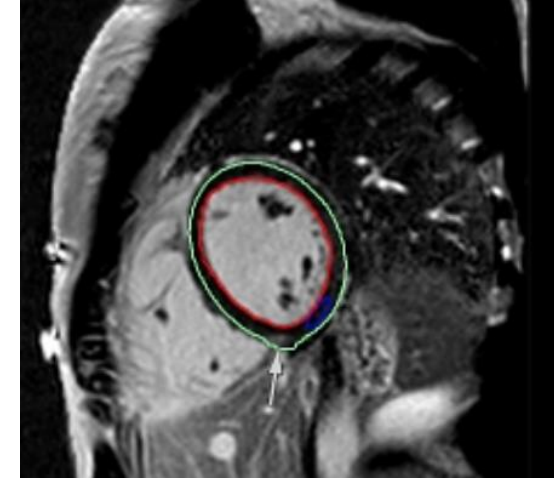


# Resting ECG



# Investigations

- Echo normal
- MRI LV normal
  - ? RV dilatation
  - at most 1 minor criteria for ARVC
  - Normal coronary arteries



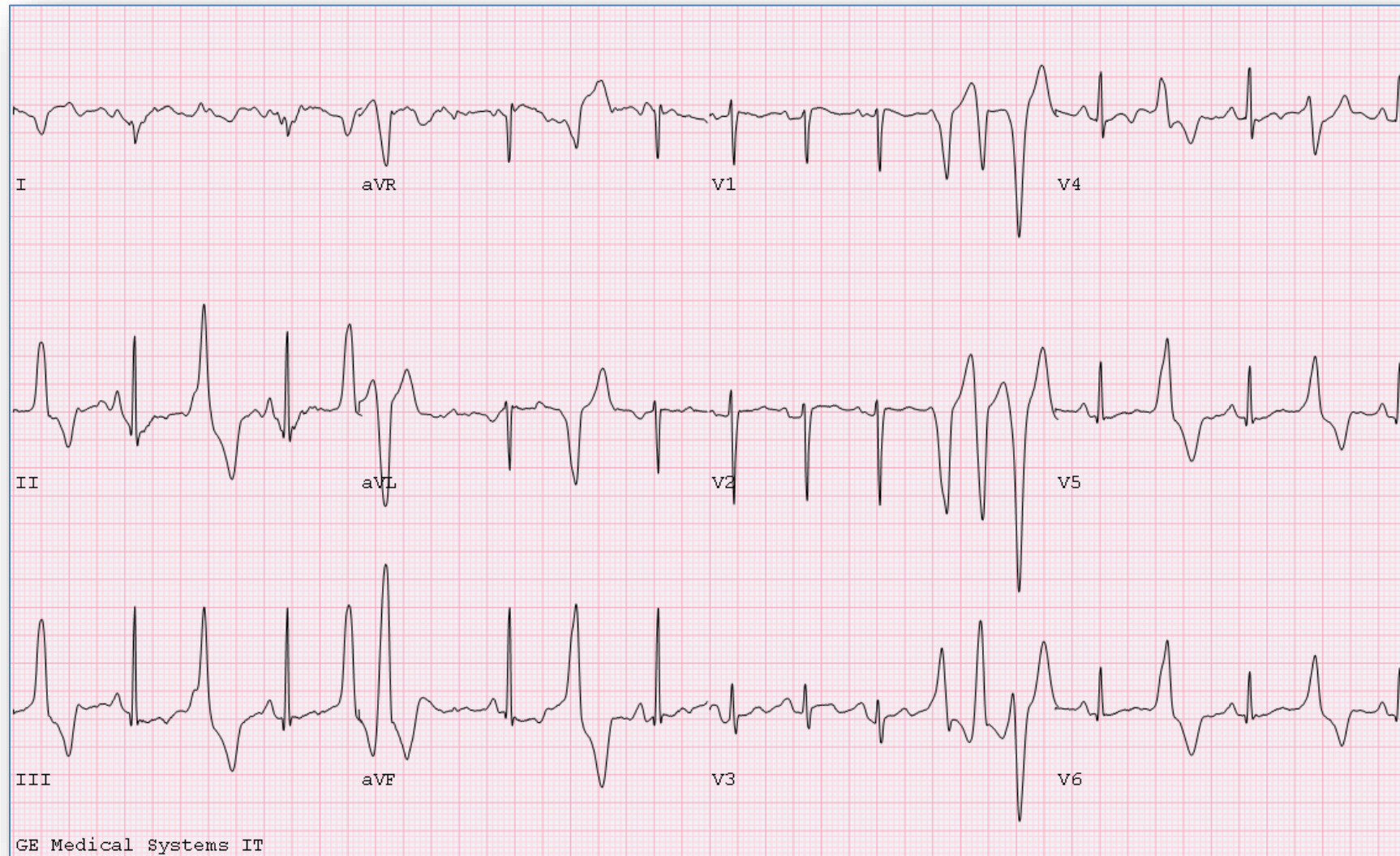
## SUMMARY

1. Normal left ventricular dimensions, wall thickness and systolic function. The LV ejection fraction is 58%.
2. The right ventricle is borderline enlarged when indexed to body surface area. There is regional wall thinning in the right ventricular outflow tract that is associated with hypokinesia. A small microaneurysm is also noted. Normal global systolic function with an ejection fraction of 60%. There is prominent trabeculation along the right ventricular free wall.
3. No evidence of intramyocardial fat or edema.
4. Non-specific mild fibrosis of the RV insertion site in the inferopetal wall.
5. Normal atrial dimensions.
6. No significant valvular heart disease.

