

# Effects of the Intracellular Ca<sup>2+</sup> Dynamics on Restitution Properties and Stability of Reentry in Rabbit Atrial Tissue Model

OV Aslanidi, MR Boyett, H Zhang

University of Manchester, Manchester, UK

## Abstract

*Atrial fibrillation (AF) is commonly associated with rapid excitation of the atria, but mechanisms of its initiation are unknown. Intracellular Ca<sup>2+</sup> dynamics has been shown to affect cell restitution properties and, as a result, patterns of rapid reentrant excitation in ventricles at early stages of ventricular fibrillation. We study effects of the intracellular Ca<sup>2+</sup> concentration changes on restitution properties and stability of reentry in atrial cell and tissue models. Our simulations show that Ca<sup>2+</sup> and action potential alternans caused by such effects are transient, and resultant break-ups of reentrant waves are reversible – but subsequent accumulation of intracellular Ca<sup>2+</sup> can lead to self-termination of reentry. Hence, other factors (such as tissue anisotropy) may play more prominent role in break-up of atrial reentry into AF.*

## 1. Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia [1]. Although not fatal itself, AF may lead to more serious conditions such as stroke, impaired cardiac output and ventricular tachycardia. The mechanisms underlying AF are not completely understood, although reentrant excitation waves have been associated with its initiation and maintenance [1, 2].

Intracellular Ca<sup>2+</sup> dynamics has been shown to affect cellular restitution properties and, as a result, patterns of reentrant activity in the ventricles during transition from ventricular tachycardia to ventricular fibrillation [3-5]. We study similar effects of intracellular Ca<sup>2+</sup> on cellular action potential (AP) properties and the genesis of reentry in the right atrial (RA) cell and tissue models.

## 2. Methods

The dynamics of electrical processes in cardiac tissues are standardly described by the following equation [6]:

$$\frac{\partial V}{\partial t} = \nabla \cdot D \nabla V - \frac{I_{\text{ion}}}{C_m}. \quad (1)$$

Here  $V$  (mV) is the membrane potential,  $\nabla$  – a spatial gradient operator,  $t$  – time (s),  $D$  – diffusion coefficient ( $\text{mm}^2 \text{ms}^{-1}$ ) that characterizes electrotonic spread of voltage via gap junctional coupling,  $I_{\text{ion}}$  – the total ionic current (pA), and  $C_m$  (pF) – the membrane capacitance.

We have developed a new detailed description of  $I_{\text{ion}}$  – and hence, a new AP model – for a rabbit RA cells based on modification of the existing Lindblad et al. [7] model in order to incorporate up-to-date experimental data [8].

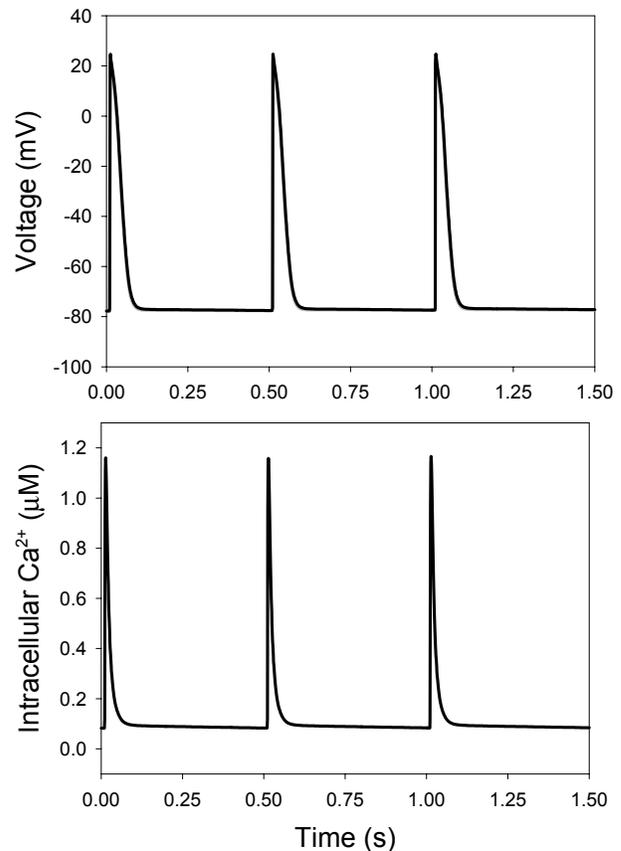


Fig. 1. Effects of Ca<sup>2+</sup> handling on electrical activity in the RA cell models. Top: APs simulated using models with buffered intracellular Ca<sup>2+</sup> (grey lines) and with full Ca<sup>2+</sup> handling (black lines). Bottom: Ca<sup>2+</sup> transients in the full model. CL = 500 ms.

