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Review

# A model of the guinea-pig ventricular cardiac myocyte incorporating a transverse–axial tubular system

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**Abstract**

A model of the guinea-pig cardiac ventricular myocyte has been developed that includes a representation of the transverse–axial tubular system (TATS), including heterogeneous distribution of ion flux pathways between the surface and tubular membranes. The model reproduces frequency-dependent changes of action potential shape and intracellular ion concentrations and can replicate experimental data showing ion diffusion between the tubular lumen and external solution in guinea-pig myocytes. The model is stable at rest and during activity and returns to rested state after perturbation. Theoretical analysis and model simulations show that, due to tight electrical coupling, tubular and surface membranes behave as a homogeneous whole during voltage and current clamp (maximum difference 0.9 mV at peak tubular $I_{Na}$ of −38 nA). However, during action potentials, restricted diffusion and ionic currents in TATS cause depletion of tubular $Ca^{2+}$ and accumulation of tubular $K^+$ (up to −19.8% and +3.4%, respectively, of bulk extracellular values, at 6 Hz). These changes, in turn, decrease ion fluxes across the TATS membrane and decrease sarcoplasmic reticulum (SR) $Ca^{2+}$ load. Thus, the TATS plays a potentially important role in modulating the function of guinea-pig ventricular myocyte in physiological conditions.


*Keywords:* t-tubule; Ion accumulation; Ion depletion; Extracellular space; TATS; Restricted diffusion; Heart; Ventricle; Myocyte; Model; Guinea-pig

**Contents**



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## 1. Introduction

The sarcolemma of cardiac ventricular myocytes has numerous invaginations which form a complex system of tubules (Pager, 1971; Page and McAllister, 1973; Forbes and Sperelakis, 1976), termed t-tubules or the transverse–axial tubular system (TATS: Forbes et al., 1984). However, unlike the t-tubular system of skeletal muscle cells (Huxley, 1964; Caillé et al., 1985), the physiological role of cardiac TATS is not fully understood.

Electrophysiologically, the capacitance current elicited by rectangular voltage-clamp pulses in cardiac ventricular myocytes shows a monoexponential decay, suggesting that the whole cell membrane is electrically well coupled. However, there is increasing evidence that many ion flux pathways are located predominantly in the TATS membrane (see reviews by Scriven et al., 2000; Brette and Orchard, 2003), thereby endowing the TATS with specialised ion transfer properties.

The importance of changes of ion concentrations in the clefts between cardiac cells is well recognised (McGuigan, 1974; Attwell et al., 1979), but the possible consequences of accumulation and depletion of ions in cardiac TATS has only occasionally been considered (Bers, 1983; Bers and MacLeod, 1986; Yasui et al., 1993; Amsellem et al., 1994, 1995; Tourneur et al., 1994; Clark et al., 2001), although it has been suggested that restricted ion diffusion in cardiac TATS may produce significant changes of ion concentrations in its lumen (Bers, 1983; Yasui et al., 1993; Tourneur et al., 1994; Clark et al., 2001).

The complex interplay between changes in ion concentrations in the TATS lumen and the activity of ion channels, pumps and transporters present in the TATS membrane has been discussed (Christé, 1999; Brette and Orchard, 2003). However, until recently, there has been no attempt to determine quantitatively its physiological importance, despite the development of a number of computer models of ventricular cell electrophysiology and excitation–contraction (EC) coupling (see reviews by Noble, 2002; Puglisi et al., 2004).

We have previously presented a model (Pasek et al., 2003) that incorporated TATS but combined features from several species such as guinea-pig, rat and dog. This model provided a general view of the physiological consequences of the TATS, but preliminary data indicated important species' differences in these