We induced a sustained ventricular arrhythmia in the previously described (Podzuweit *vivo* provoked by catecholamines or exercise (Lerman et al., Circ Res 44:434-445, 1977), all of which modulate the levels of intracellular calcium in ventricular myocytes. We induced a sustained ventricular arrhythmia in the *vivo* non-ischemic pig heart using a localized subendocardial infusion of noradrenaline (NA) as previously described (Podzuweit, Basic Res Cardiol 55:772-779, 1980). Our aim was to characterize the ventricular epicardial activation sequence in 3D during this arrhythmia to test whether local adrenergic imbalance caused an abnormal electrical activation pattern due to the formation of a new pacemaker at the infarct site. To elucidate the electrophysiological basis underlying this arrhythmia, we attempted to reconstruct it in 2D using a network model of 269 by 256 resistively coupled ventricular cells, for which the central region had high adrenergic tone.

### Results

#### 2D ventricular epicardial activation sequence

![Diagram](image1.png)

- Epicardial pacing mimics events observed during the NA-induced arrhythmia

#### 3D epicardial mapping

![Diagram](image2.png)

- Epicardial signals were recorded using an elasticated sock with 63 epicardial electrodes (0.5-1.5 V, 2 ms width, 3 s duration, 50 Hz). The pacing rate was matched to the epicardial activation time for each electrode.

#### Ventricular activation precedes right atrial activation during the arrhythmia

![Diagram](image3.png)

1. Epicardial activation sequences during (A) normal sinus rhythm and ventricular arrhythmias induced (B) chemically, by subendocardial noradrenaline, and (C) electrically, using epicardial electrical stimulation (STEM). Activation maps are superimposed on a 3D mathematical model of ventricular anatomy, highlighting regions of earliest and latest (*) epicardial activation. Thick lines represent the left anterior descending (LAD) and posterior descending (PDA) coronary arteries. During the ventricular arrhythmias, the location of earliest epicardial activation shifted to the left anterior descending (LAD) coronary artery.

#### Conclusions

- 3D characterization of the epicardial electrical events during the NA-induced ventricular arrhythmia revealed activation patterns consistent with a region of abnormal automaticity near the infarct site, which could be comprehensively mimicked by epicardial pacing.
- 2D computational reconstruction of the NA-induced arrhythmia implicated abnormal pacemaking by the sodium-calcium exchange due to calcium overload near the infarct site.
- Interventions that reduce regional inhomogeneities in NA and intracellular calcium may prevent or terminate this type of arrhythmia.

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**Figure 4.** Right atrial (RA) versus earliest ventricular (Vepi) epicardial electrophysiological recordings at the onset of a NA-induced ventricular arrhythmia. Under control conditions (first two cycles) RA activation precedes Vepi. However, spontaneous ventricular activation marks the onset of the arrhythmia, after which RA activation follows. Vepi/RA activation on a one-to-one basis.

**Figure 6.** The control spread of activation (first three cycles) is right to left, where red and blue represent regions of depolarised and repolarised tissue, respectively. The central cells were last to repolarise, once the entire region of electric potential was extended due to the localised inhomogeneities in the calcium currents. (A) BROOD became apparent three cycles later, when the central region spontaneously depolarised just prior to the arrival of the control activation sequence. (C) A further seven cycles later, the central tissue was the dominant pacemaker and completely captured the activation sequence. The full animation may be viewed at the Internet address: http://netres.g氧化al.com/PAPJ/brood.html.png

**Figure 7.** A novel, model-based approach to identify local inhomogeneities in calcium dynamics in the heart. The model fits a 3D anatomically accurate mathematical model of the ventricle, for which seno-calcium and potassium are known to be independent of calcium passive conductance (PDA) coronary arteries have been superimposed on anatomical data.