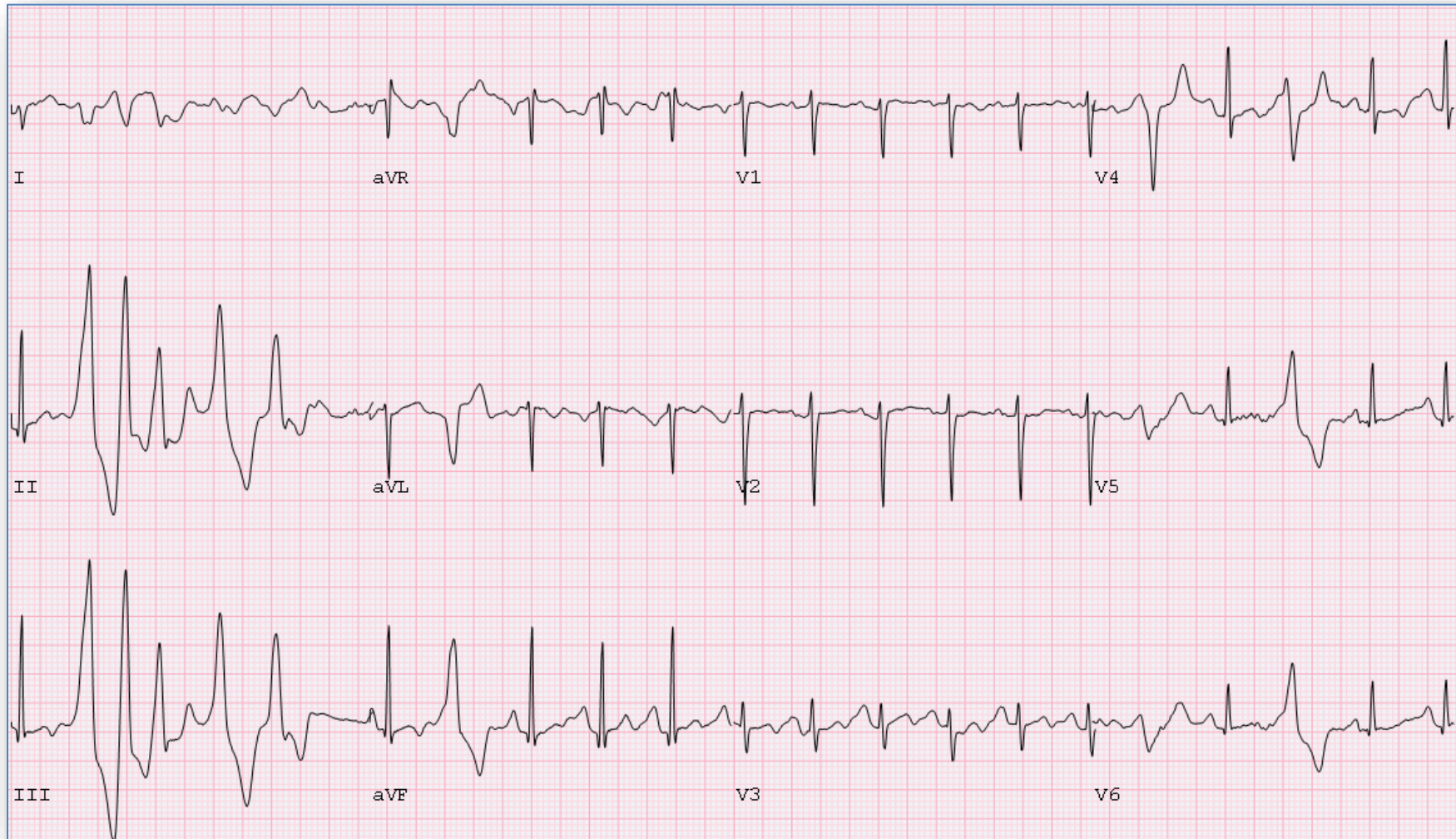
Overall, there are sufficient RV findings to classify a minor criterion for the diagnosis of a right ventricular cardiomyopathy (ARVC). There is no evidence of any other non-ischemic cardiomyopathic process that could explain the presenting arrhythmia. The coronary arteries are normal in origin and course.



