Utility of Electrophysiological Study for Diagnosis and Risk Stratification and the Effect of Flecainide in a Novel Channelopathy: RYR2 Calcium Release Deficiency Syndrome (CRDS)

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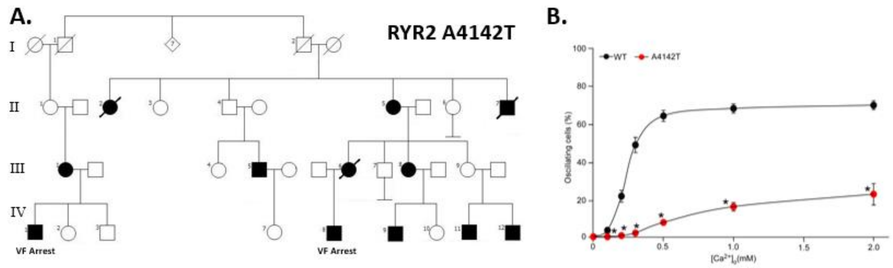
Background – A novel familial arrhythmia syndrome**,** RyR2 Calcium Release Deficiency Syndrome (CRDS), has recently been described[1]. This channelopathy is characterised by unheralded sudden cardiac death with no clear phenotype on standard clinical testing, and hence represents a significant diagnostic and management challenge. In contrast to Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT), where gain-of-function of RyR2 is the most common underlying cause, CRDS is caused by RyR2 loss-of-function. We evaluated a large and well characterised family, in which 5 individuals have had cardiac arrests, to assess provocation testing, risk stratification and response to anti-arrhythmic therapy with flecainide in CRDS.

Methods and Results – The proband presented with aborted sudden cardiac death (aSCD) age 23 during sleep. SCD/aSCD at rest had occurred in several relatives at young ages, including the proband's mother. Standard clinical testing with exercise and ambulatory ECG recording in individuals who had aSCD, or were obligate affected did not show a clear phenotype. No subject who had suffered cardiac arrest had any prior known symptoms and in the wider family, in contrast to CPVT, syncope prior to evaluation or during follow-up was very rare. Monomorphic non-sustained VT (NSVT) was occasionally recorded during prolonged ambulatory monitoring and in the early exercise and recovery phases of exercise testing (**Table 1**), but no subject showed bidirectional, polymorphic or monomorphic sustained VT on increasing exercise. Genetic analysis, including whole genome sequencing, firmly established that a missense mutation in *RYR2,* Ala4142Thr, was the underlying cause of disease in the family (**Fig. 1A**); family testing identified several asymptomatic at risk individuals. Functional study of the Ala4142Thr variant in a cell model showed RyR2 loss-of-function, indicating that the family was affected by CRDS (**Fig. 1B**). Electrophysiological study (EPS) using the Long Burst Long Pause Short-coupled (LBLPS, **Fig. 1C**) protocol was undertaken in 9 variant carriers, including a survivor of aSCD. The study was repeated after administration of flecainide (100mg IV or 1mg/kg in those <60kg). There was a clear gradation in inducibility of non-sustained VT and sustained ventricular arrhythmia between subjects during the baseline study (**Table 1**), with the survivor of aSCD being the most inducible subject. This suggests that the LBLPS protocol might be useful in determining risk of future arrhythmia. Administration of flecainide substantially reduced arrhythmia inducibility in the survivor of aSCD and entirely abolished arrhythmia in all other subjects (**Fig. 1D** and **Table 1**).

Conclusions - The Ala4142Thr mutation of *RYR2* causes the novel heritable arrhythmia syndrome CRDS, which is characterised by familial sudden death in the absence of prior symptoms or a recognisable phenotype on ambulatory monitoring or exercise stress testing. We increase the experience of the LBLPS EPS protocol in human subjects and show that in CRDS it is helpful in establishing the clinical status of asymptomatic variant carriers, with potential utility for risk stratification. This is important as the results of standard tests do not appear to correlate with risk, with the only predictor of future arrhythmia being prior cardiac arrest. Our data provide the first evidence that flecainide is protective against arrhythmia in human subjects with CRDS, consistent with the effect previously shown in a mouse model. Flecainide is widely available, with an established safety profile, and is therefore suitable as a long-term preventative therapy.



			EPS	
Subject	**Ambulatory ECG**	**Exercise ECG**	**Baseline**	**+Flecainide**
III:1	+	-	+	-
IV:1 (aSCD)	-	-	++	+
IV:2	-	-	++	-
IV:11	-	-	-	-
IV:12	-	-	+	-
III:9	-	-	-	-
IV:9	+	-	+	-
III:8	-	-	+	-
II:5	+	+	++	-

Table 1. Summary of findings in individuals who underwent electrophysiological testing. **+** = NSVT (3 or more beats, >120bpm); **++** = sustained VA requiring cardioversion

References

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