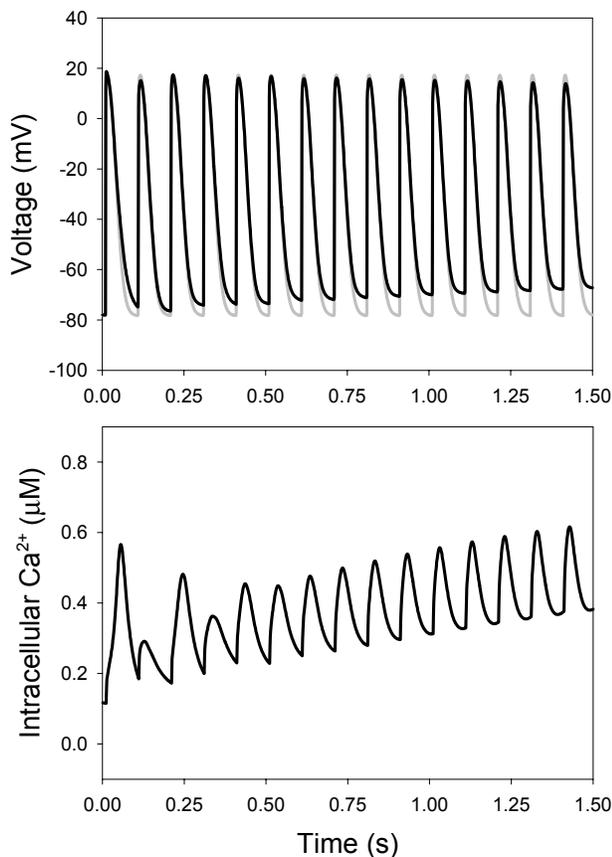


Fig. 2. Effects of  $\text{Ca}^{2+}$  handling on electrical activity in the RA cell models during rapid pacing. Top: APs simulated using models with buffered intracellular  $\text{Ca}^{2+}$  (grey lines) and with full  $\text{Ca}^{2+}$  handling (black lines). Bottom: the intracellular  $\text{Ca}^{2+}$  dynamics in the full model. CL = 100 ms.

$\text{Ca}^{2+}$  handling was either described by the full kinetic model [7], or buffered to a constant level of 73 nM.

Eq. (1) was used to simulate AP propagation in the respective  $30 \times 30 \text{ mm}^2$  atrial tissues. The diffusion coefficient was set to the value  $D = 5 \text{ mm}^2 \text{ ms}^{-1}$ , which produced the AP conduction velocity of  $\sim 0.5 \text{ m/s}$ , as seen in experiments [9]. Eq. (1) was solved using the explicit Euler's method with the time and space steps  $\Delta t = 0.005 \text{ ms}$  and  $\Delta x = 0.1 \text{ mm}$ , respectively.

### 3. Results

APs simulated with the full model and buffered  $\text{Ca}^{2+}$  model had similar morphologies at a slow pacing cycle length (CL) of 500 ms; neither APs nor  $\text{Ca}^{2+}$  transients in the full model showed beat-to-beat variations (Fig. 1). However, rapid pacing at CL less than 100 ms resulted in alternating  $\text{Ca}^{2+}$  transients – as a result, respective APs also had alternating diastolic membrane potential (DMP)

and the action potential duration (APD) – whereas APs in the buffered model did not alternate (Fig. 2). However,  $\text{Ca}^{2+}$  alternans were transient, followed by accumulation of intracellular  $\text{Ca}^{2+}$  after  $\sim 500 \text{ ms}$ , which produced elevated DMP and decreased APD compared to the buffered model. These APD changes were reflected in detailed restitution curves calculated for both models (Fig. 3). Note that similar effects have also been observed during rapid pacing in ventricular cells [4].