# Exercise Test

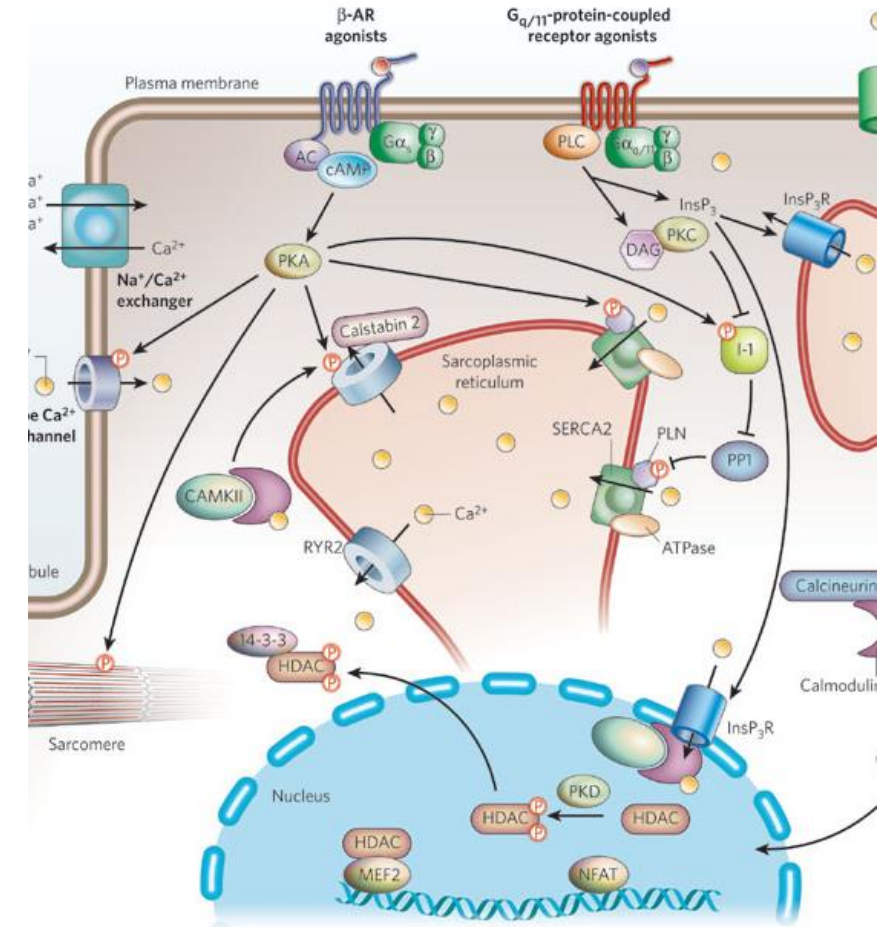


# Exercise Test



# Catecholaminergic Polymorphic Ventricular Tachycardia CPVT

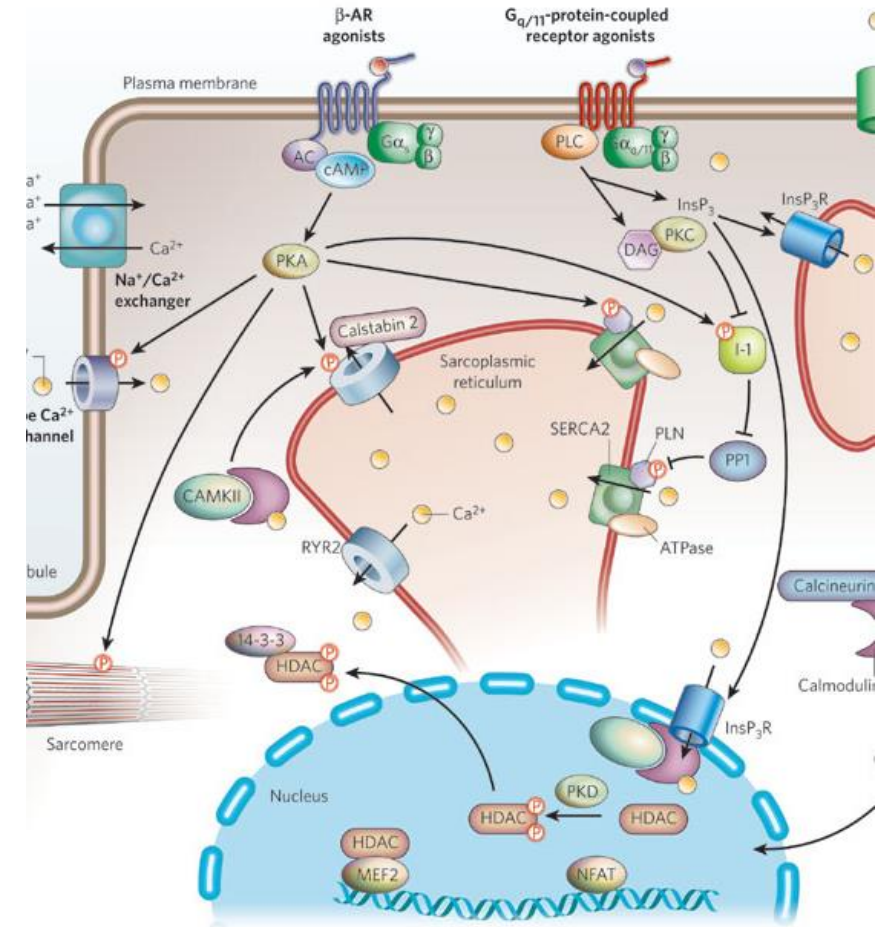
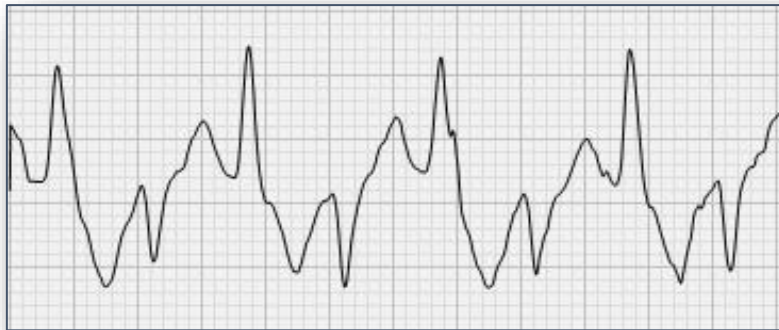
- Mendelian cause of adolescent exertional syncope and cardiac arrest
- Causative genetic variant identified in ~60% of cases
  - RyR2 gain-of-function
  - CASQ2 (rare)
  - TECRL (ultra-rare)
- Established therapies:
  - Beta-blocker
  - Flecainide
  - Left cardiac sympathectomy
  - ICD (probably not!)





# CPVT

- Intracellular  $\text{Ca}^{++}$  overload
- Exercise/swimming induced syncope / SCD
- Hallmark rhythm is bidirectional VT



# CPVT is an important cause of SCA & SCD in young people with a structurally normal heart

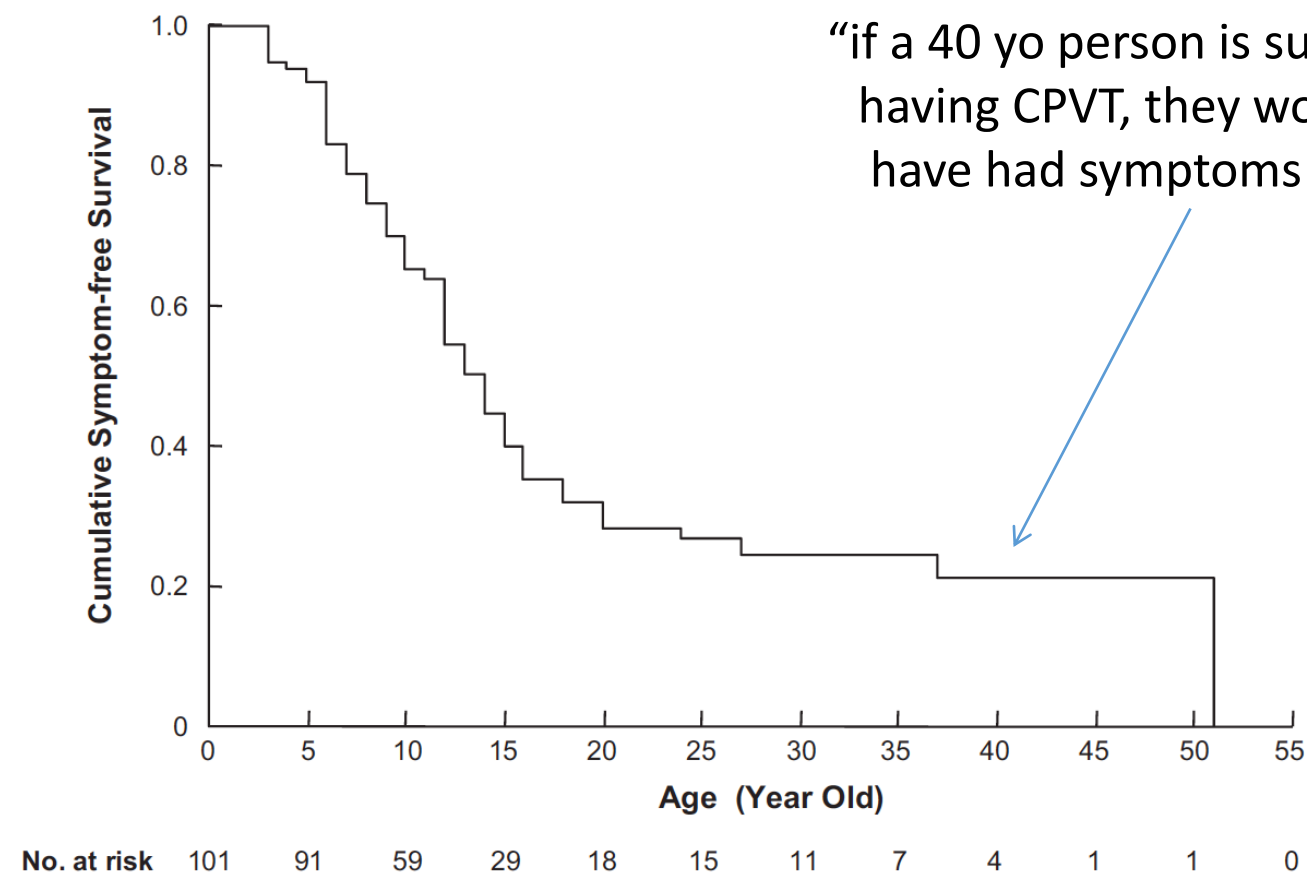
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## Perfect electrical assassin:

