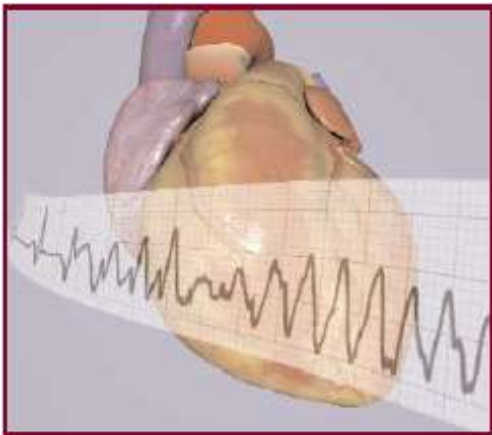


MAPPING OF SPONTANEOUS RE-ENTRANT POLYMORPHIC VENTRICULAR TACHYCARDIA IN A MOUSE MODEL OF BRUGADA SYNDROME

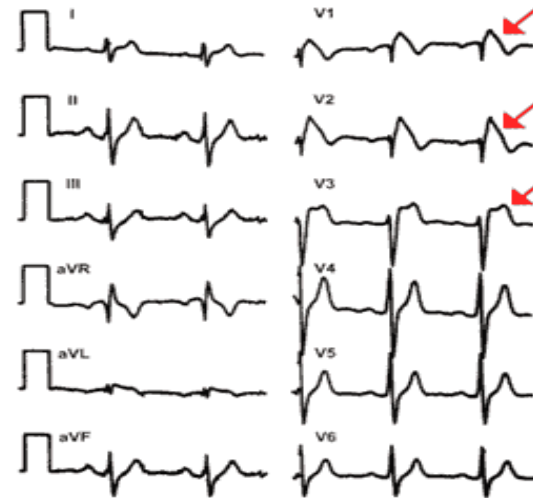
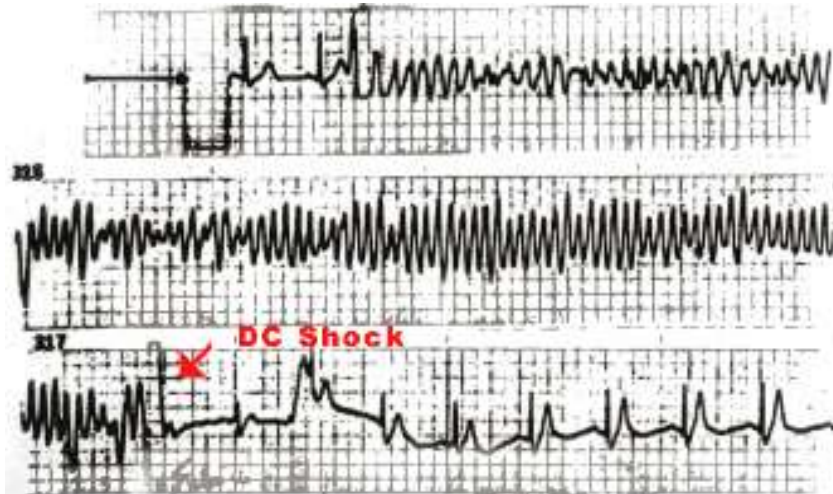
Claire A Martin¹, Laila Guzadhur¹, Ming Lei²,
Andrew A Grace¹, Christopher L-H Huang¹

1. University of Cambridge, 2. University of Manchester



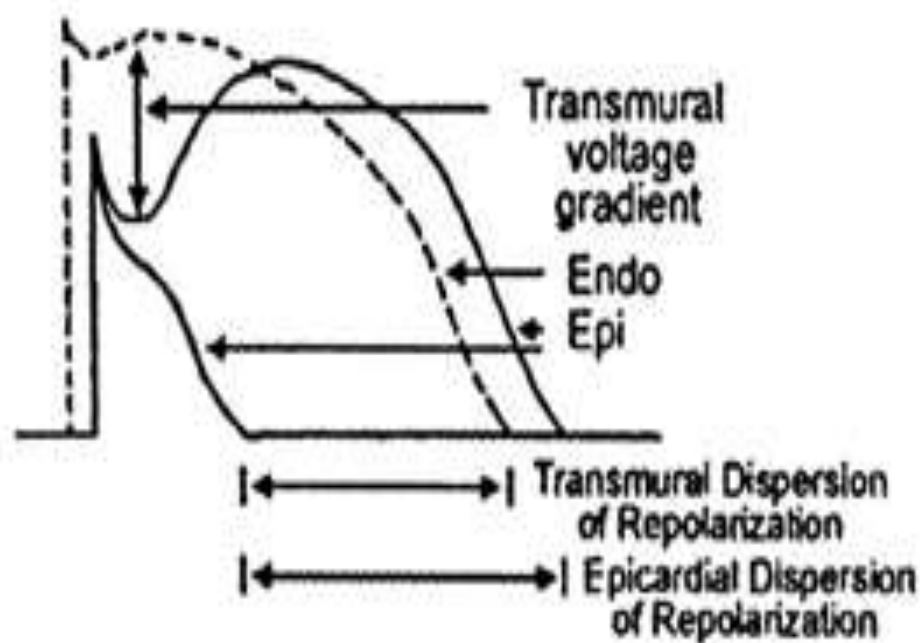
Brugada Syndrome (BrS)

- Episodes of polymorphic VT and sudden cardiac death
- ST segment elevation and right bundle branch block in right precordial leads



Depolarization or repolarization?

