There is no transmural heterogeneity in an index of action potential duration in the canine left ventricle

Frederik Voss, MD,* Tobias Opthof, PhD,†‡ Jens Marker, MD,* Alexander Bauer, MD,* Hugo A. Katus, MD,* Ruediger Becker, MD*

*From the *University of Heidelberg, Department of Cardiology, Heidelberg, Germany, †Experimental Cardiology Group, Center for Heart Failure Research, Academic Medical Center, Amsterdam, The Netherlands, ‡Department of Medical Physiology, University Medical Center Utrecht, Utrecht, The Netherlands.*

BACKGROUND Transmural heterogeneity in ventricular repolarization demonstrated in vitro has been difficult to confirm in vivo. Whether this discrepancy reflects a physiological phenomenon or a methodological problem remains a vivid matter of debate despite a plethora of experimental work. Therefore, we have measured the relevant electrophysiological parameters first in vivo and repeated these in the same heart and at identical sites in vitro. Methodological issues were tackled by using both unipolar and bipolar recordings. Physiological issues were explored by measuring both local and functional electrophysiological parameters.

METHODS In 10 healthy dogs, 2 high-resolution needle electrodes were inserted into the left ventricle. Effective refractory periods (ERP) as well as activation recovery intervals (ARI) were determined at each electrode along both needles at basic cycle lengths (BCL) of 850 and 300 ms, respectively. After excision of the heart, ERP and ARI measurements were repeated in the arterially perfused wedge preparations.

RESULTS First, we observed that ERPs and ARIs were significantly shorter in vivo than in vitro. Mean ERPs and ARIs of all muscle layers were relatively uniform throughout the ventricular wall in vivo. The transition from the in vivo to the in vitro preparation was associated with a significant albeit small increase of mean ARIs in the subendocardium, whereas interlayer differences in mean ERPs did not reach statistical significance as in vivo.

CONCLUSION In the intact canine left ventricular wall, a more or less homogeneous distribution in transmural ERP and ARI is present.

KEYWORDS Arrhythmia; Cardiac heterogeneity; Transmural heterogeneity; M cell; Repolarization; Torsade de pointes

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Introduction

Several in vitro studies have identified a subpopulation of ventricular muscle cells with unique electrophysiological properties located preferentially in the midmyocardium of the canine heart, referred to as M cells.[1,2] In vitro, M cells are distinguished from other cells in displaying a smaller slowly activating delayed rectifier current (I_{Ks}),[3] but a larger late sodium current (late I_{Na}) and sodium–calcium exchange current ($I_{Na\text{-}Ca}$).[4] M cells show a longer action potential duration (APD) and a steeper cycle length–APD relationship (restitution curve). This may be instrumental to disproportionate prolongation of APD in response to slowing of the heart rate or to class III antiarrhythmic agents.[2] Because of these electrophysiological properties, M cells have been suggested to account for transmural heterogeneity of repolarization not only at very long (>2,000 ms) but also at physiological cycle lengths in the in vitro condition.[2] However, in in vivo studies in the dog, transmural heterogeneity (in indices) of repolarization has not been observed.[5–10] In one other study in the in vivo canine ventricle, there was no physiologically relevant transmural difference in activation–recovery intervals (ARIs), an index of APD and/or refractoriness.[11] Also, in an in vivo study by Weissenburger et al,[12] an assessment was made of transmural differences in monophasic APDs. At 1,000 ms cycle length, there was only a dispersion of about 20 ms without a midmural zenith, regardless of whether pentobarbital or halothane anesthesia was applied (Figures 3A and 3B in Weissenburger et al[12]). Moreover, the difference between endocardial and epicardial monophasic APDs was of the same order as the conduction time (Table 1 in Weissenburger et al[12]) with as an interesting physiological implication that there was neither a midmural zenith in monophasic APD nor a relevant transmural gradient in repolarization time).[12]

In the human heart, there are hardly any in vitro data available in wedge preparations. In one study (with 4 preparations only), M cells seemed to be present, albeit at a subepicardial position,[13] different from what has been reported in animal studies. In another human study with a wedge preparation, there was no midmyocardial zenith in ARIs.[14] In in vivo studies in the human heart, there are indications for neither transmural differences in ARIs[15] nor

Address reprint requests and correspondence: Dr. Frederik Voss, University of Heidelberg, Department of Cardiology, Im Neuenheimer Feld 410, 69120 Heidelberg, Germany. E-mail address: Frederik_Voss@med.uni-heidelberg.de. (Received August 7, 2008; accepted March 14, 2009.)