- Fainting history common in general population
- Children with CPVT are often the first in their family to be diagnosed
- *de novo* variants are common
- Normal ECG
- Normal ECHO
- Low use of stress test



# High Probability of Symptoms



Symptom free survival in CPVT

Hayashi et al, Circulation 2009



# Fainting

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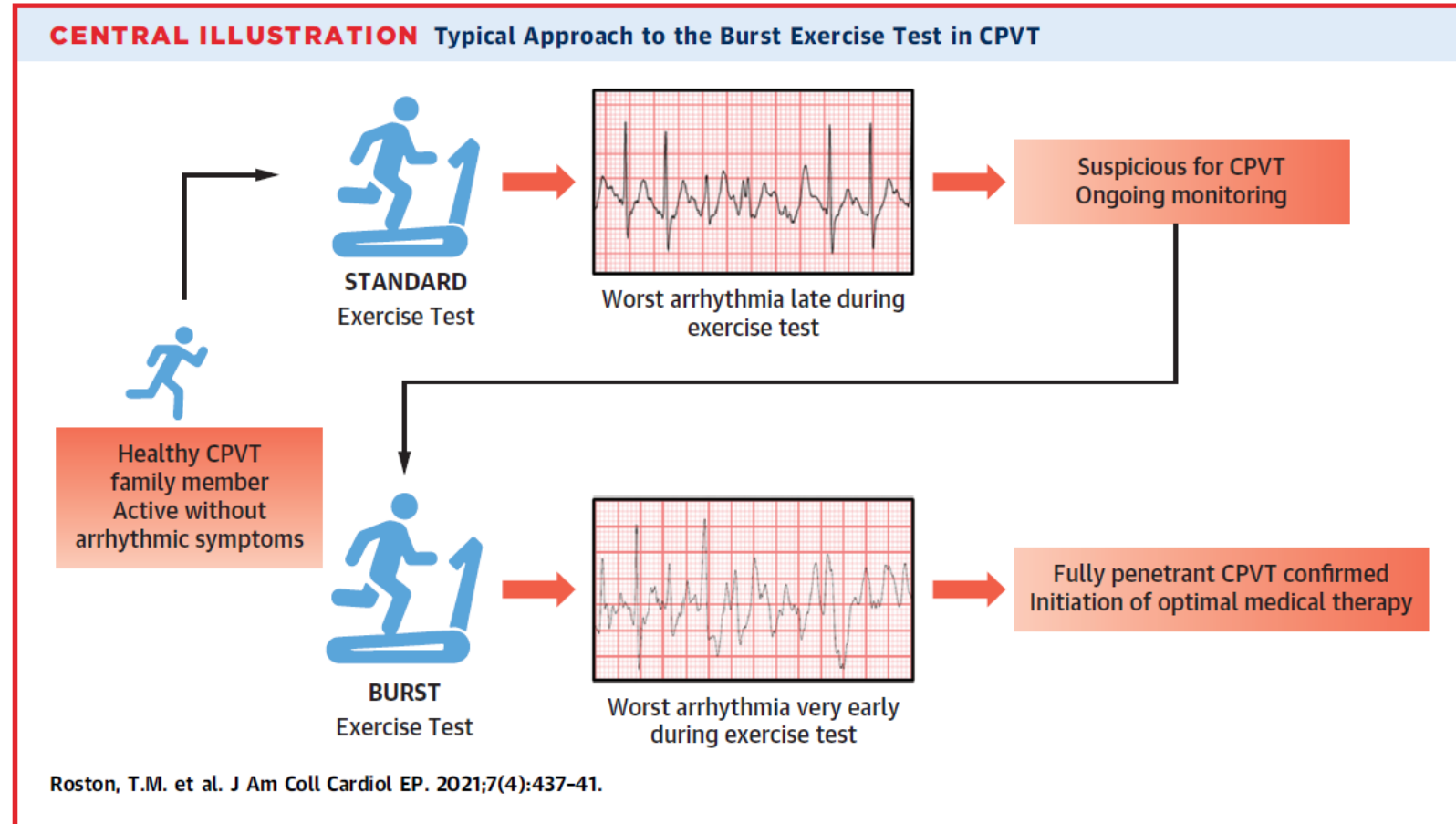
- History is the key
  - The syncope of CPVT is not usually during expected intense exertion
- It is possible to have both a benign common faint and also have a life-threatening condition
- Most faints do not need the emergency department or a genetic cardiologist review
- Red flags: drowning, mid-activity faint, positive family history



# Diagnostic Advances: Exercise Testing

## “BURST” exercise test?

- Start the ETT at highest stage reached on Bruce
  - 6 patients, in 5 the Burst induced more arrhythmias than the Bruce
- Multicenter evaluation ongoing, to determine if:
  - Can unmask worst VE
  - Can confirm suppression on therapy
  - Can diagnose unexplained adrenergic VF event