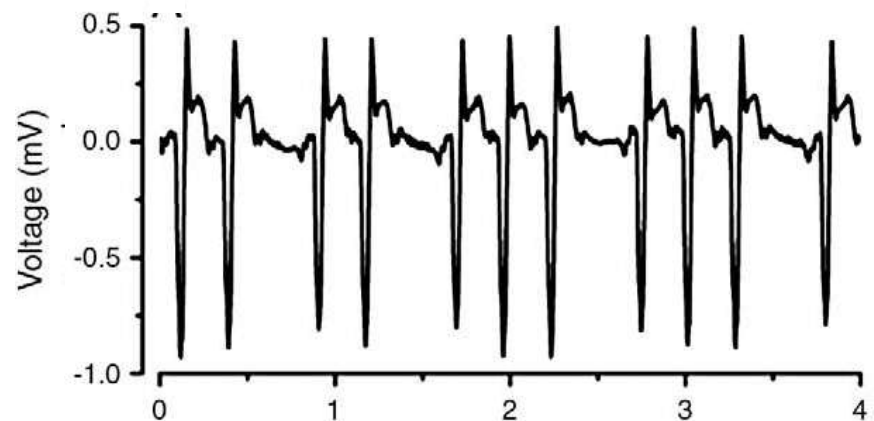
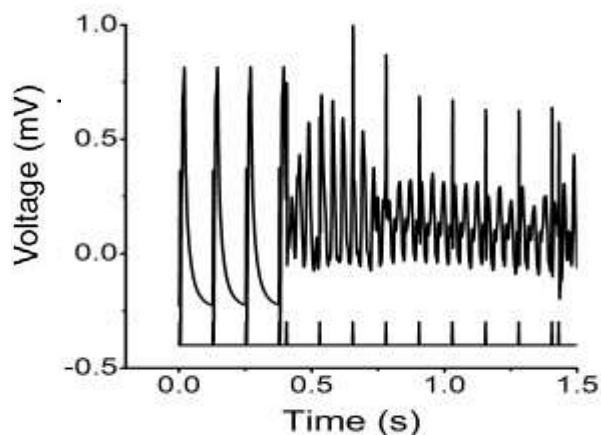
- Depolarization:
 - Clinical studies limited by non-invasive techniques
- Repolarization:
 - Human experiments technically difficult
 - Loss of spike and dome action potential morphology in canine arterial wedge preparation



From Meregalli et al. 2005

Genetic *Scn5a*^{+/-} model

- Up to 30% of patients have mutations in the SCN5A gene, which encodes the cardiac sodium channel α -subunit
- Mouse shows:
 - Episodes of polymorphic VT, exacerbated by flecainide and reduced by quinidine
 - ST elevation, slowed conduction and increased RV transmural gradients¹



¹Martin *et al*, 2010

Aims

- Use multi-electrode mapping system to analyze:
 - activation times (ATs)
 - repolarization times (RTs)
 - activation recovery intervals (ARIs)
 - calculate dispersions between values
- Clarify interactions between depolarization and repolarization disorders in *Scn5a*^{+/-} heart

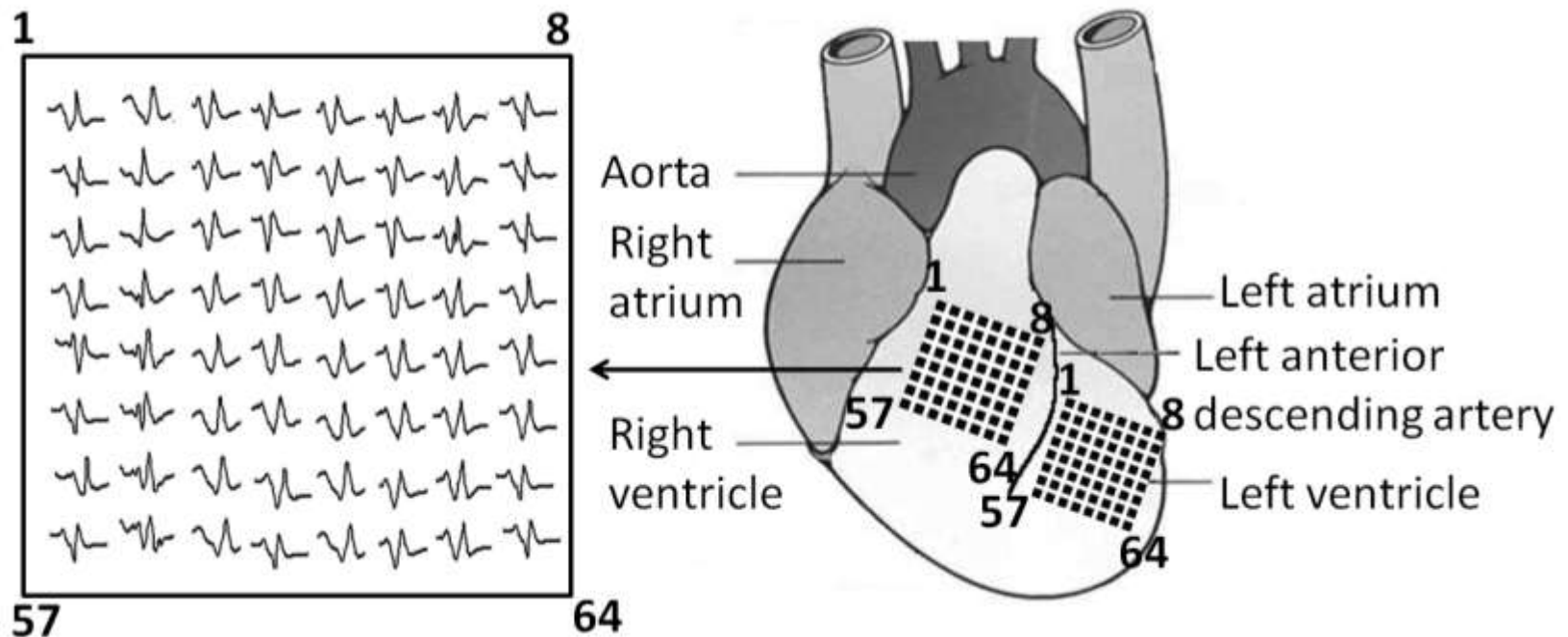
Methods

- Langendorff-perfused preparation
 - Aged 4-8 months
 - WT and *Scn5a*^{+/-} hearts (n=5 each)
- Monophasic action potentials
 - Miniaturized MAP electrode
 - APD at 70% repolarization measured



