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Review

Repolarization gradients in the intact heart: Transmural or apico-basal?☆

Michiel J. Janse [a], Ruben Coronel [a], Tobias Opthof [a,b,*], Eugene A. Sosunov [c], Evgeny P. Anyukhovsky [c], Michael R. Rosen [c]

[a] The Experimental Cardiology Group, Heart Centre, Academic Medical Centre, Amsterdam, The Netherlands
[b] Department of Medical Physiology, University Medical Centre, Utrecht, The Netherlands
[c] Center for Molecular Therapeutics, Department of Pharmacology, College of Physicians and Surgeons, Columbia University, NY, USA

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ABSTRACT

Controversies regarding the genesis of the T wave in the electrocardiogram and the role of midmural M cells in the intact heart include:

- whether transmural or apico-basal gradients in repolarization times are responsible for the T wave.
- whether M cells are involved in creating a transmural repolarization gradient thereby contributing to drug-induced Torsade de Pointes.

In normal, intact canine and human hearts there is no significant transmural gradient in repolarization times. The T wave results primarily from apico-basal differences in repolarization times. Also, in the intact heart there is no midmural region of prolonged action potential duration. This contrasts with isolated preparations, such as the wedge preparation or myocardial slices or disaggregated myocytes in which M cells, with action potentials longer than those of endocardial and epicardial myocardium, can be found. This disparity in action potential duration probably results from partial uncoupling of myocardial cells in the regions where measurements are made, e.g., the cut surface of a wedge preparation. In regions of a wedge where cellular coupling is normal, or in isolated myocardial bundles or sheets, no evidence for M cells is detected. In some wedge preparations, a drug-induced large transmural repolarization gradient, involving M cells, can lead to Torsade de Pointes, possibly caused by so-called phase two reentry. In contrast, when a gradient of repolarization times of more than 100 ms was created in intact hearts, no evidence for reentry was found and no spontaneous arrhythmias occurred.

In conclusion, in the intact heart, M cells appear not to contribute to repolarization gradients and arrhythmias. Furthermore, no significant repolarization gradients between endocardium and epicardium exist. The T wave in the body surface electrocardiogram is caused by apico-basal and anterior–posterior differences in repolarization times.

Contents

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* Corresponding author. The Experimental Cardiology Group, Centre for Heart Failure Research, Academic Medical Centre, Room K2-105, Meibergdreef 9, 1105 AZ Amsterdam, The Netherlands. Tel.: +31 20 5663263; fax: +31 20 6975458.
E-mail address: t.opthof@inter.nl.net (T. Opthof).

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1. Introduction

In modern Cardiology textbooks, the T wave of the electrocardiogram (ECG) is considered to result from transmural differences in repolarization times, with the epicardium repolarizing earlier than the endocardium (Barr, 1989; Bayes de Luna et al., 2006; Garibyan and Lilly, 2007; Mirvis and Goldberger, 2005). The consensus appears to be that transmural activation and repolarization gradients are opposite: that activation proceeds from endocardium to epicardium, that repolarization starts in the epicardium and occurs later in midmural and endocardial layers. The concept has emerged that morphology of the T wave of the ECG can be considered to result from the difference between endocardial and epicardial action potentials. This would account for the fact that the human ECG manifests concordant QRS complexes and T wave in most leads (see Fig. 1).

The work of Antzelevitch et al. (Antzelevitch, 2001; Yan and Antzelevitch, 1998) on the arterially perfused canine wedge preparation has expanded the notion of transmural repolarization gradients. The wedge preparation is made by cannulating a branch of a coronary artery, perfusing it with Tyrode's solution, and removing the non-perfused part of the left ventricular wall. This preparation is submerged in a bath filled with Tyrode's solution, and a pseudo ECG is recorded with two large electrodes placed in the bath at the epicardial and endocardial sides of the preparation. In the wedge preparation the peak of the T wave coincides with the end of epicardial repolarization, and the end of the T wave coincides with the end of repolarization of the midmural M cells. The interval between peak and end of the T wave (TpTe) has been proposed as an index of transmural repolarization (see Fig. 2). However, the QRS complex and the T wave in the pseudo ECG of the canine wedge preparation are concordant, whereas they are discordant in most leads in the intact dog (Janse et al., 2005; Volders et al., 1999). Thus, repolarization in a wedge does not represent that in a heart (Opthof et al., 2007a).