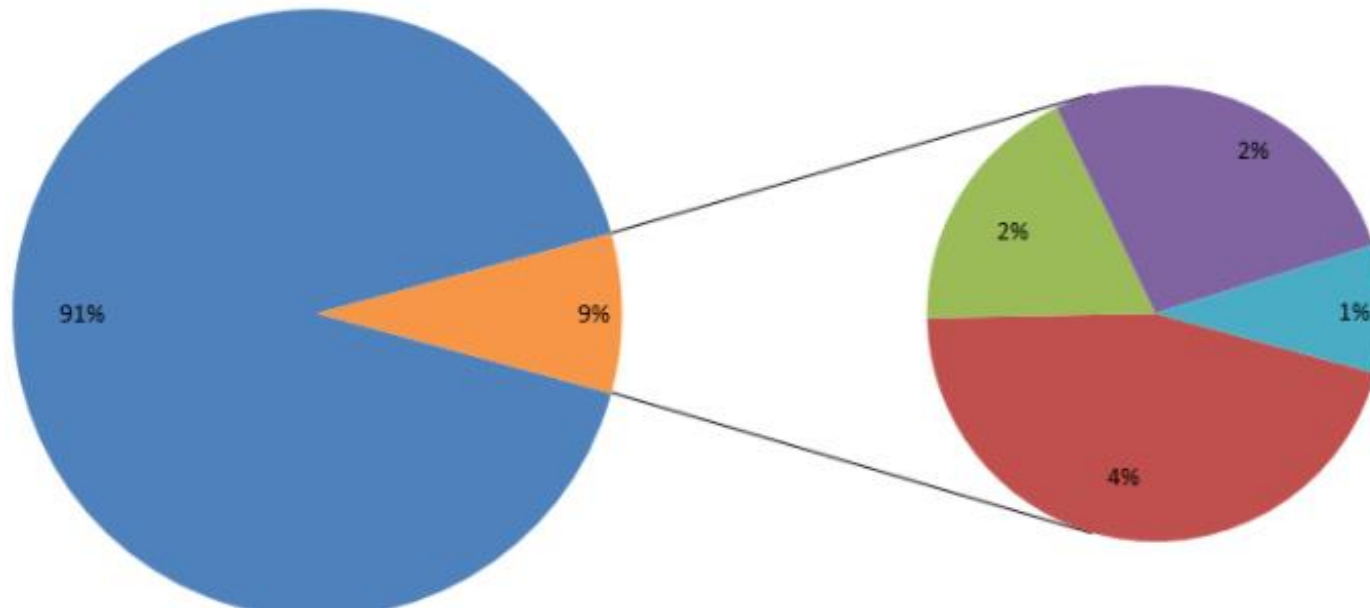


# Diagnostic Advances: Atrial Phenotype

Original PACES retrospective registry showed 22% of children had atrial arrhythmia

- Genetic and prognostic importance of atrial arrhythmia not known

■ No atrial arrhythmia ■ AF ■ AFL ■ AT ■ AVNRT



- **Mayo Clinic experience**

- 10 of 127 pts had AA (8%)
- 80% were symptomatic from AA, including syncope
- Medical therapy appeared to usually work

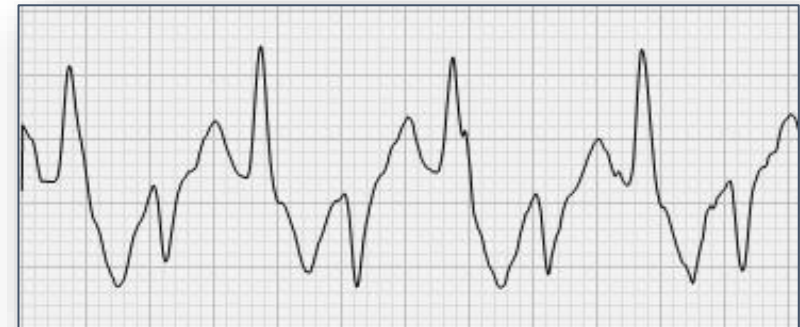
# Treatment

## PATIENT

- Beta blockers
  - Nadolol
- Flecainide
- Cardiac denervation
- Lifestyle modifications
  - Education
  - Safety plan

## FAMILY & COMMUNITY

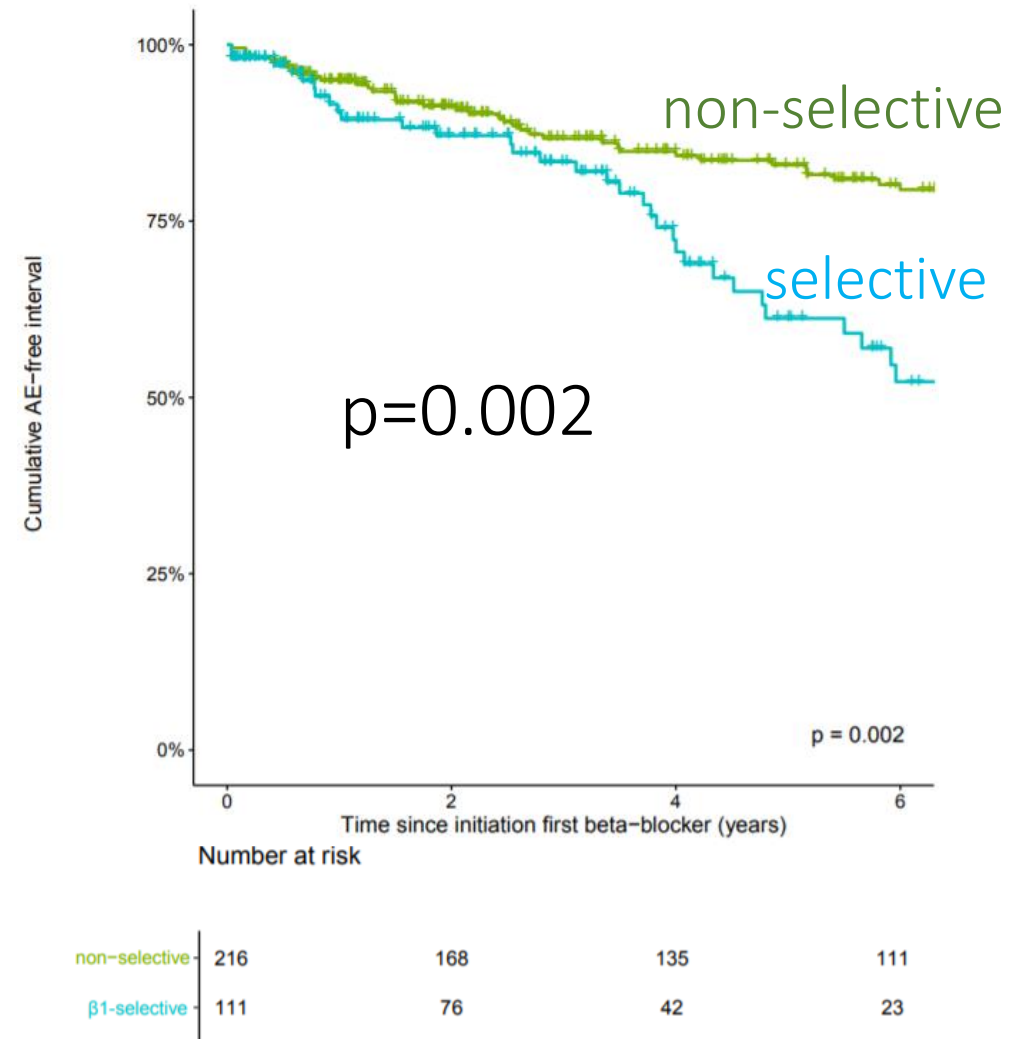
- Family screening
- Safety plan
  - CPR & AED
  - Don't stop the betablocker for low heart rates!