Multi-electrode array

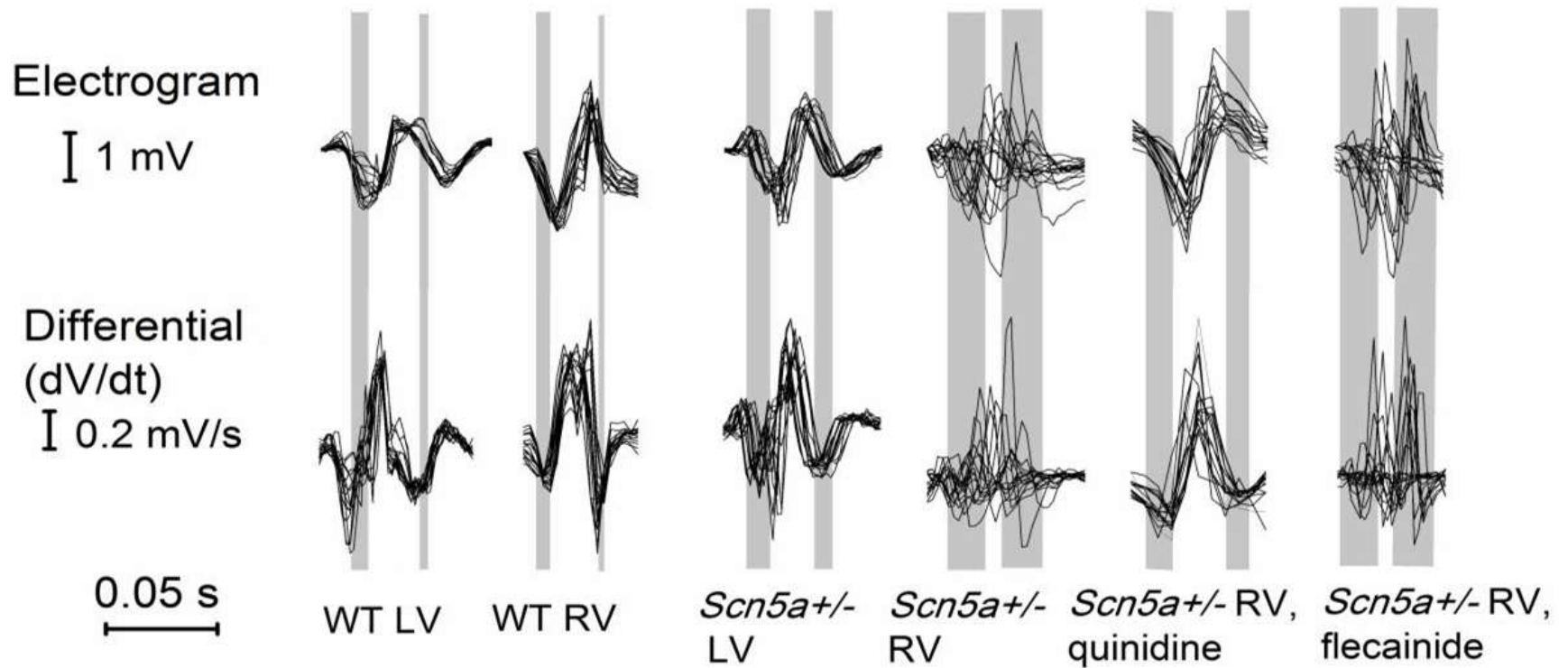
- Custom built, 64 electrodes in 8 x 8 configuration
- Interelectrode distance = 0.55 mm



Measurements

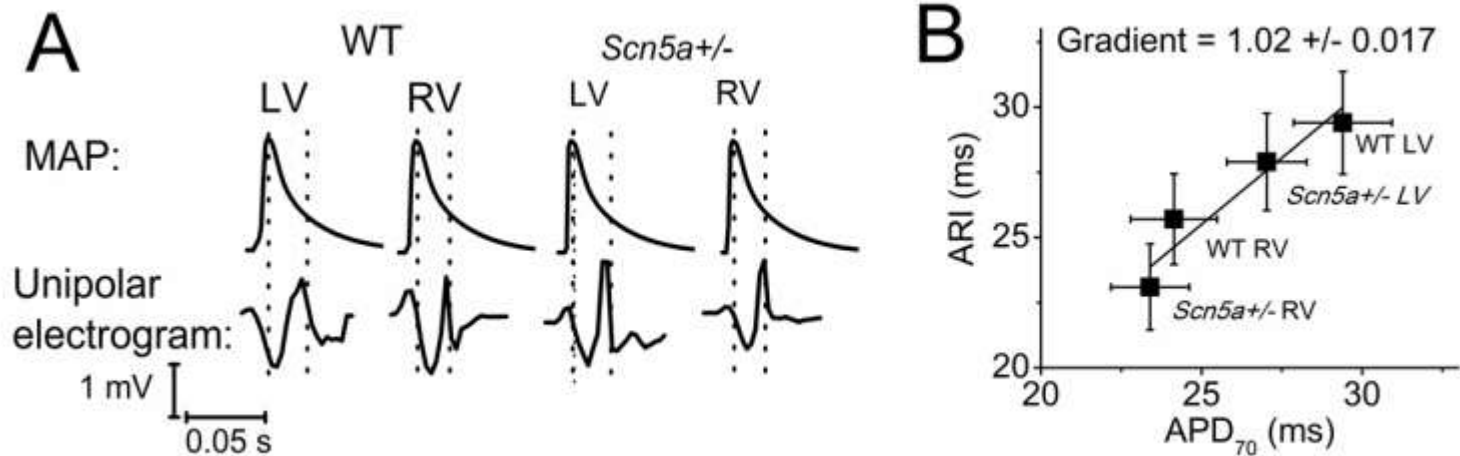
- AT = point of initial maximal -ve slope dV/dt_{\min}
- Isochronal propagation maps derived
- RT = point of dV/dt_{\min} of T-wave
- ARI = interval between AT and RT
- Differences between first and last of these values in each electrogram
- Conduction velocity estimated from distance covered by a line drawn normally to a succession of contours