Both the older literature and more recent experimental studies on intact hearts provide numerous data showing the absence of significant transmural repolarization gradients across the left ventricular wall. We will review these studies in some detail, as well as the studies in (mostly) wedge preparations that claim substantial transmural gradients in repolarization. We will also discuss the possible role of midmural M cells on repolarization gradients and arrhythmogenesis. We do this not to persevere on what has become a seemingly endless discussion, but rather to lie to rest what has been a long running controversy.

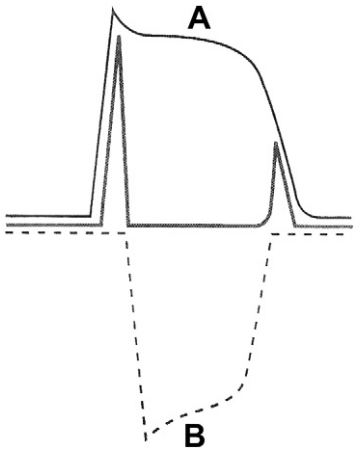

Fig. 1. Schematic representation of "global" action potentials of the subendocardial (A) and subepicardial layers (B). Depolarization starts in the subendocardium and repolarization ends in the subendocardium. When A is subtracted from B, the ECG pattern results (reproduced from Bayés de Luna et al. (2006) with permission).

2. Studies on intact hearts in animal models

In 1880, Burdon-Sanderson and Page (1879) recorded the ECG of the frog simultaneously with monophasic action potentials from the base and the apex of the left ventricle and noted that repolarization occurred earlier at the base than at the apex. Warming the base resulted in a shortening of the basal action potential, leading to a deeper, longer T wave in the ECG. Similar findings were reported by Bayliss and Starling (1892) and by Mines (1913). This early literature has been admirably reviewed by Noble and Cohen (1978). Thus, by the early 20th century, the notion that the T wave is caused by apico-basal gradients in repolarization was well established. At that time, it was not possible to determine repolarization times at intramural sites.

With the development of intramural plunge electrodes, containing multiple electrode terminals spaced at 2 mm, by Durrer and van der Tweel in the 1950's (Durrer and van der Tweel, 1954) it became possible to determine moments of activation and moments of repolarization (and refractory periods by subtraction) at multiple intramural sites (van Dam and Durrer, 1961). Strength–interval curves for cathodal stimuli were determined at successive intramural electrodes. The absolute refractory period (ARP) was defined

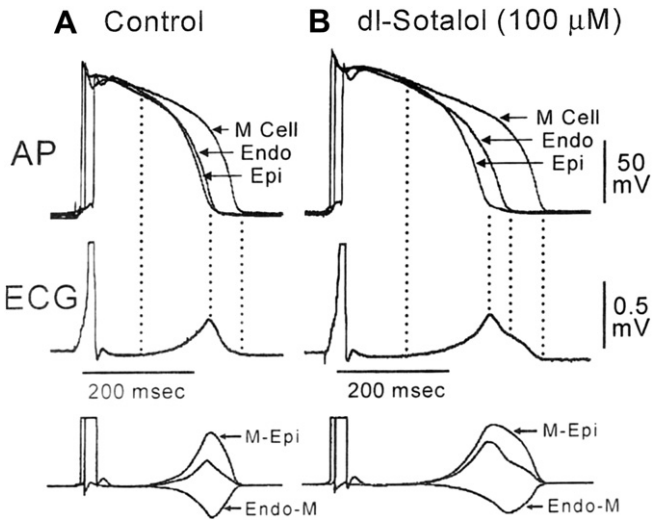

Fig. 2. Transmembrane potentials and a transmural ECG recorded from two different arterially perfused wedge preparations. In both cases repolarization of the epicardium is coincident with the peak of the T wave, whereas repolarization of the M cells coincides with the end of the T wave the duration of the endocardial action potential is intermediate. Note that sotalol caused a greater prolongation in the action potential duration of the M cell than in the other cells, and that the Tpeak-end interval is prolonged. Basic cycle length 2000 ms (modified from Yan and Antzelevitch (1998)).