# Therapeutic Advances: $\beta$ -blockers

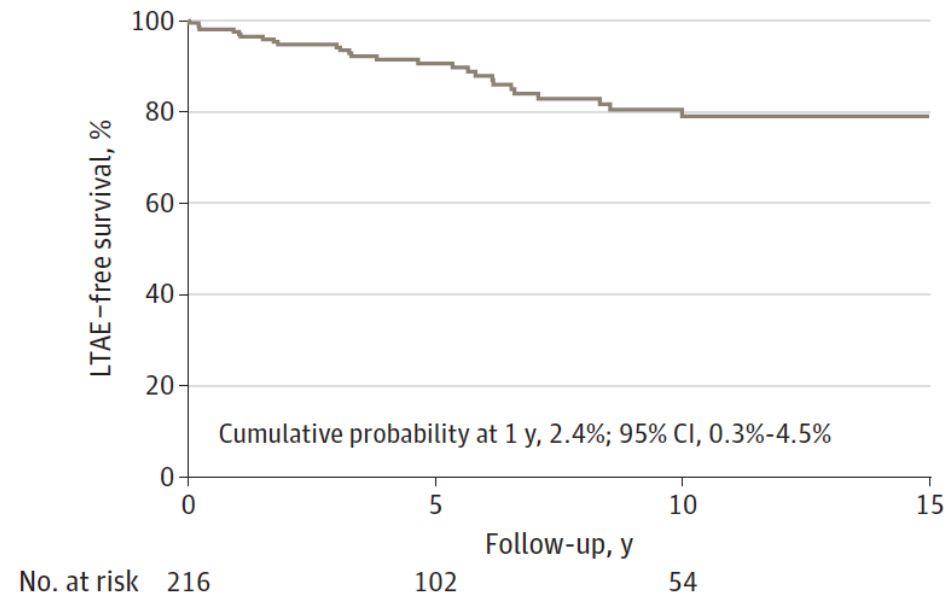
- Combined Int'l and Pediatric registries
  - 329 symptomatic CPVT children followed for 6.6 yrs (median)
  - Compared types and classes of  $\beta$ -blockers and risk of LTE in follow-up
  - Non-selective better than selective
  - Nadolol probably best
  - Breakthrough events – 39% non adherent, 24% under dosed
  - 4 deaths

Peltenburg et al. Circulation.  
2022;145:333

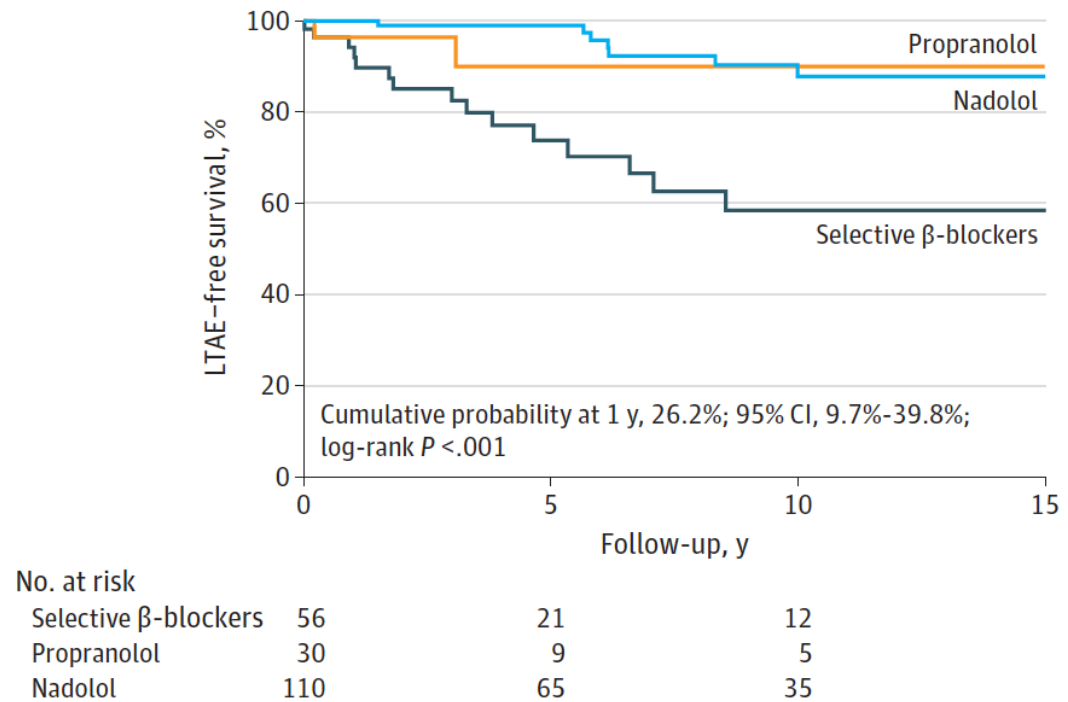


**Figure 3. Clinical Course of Patients With *RYR2* Catecholaminergic Polymorphic Ventricular Tachycardia During  $\beta$ -Blocker Therapy Only**