Electrograms



1. ARIs correlate well with APD_{70} measurements made by MAP catheter

- Gradient of the slope not significantly different from 1.0
- Validates use of multi-electrode array

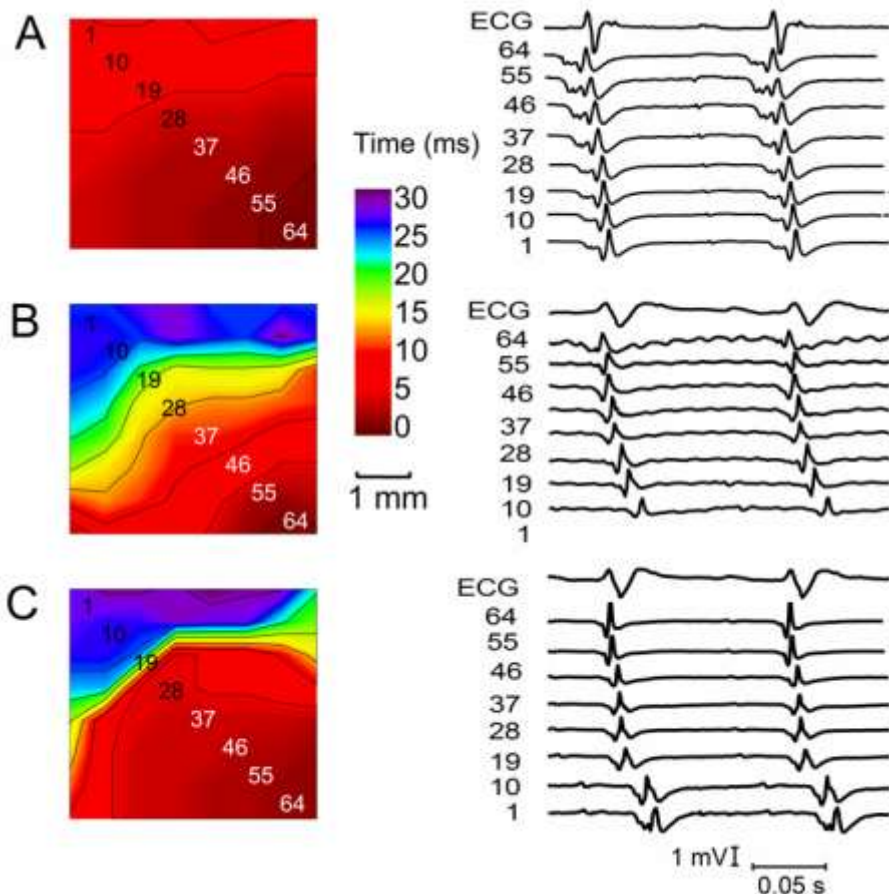


2. Scn5a+/- hearts show low incidence of VT but this is exacerbated by flecainide

VT incidence	WT	Scn5a+/-
Before drug	0/48 (0%)	2/48 * (4%)
Flecainide 10 mM	0/48 (0%)	5/24 * (21%)
Quinidine 5 mM	0/24 (0%)	0/24 (0%)