A reentrant spiral wave in the tissue model with buffered  $\text{Ca}^{2+}$  rotated stably with a period of  $\sim 90 \text{ ms}$  – whereas in the full model reentry was unstable, breaking up within 500 ms of rotation as  $\text{Ca}^{2+}$  and APD alternated (Fig. 4). However, break-ups stopped as  $\text{Ca}^{2+}$  alternans transitioned to  $\text{Ca}^{2+}$  accumulation; the period of reentry progressively decreased and after  $\sim 1000 \text{ ms}$  it self-terminated. This can be explained by the emergence of large conduction block areas within the tissue due to local elevations of intracellular  $\text{Ca}^{2+}$  [4, 10], which leaves the spiral wave no space for rotation.

### 4. Discussion and conclusions

Effects of the intracellular  $\text{Ca}^{2+}$  dynamics on electrical excitation in cardiac cells and tissues are well documented: they have been shown to affect cellular AP properties during AF [1], as well as alter the AP restitution leading to APD alternans and break up of reentry into fibrillation-like states in the ventricles [3-5].

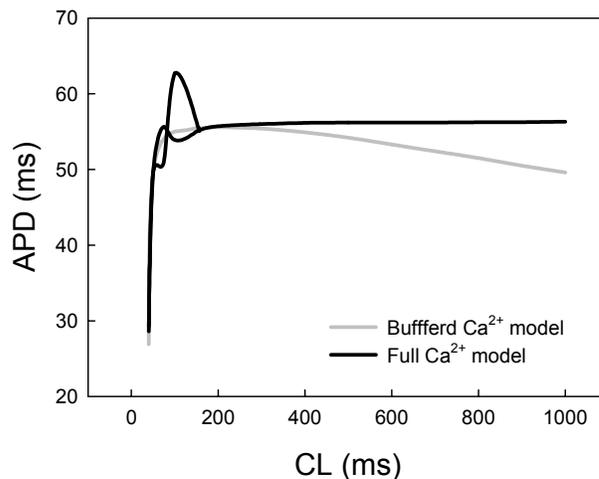


Fig. 3. Effects of  $\text{Ca}^{2+}$  handling on restitution properties in the RA cell models. Restitution curves simulated using models with buffered intracellular  $\text{Ca}^{2+}$  (grey lines) and with full  $\text{Ca}^{2+}$  handling (black lines) are shown. The latter demonstrates loops characteristic of APD alternans at CL of  $\sim 50\text{-}175 \text{ ms}$ . At higher CLs the APD in the full model is increased in comparison to the buffered  $\text{Ca}^{2+}$  model. APD is measured at 90% repolarization after 500 ms of pacing at a given CL.

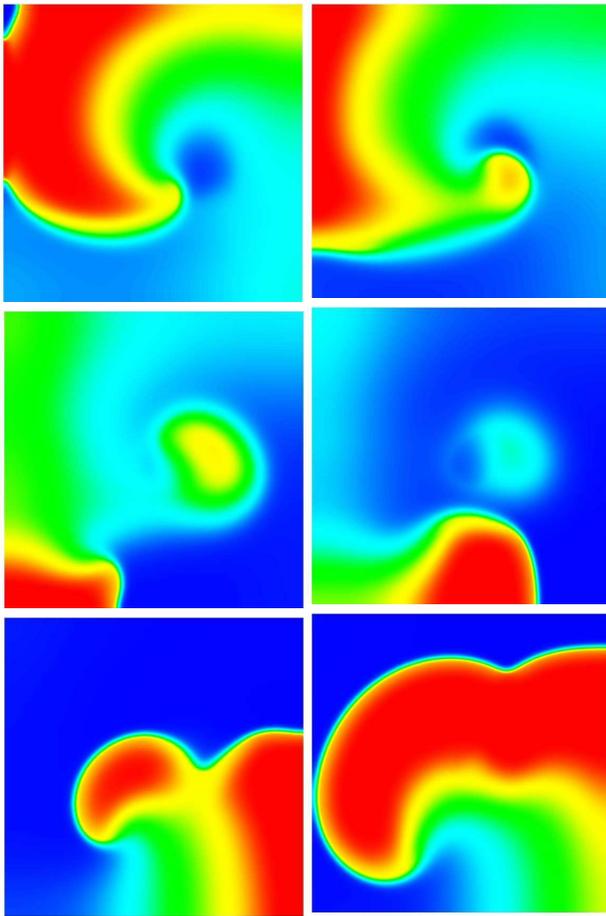


Fig. 4. Break-up and recovery of a reentrant spiral wave in 2D atrial tissue due to the intracellular  $\text{Ca}^{2+}$  dynamics. Successive positions of the spiral are shown at 350, 375, 400, 425, 450 and 475 ms (left to right, top to bottom). Voltage distribution in the tissue is color-coded using the standard rainbow palette. APD alternans are reflected in changing wavelength of the spiral.