**A** First LTAE while taking  $\beta$ -blocker therapy

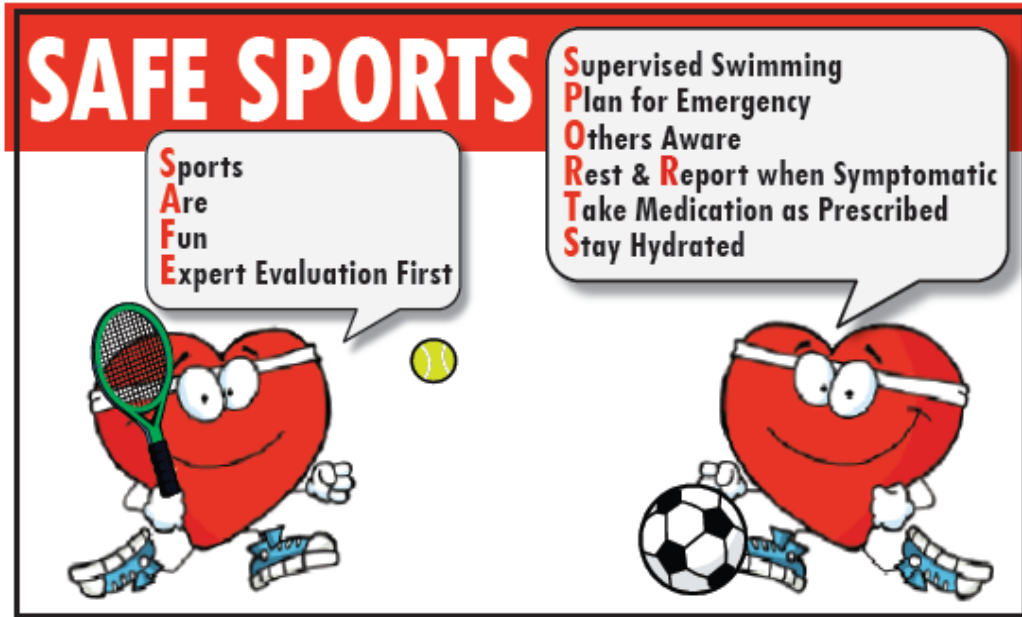


**B** First LTAE stratified by type of  $\beta$ -blocker used



A, Kaplan-Meier estimate of cumulative survival free from the first life-threatening arrhythmic events (LTAEs) in  $\beta$ -blocker therapy only shows the cumulative probability of experiencing a first catecholaminergic polymorphic ventricular tachycardia while taking  $\beta$ -blocker therapy was 2.4% (95% CI, 0.3%-4.5%), 9.3% (95% CI, 4.8%-13.6%), and 20.8% (95% CI, 12.9%-28.0%) at 1, 5, and 10 years of follow-up, respectively. B, Kaplan-Meier estimate of cumulative survival free from the first LTAE stratified by time-varying type of principal  $\beta$ -blocker used demonstrates that the cumulative probability of experiencing a first LTAE while taking  $\beta$ -blocker therapy only was 26.2% (95% CI, 9.7%-39.8%), 10.0% (95% CI, 0.0%-22.9%), and 1.0% (95% CI, 0%-3.0%) at 5 years of follow-up for selective  $\beta$ -blockers, propranolol, and nadolol, respectively.

# Recommendations for Safe Sports in CPVT



Believe it or not, exercise training may be protective in CPVT!

Manotheepan et al. Cardiovasc Res, 2016

- ✓ Get an **Expert Evaluation**
- ✓ Ensure **swimming** is supervised
- ✓ Plan for **emergency**
- ✓ **Rest and report** when symptomatic
- ✓ **Take medications** as prescribed
- ✓ Stay **hydrated**





Most CPVT patients do not need an ICD ever... even after a cardiac arrest!

## Implantable cardioverter-defibrillators in previously undiagnosed patients with catecholaminergic polymorphic ventricular tachycardia resuscitated from sudden cardiac arrest

Christian van der Werf<sup>1\*†‡</sup>, Krystien V. Lieve<sup>1†‡</sup>, J. Martijn Bos<sup>2,3,4</sup>, Conor M. Lane<sup>2,3,4</sup>, Isabelle Denjoy<sup>5‡</sup>, Ferran Roses-Noguer <sup>6</sup>, Takeshi Aiba<sup>7</sup>, Yuko Wada <sup>8</sup>, Jodie Ingles <sup>9,10,11</sup>, Ida S. Leren <sup>12</sup>, Boris Rudic<sup>13,14</sup>, Peter J. Schwartz <sup>15‡</sup>, Alice Maltret <sup>16</sup>, Frederic Sacher<sup>17</sup>, Jonathan R. Skinner <sup>18,19</sup>, Andrew D. Krahn <sup>20</sup>, Thomas M. Roston <sup>20,21,22</sup>, Jacob Tfelt-Hansen<sup>23</sup>, Heikki Swan<sup>24</sup>, Tomas Robyns <sup>25‡</sup>, Seiko Ohno<sup>8,26</sup>, Jason D. Roberts<sup>27</sup>, Maarten P. van den Berg<sup>28</sup>, Janneke A. Kammeraad<sup>29</sup>, Vincent Probst<sup>30‡</sup>, Prince J. Kannankeril <sup>31</sup>, Nico A. Blom<sup>32,33</sup>, Elijah R. Behr <sup>34,35‡</sup>, Martin Borggrefe<sup>13,14</sup>, Kristina H. Haugaa<sup>12</sup>, Christopher Semsarian<sup>9,10,11</sup>, Minoru Horie <sup>8</sup>, Wataru Shimizu<sup>7,36</sup>, Janice A. Till<sup>6</sup>, Antoine Leenhardt<sup>5‡</sup>, Michael J. Ackerman<sup>2,3,4¶</sup>, and Arthur A. Wilde <sup>1,37‡¶</sup>

### Conclusion

In previously undiagnosed patients with CPVT who presented with SCA, an ICD was not associated with improved survival. Instead, the ICD was associated with both a high rate of appropriate ICD shocks and inappropriate ICD shocks along with other device-related complications. Strict adherence to guideline-directed therapy without an ICD may provide adequate protection in these patients without all the potential disadvantages of an ICD.