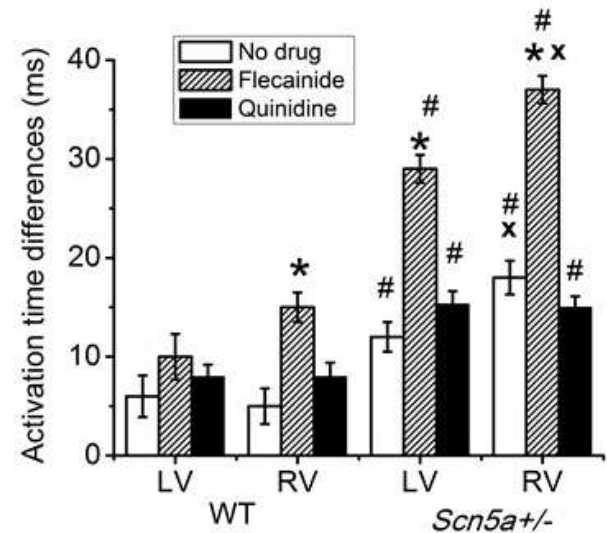
- All incidences were of polymorphic VT

3. *Scn5a*^{+/-} hearts show slowed conduction and lines of block



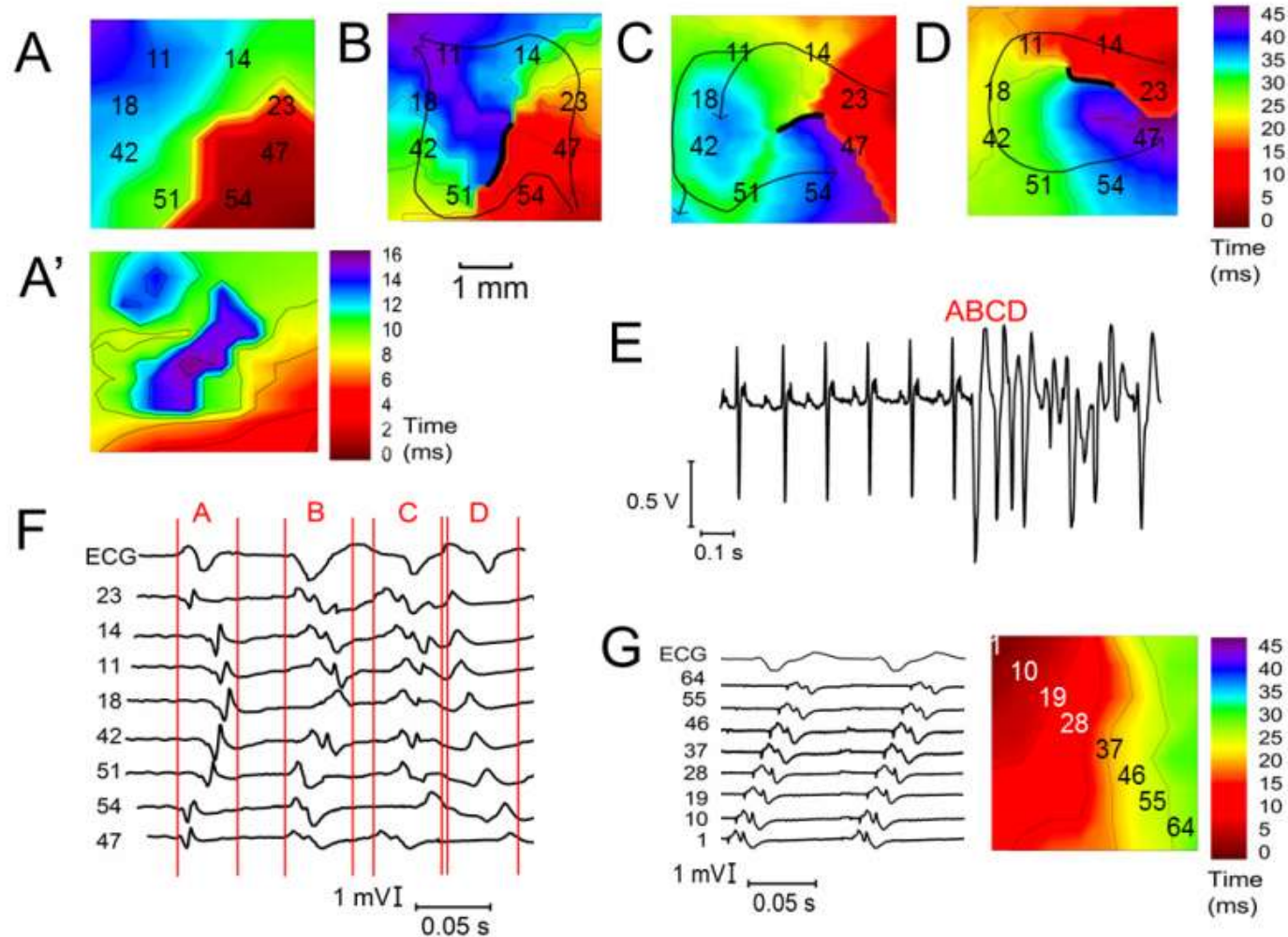
- Single planar propagating wavefront travelling from apex to base of heart (A,B)
- Slower propagation of waves in *Scn5a*^{+/-} hearts (B)
- Heterogeneities in conduction velocity in RV of *Scn5a*^{+/-} hearts, shown by regions of isochronal line crowding (C)

3. *Scn5a*^{+/-} hearts show slowed conduction and lines of block cont.

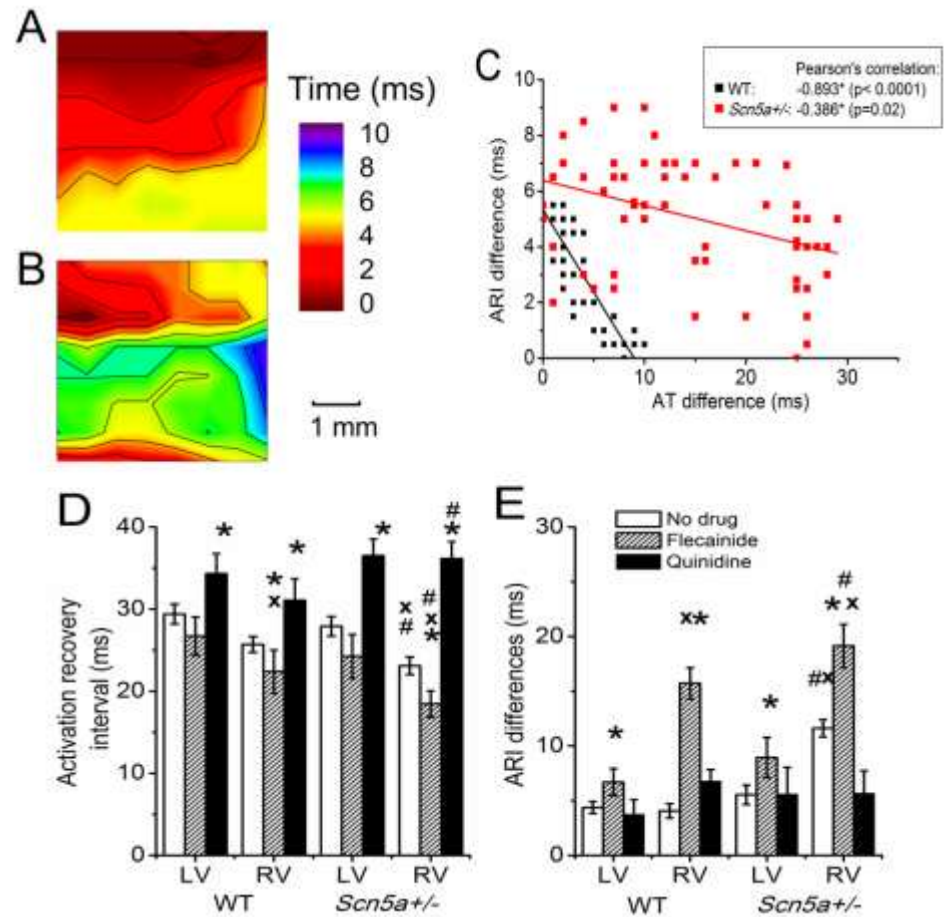


Conduction velocity (m/s)	WT		<i>Scn5a</i> ^{+/-}	
	LV	RV	LV	RV
Before drug	0.36 +/- 0.02	0.37 +/- 0.02	0.23 +/- 0.02	0.18 +/- 0.02
Flecainide 10 mM	0.28 +/- 0.04	0.27 +/- 0.04	0.17 +/- 0.04	0.11 +/- 0.03
Quinidine 5 mM	0.33 +/- 0.04	0.34 +/- 0.05	0.20 +/- 0.04	0.16 +/- 0.03