We demonstrated that  $\text{Ca}^{2+}$  dynamics altered electrical activity in both atrial cell and tissue models during rapid electrical excitations. However, observed  $\text{Ca}^{2+}$  and AP alternans were transient, and resultant reentry break-ups were reversible. Such small impact of  $\text{Ca}^{2+}$  handling on electrical activity in the rabbit RA in comparison to ventricular tissues [3-5] can be explained to the relatively short  $\text{Ca}^{2+}$  transient in the rabbit atrial cell [11, 12]. Long-term accumulation of intracellular  $\text{Ca}^{2+}$  lead to APD shortening and self-termination of reentry, as observed previously in 2D human atrial tissue models [13].

We conclude that although the intracellular  $\text{Ca}^{2+}$  dynamics can be important in many types of macroscopic phenomena in cardiac cells and tissue, other factors such as tissue anisotropy may play more prominent role in cascading break-up of atrial reentry into AF.

## Acknowledgements

This research was supported by the BBSRC (UK).

## References

- [1] Nattel S, Shiroshita-Takeshita A, Brundel BJ, Rivard L. Mechanisms of atrial fibrillation: lessons from animal models. *Prog Cardiovasc Dis* 2005; 48: 9-28.
- [2] Jalife J, Berenfeld O, Mansour M. Mother rotors and fibrillatory conduction: a mechanism of atrial fibrillation. *Cardiovasc Res* 2002; 54: 204-16.
- [3] Lakatta EG, Guarnieri T. Spontaneous myocardial calcium oscillations: are they linked to ventricular fibrillation? *J Cardiovasc Electrophysiol* 1993; 4: 473-89.
- [4] Chudin E, Goldhaber J, Garfinkel A, Weiss J, Kogan B. Intracellular  $\text{Ca}^{2+}$  dynamics and the stability of ventricular tachycardia. *Biophys J* 1999; 77: 2930-41.
- [5] Goldhaber JJ, Xie LH, Duong T et al. Action potential duration restitution and alternans in rabbit ventricular myocytes: the key role of intracellular calcium cycling. *Circ Res* 2005; 96: 459-66.
- [6] Benson AP, Aslanidi OV, Zhang H, Holden AV. The canine virtual ventricles: a platform for dissecting pharmacological effects on propagating and arrhythmogenesis. *Prog Biophys Mol Biol* 2008; 96: 187-208.
- [7] Lindblad DS, Murphey CR, Clark JW, Giles WR. A model of the action potential and underlying membrane currents in a rabbit atrial cell. *Am J Physiol* 1996; 271: H1666-96.
- [8] Aslanidi OV, Dewey RS, Morgan AR, Boyett MR, Zhang H. Electrophysiologically detailed models of the right and left rabbit atria: pharmacological impacts on propagation and arrhythmogenesis. *Comp Cardiol* 2008; this volume.
- [9] de Groot JR, Veenstra T, Verkerk AO et al. Conduction slowing by the gap junctional uncoupler carbenoxolone. *Cardiovasc Res* 2003; 60: 288-97.
- [10] Bondarenko V, Rasmusson RL. Simulations of propagated mouse ventricular action potentials: effects of molecular heterogeneity. *Am J Physiol* 2007; 293: H1816-32.
- [11] Endoh, M. Muscarinic regulation of  $\text{Ca}^{2+}$  signaling in mammalian atrial and ventricular myocardium. *Eur J Pharmacol* 1999; 375: 177-96.
- [12] Hilgemann DW, Noble D. Excitation-contraction coupling and extracellular calcium transients in rabbit atrium: reconstruction of basic cellular mechanisms. *Proc R Soc Lond B* 1987; 230: 163-205.
- [13] Simitov RD, Biktashev VN. Conditions for propagation and block of excitation in an asymptotic model of atrial tissue. *Biophys J* 2006; 90: 2258-69.

## Address for correspondence

Oleg Aslanidi, Ph.D.

School of Physics and Astronomy  
University of Manchester  
Manchester M13 9PL  
United Kingdom

oleg.aslanidi@manchester.ac.uk