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## Alternans of Diastolic Intracellular Calcium Elevation as the Mechanism of Bidirectional Ventricular Tachycardia in a Rabbit Model of Andersen-Tawil Syndrome

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### Keywords

Bidirectional ventricular tachycardia; Andersen-Tawil Syndrome; Alternans

Bidirectional ventricular tachycardia (VT) is characterized by beat-to-beat alternation of the QRS morphology and axis on ECG. It classically occurs in patients with digitalis toxicity, but also has been noted in genetic disorders such as catecholaminergic polymorphic VT and Anderson-Tawil syndrome (ATS). Mutations in *KCNJ2*, which encodes the inward rectifier  $K^+$  channel Kir2.1 (current:  $I_{K1}$ ), were identified in patients with ATS. However, the mechanism of bidirectional VT remains unclear.

Here we present an image of bidirectional VT due to beat-to-beat alteration in diastolic level of  $[Ca^{2+}]_i$  and triggered activity in a rabbit model of ATS. The isolated heart was perfused with 37°C oxygenated Tyrode's solution, and stained with Rhod-2 AM and RH237 to optically monitor changes in epicardial  $[Ca^{2+}]_i$  and membrane voltage ( $V_m$ ), respectively ( $0.35 \times 0.35 \text{ mm}^2$  per pixel, 2 ms/frame). The ATS model was created by 5 mmol/L cesium chloride which mainly blocks  $I_{K1}$  at this concentration.<sup>1</sup> Supraventricular origin of cardiac arrhythmias was excluded by creating AV block. An episode of bidirectional VT occurred after addition of 0.3  $\mu\text{mol/L}$  isoproterenol and rapid ventricular pacing (Figure). The R-R interval during the VT was constant at 360 ms, except the period before spontaneous VT termination when R-R intervals were gradually prolonged. The odd VT beats (unfilled circles) arose from the outside of the mapped region. The even VT beats (filled circles) displayed a focal activation pattern originating from the right ventricular outflow tract (RVOT). The optical tracings shown in the Figure were obtained from the site marked by an asterisk. The even VT beats likely arose from that epicardial site because the local activation preceded the onset of QRS in ECG. However, it is also possible that these beats originated from Purkinje cells or deeper layers of myocardium and broke through the epicardium prior to QRS onset. During the diastole of the VT, spontaneous  $[Ca^{2+}]_i$  elevation (red arrowheads) and delayed afterdepolarizations (upward arrows) were observed at this site. Because the

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DAD amplitudes in intact hearts were smaller than that observed in single cell recordings due to electrotonic interactions between cells with and without DADs and signal averaging in optical mapping,<sup>2</sup> we magnified the  $V_m$  tracing to make the DADs more visible. Note that the maximal slopes of the diastolic  $[Ca^{2+}]_i$  elevation alternate from beat to beat. The larger of the two slopes was associated with a DAD with a faster upstroke triggering an action potential (red upward arrows), forming the even beats. The diastolic  $[Ca^{2+}]_i$  elevation with gentle slopes was associated with a failure to trigger (black upward arrows), allowing an outside wavefront to activate the mapped region, forming the odd beats. Phase plots of  $[Ca^{2+}]_i$  versus  $V_m$  show a counterclockwise trajectory in the odd beat, but clockwise trajectory in the even beat, indicating that the RVOT site was passively activated by a propagated wavefront, followed by secondary increase in  $[Ca^{2+}]_i$  during the odd beat (i.e.  $Ca^{2+}$ -induced  $Ca^{2+}$  release), while  $[Ca^{2+}]_i$  event occurred before  $V_m$  event during the even beat (i.e. spontaneous  $Ca^{2+}$  release from the SR). It is likely that two foci of triggered activities alternately trigger rather than compete with each other to generate bidirectional VT.

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## Abbreviations

<b>ATS</b>	Andersen-Tawil Syndrome
<b>AU</b>	arbitrary unit
<b>RVOT</b>	right ventricular outflow tract
<b>VT</b>	ventricular tachycardia

## Reference

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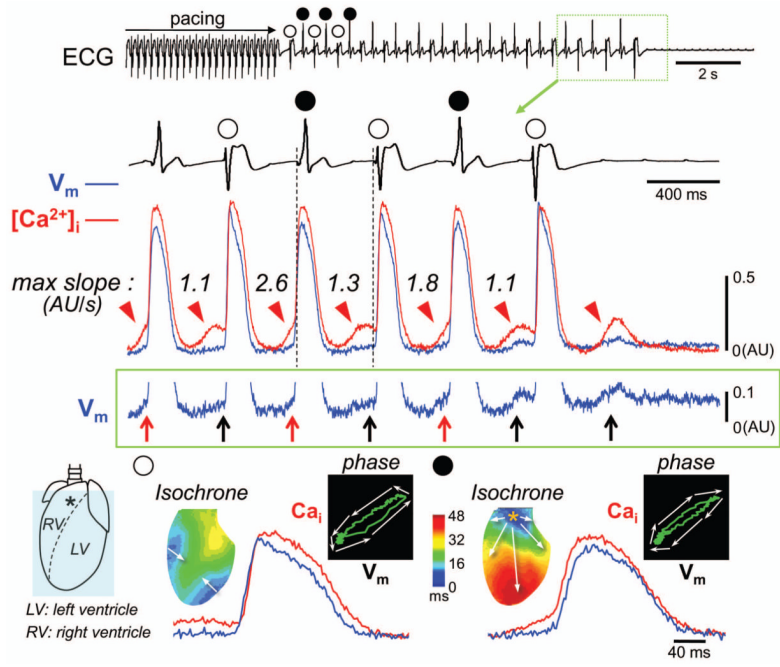


Figure.