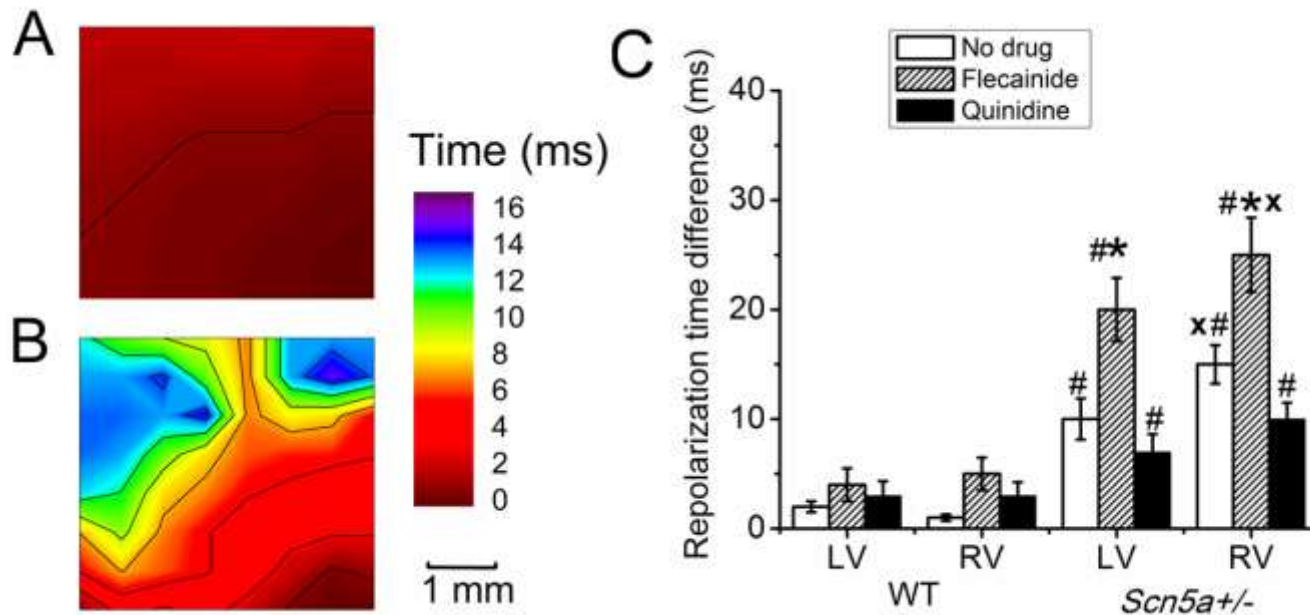
4. VT arises from lines of conduction block leading to re-entrant circuits



5. Activation recovery intervals are shorter, but more heterogeneous, in *Scn5a*^{+/-} hearts



6. Heterogeneity in repolarization times is greatly increased in *Scn5a*^{+/-} hearts



Discussion

- Integration of the two main proposed mechanisms of arrhythmogenesis in BrS
- Multi-electrode mapping techniques used to demonstrate areas of repolarization heterogeneity in which lines of conduction block can form following a premature ventricular beat
- In the presence of slowed conduction, this results in formation of re-entrant circuits and initiation of VT
- Spatial repolarization heterogeneities may also cause the lines of block to become non-stationary and thus result in geometrically changing re-entrant circuits and VT of polymorphic nature

Further work and limitations

- Why are both depolarization and repolarization changes localized to RV?
 - LV has higher depolarization reserve compared with RV?
 - Increased I_{to} current in RV?
- Main limitations to clinical interpretation = differences between mouse and human hearts
 - Thin RV wall
 - Lack of AP plateau phase
- However, activation mapping using unipolar electrogram arrays previously successful in range of transgenic mice
- Ability to analyze epicardium and effects of drugs, and map onset of spontaneous arrhythmogenesis

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Wim Lammers, Department of Physiology, United Arab Emirates University
- produced prototype model of multi-electrode array used in this study