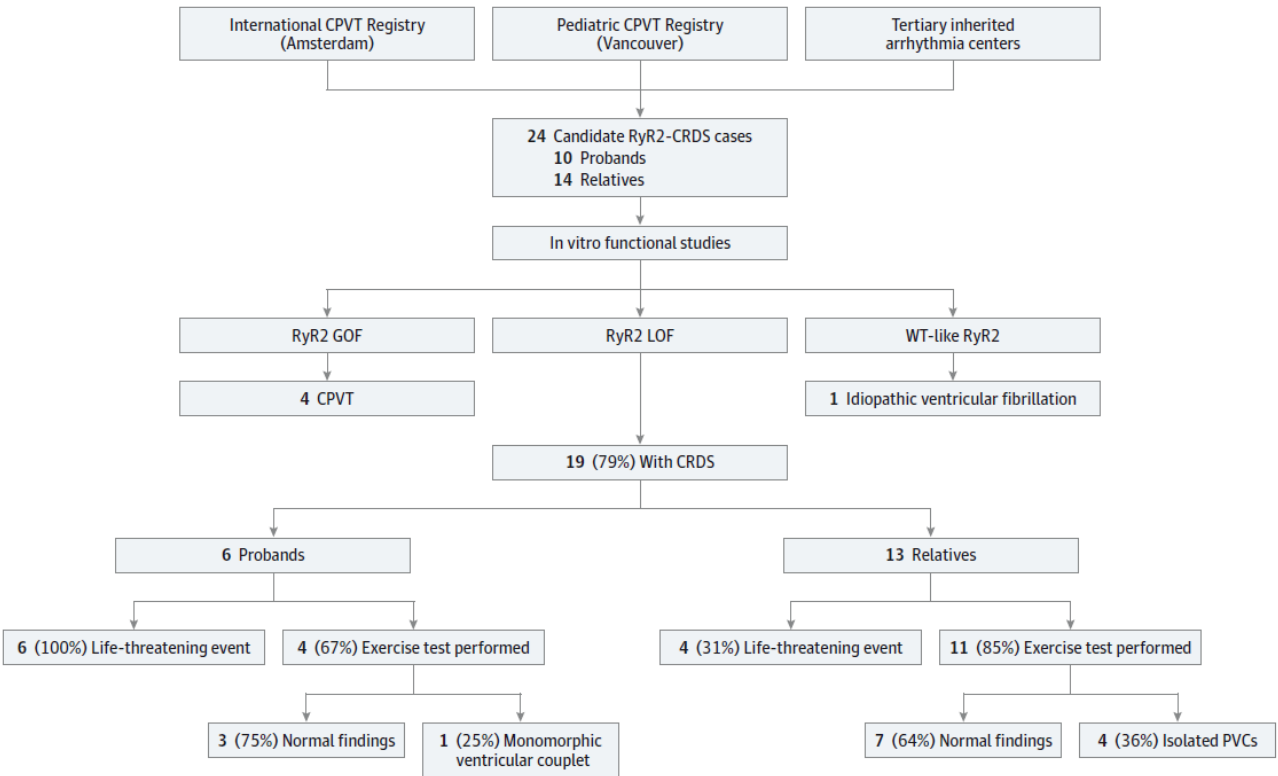
# Calcium Release Deficiency Syndrome

JAMA Cardiology | Original Investigation

## Clinical and Functional Characterization of Ryanodine Receptor 2 Variants Implicated in Calcium-Release Deficiency Syndrome

Thomas M. Roston, MD, PhD; Jinhong Wei, PhD; Wenting Guo, PhD; Yanhui Li, MD, PhD; Xiaowei Zhong, PhD; Ruiwu Wang, PhD; John Paul Estillore, MD; Puck J. Peltenburg, MD; Ferran Rosés I. Noguer, MD; Jan Till, MD; Lee L. Eckhardt, MD, MS; Kate M. Orland, MS; Robert Hamilton, MD; Martin J. LaPage, MD, MS; Andrew D. Krahn, MD; Rafik Tadros, MD, PhD; Jeffrey M. Vinocur, MD; Dania Kallas, MSc; Sonia Franciosi, PhD; Jason D. Roberts, MD, MAS; Arthur A. M. Wilde, MD, PhD; Henrik K. Jensen, MD, DMSc, PhD; Shubhayan Sanatani, MD; S. R. Wayne Chen, PhD

Figure 1. Summary of Ryanodine Receptor 2 (RyR2)–Calcium-Release Deficiency Syndrome (CRDS) Case Ascertainment and Outcomes in the Multicenter Cohort

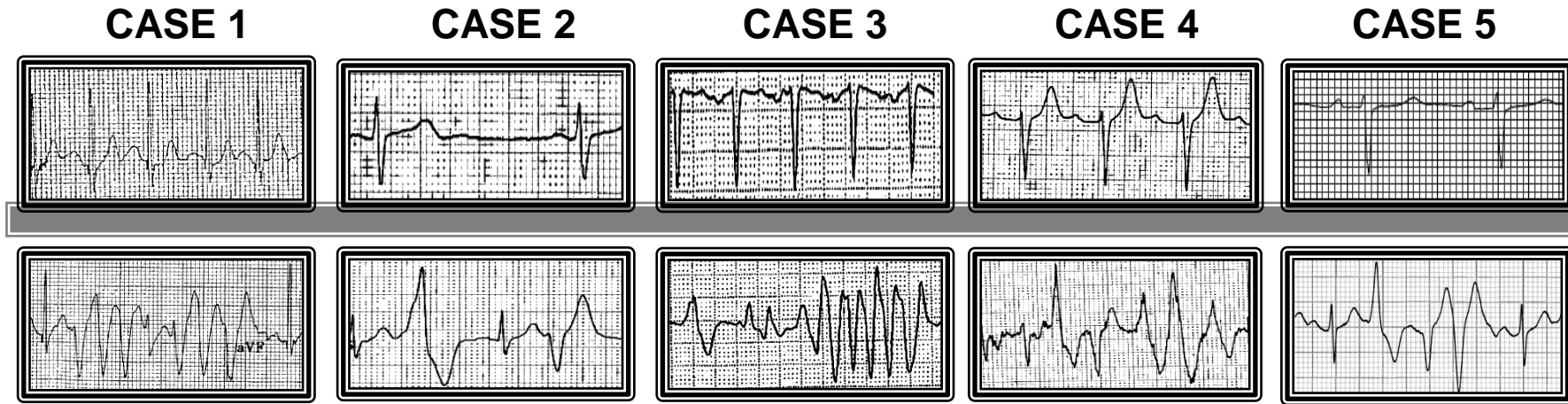


LOF variants:

- Q2275H
- E4451del
- F4499C
- **V4606E**
- R4608Q
- R4608W

Roston & Wei et al. JAMA Cardiol 2021

# Benign Polymorphic VT?



- Benign variant?
  - 5 middle aged males (age  $52 \pm 5$  yrs)
  - Incidental detection of PVCs on health check
  - Negative family history, structurally normal heart
  - Limited genetics negative
  - Suppressed with beta blocker

# Conclusions

- CPVT is a rare treatable cardiac channelopathy
- Diagnosis is likely enabled by burst exercise testing
- Breakthrough events on optimal treatment are very infrequent
- Safe sports following guidelines should be encouraged with shared decision making
- Our basic science colleagues have a lot to contribute