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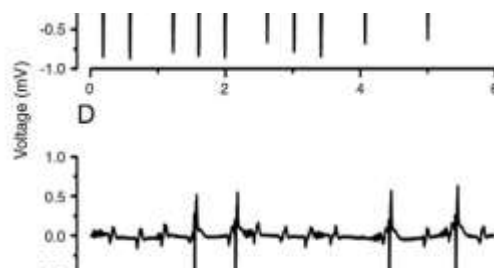
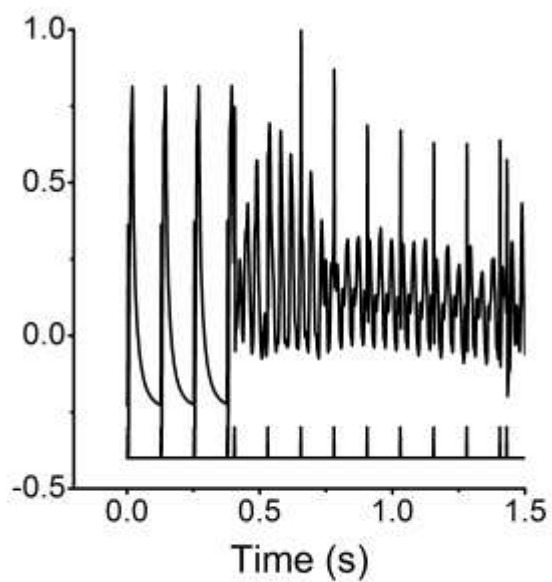
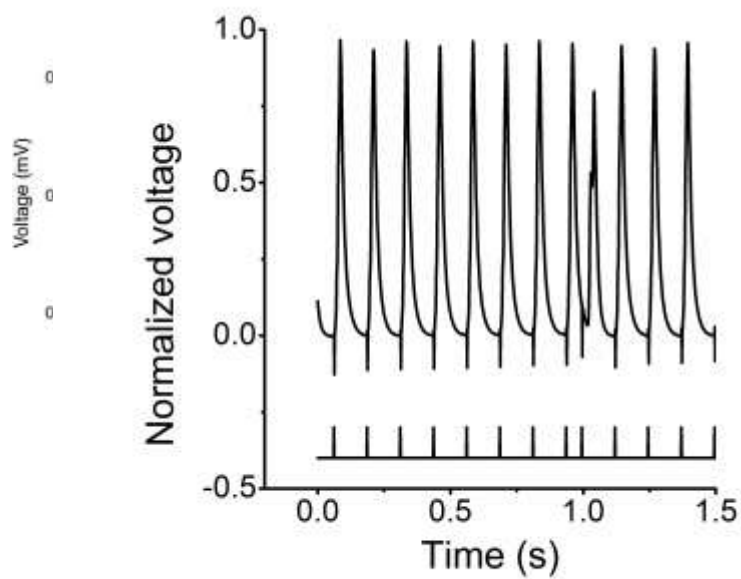
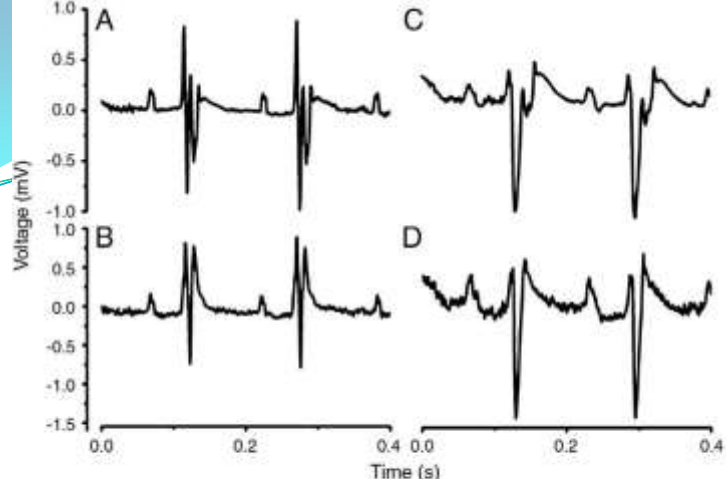


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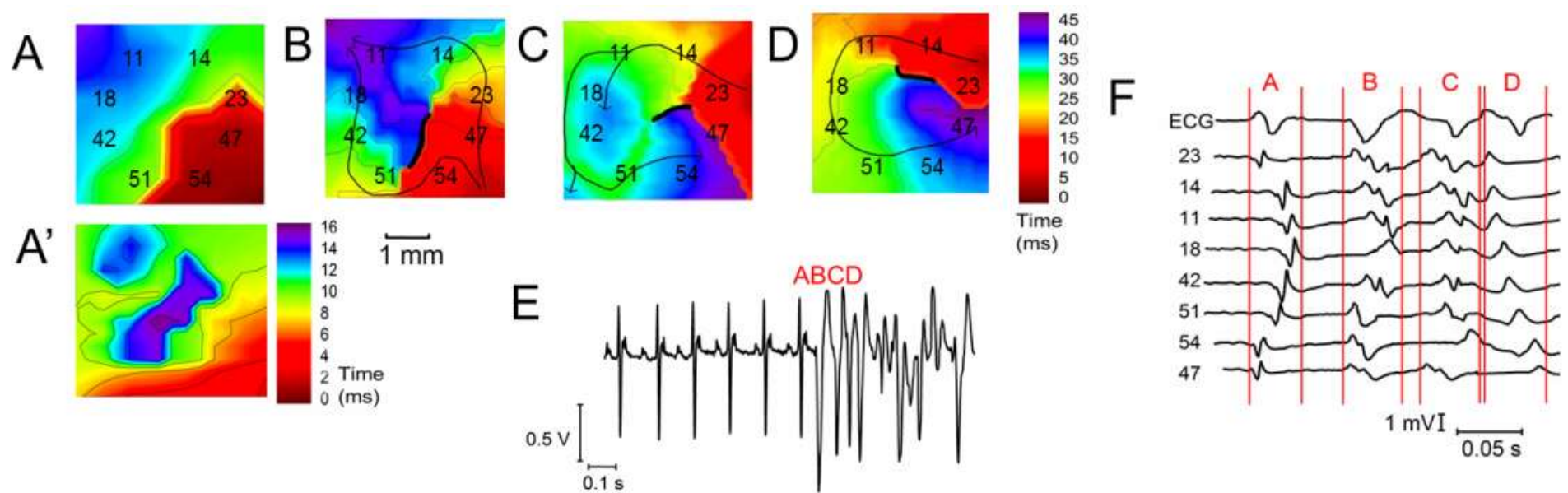
Gonville and Caius College, Cambridge



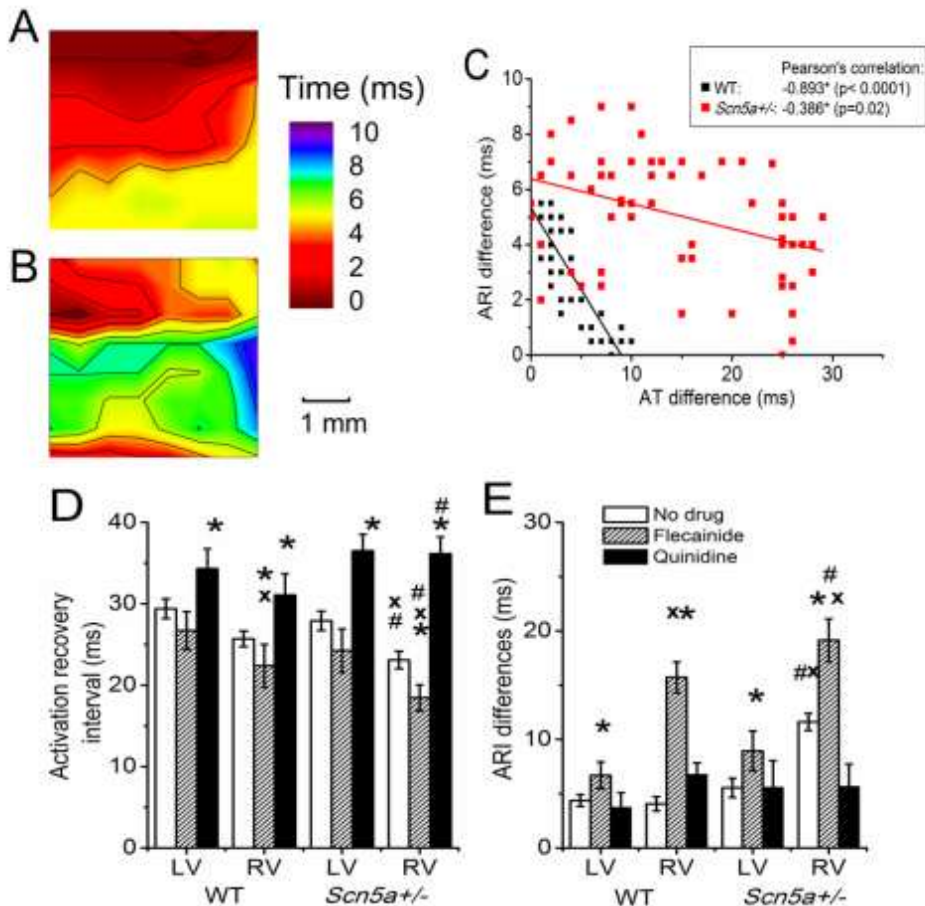


Development of premature ventricular beat leading to initiation of VT

- Last sinus beat: crowded isochronal lines indicate area of conduction slowing (A)
- Corresponding repolarization map shows increased repolarization heterogeneities (A')
- Superimposed premature ventricular beat leads to line of block with impulse propagation flowing around it (B) and fractionated electrograms (point B in panel E)
- Further ventricular ectopic results in formation of macro re-entrant circuit, initiating VT (C)
- Circuit continues into next beat but line of block changes, creating non-stationary vortex, accounting for polymorphic character of VT (D)



are shorter, but more heterogeneous, in *Scn5a*^{+/-} hearts



ARIs were of similar length in the LV and RV of WT hearts but were longer in the LV than the RV of *Scn5a*^{+/-} hearts (Figure 5D). They were shorter in *Scn5a*^{+/-} hearts than WT for the RV but not LV. Flecaïnide decreased the ARI in both WT and *Scn5a*^{+/-} hearts, whilst quinidine increased it. This was significant in both the LV and RV of WT and *Scn5a*^{+/-} hearts for quinidine, but only significant for flecaïnide in the RV of WT and *Scn5a*^{+/-} hearts. In consequence in the presence of flecaïnide the ARI in the RV of the *Scn5a*^{+/-} is significantly smaller than that of the WT.

The ARIDs, measured from the differences between shortest and longest ARIs, were equal between LV and RV in WT hearts, but greater in the RV than LV for *Scn5a*^{+/-} hearts (Figure 5E). They were greater in *Scn5a*^{+/-} hearts than WT in the RV but not

6. Heterogeneity in repolarization times is greatly increased in *Scn5a*^{+/-} hearts

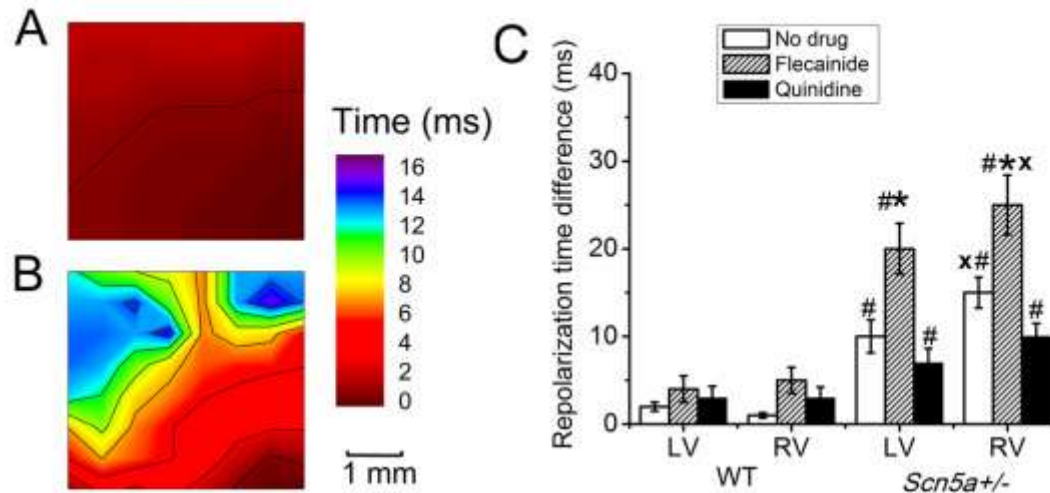


Figure 6(A,B) demonstrates maps of RT differences (RTDs) in the RV of (A) WT and (B) *Scn5a*^{+/-} hearts. RTDs were of similar length in the LV and RV of WT hearts, and although slightly increased by flecainide, this change was not significant (Figure 6C). RTDs were significantly longer in the RV than LV of *Scn5a*^{+/-} hearts. They were also longer in *Scn5a*^{+/-} hearts than WT, both in the