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for transmural differences in repolarization.[14] Also, in the human Langendorff-perfused heart, to avoid complications with the effects of anesthesia, there were no midmural zeniths in APD.[14] Obviously, there are numerous biological differences between in vitro and in vivo preparations, such as autonomic, humoral, or hemodynamic influences. On the other hand, the type of preparation also implies methodological differences in the assessment of local repolarization parameters. This relates to very slow heart rates, isolation of individual cells or cell layers, and microelectrode action potential measurements in vitro, as opposed to faster heart rates, preservation of an intact myocardial syncytium, and measurements of either refractory periods, monophasic action potentials, or ARIs in vivo. Thus, in the present study, while turning an in vivo into an in vitro preparation, measurements of effective refractory periods (ERP) with extracellular bipolar electrodes and ARIs with extracellular unipolar electrodes were repeated under otherwise identical conditions in an effort to further elucidate the basis of the apparent discrepancies in transmural action potential duration and/or repolarization patterns with different experimental preparations. Our in vitro method has the additional advantage that the measurements were made within the wedge preparation, far away from its cut and healed transmural surface.

Methods

All animal experiments complied with the *Position of the American Heart Association on Research Animal Use* adopted in November 1984. Studies were performed in 10 foxhounds of either sex with a body weight of 28 to 36 kg.

In vivo experimental setup

Anesthesia was initiated with propofol (2.0 mg/kg intravenously) and maintained by continuous ventilation with halothane 0.5 vol-% (initial vapor concentration 1.0%). Buprenorphine 0.3 mg intravenously was administered before starting any procedure. Electrocardiograph leads I, II, and aVF and aortic blood pressure were continuously monitored with a physiological recorder (VR 12, Electronics for Medicine, Pleasantville, New York). To achieve slow heart rates, acute atrioventricular (AV) block was induced by transvenous radiofrequency catheter ablation of the compact AV node (Cerablate easy 745, 4-mm tip, Sulzer Osypka GmbH, Grenzach-Wyhlen, Germany; HAT 200 RF generator, Sulzer Osypka GmbH, Grenzach-Wyhlen, Germany). The heart was then exposed through a midsternal thoracotomy and suspended in a pericardial cradle. Two needle electrodes were inserted into the anterior left ventricular wall close to the interventricular septum, approximately 1.0 cm lateral to the left anterior descending coronary artery just below the second diagonal branch (Figure 1). To prevent surface cooling of the heart, the chest was covered with gauze and warmed saline (37°C) was applied intermittently to the heart. A heating lamp in conjunction with intravenous infusion of warmed saline was used to maintain body temperature at 37°C, which was continuously monitored using an electronic thermometer.

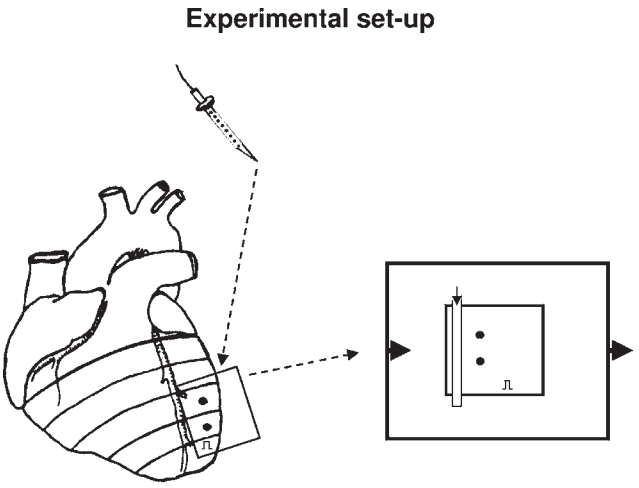

Figure 1 Schematic illustration of the experimental setup. **Left:** In vivo preparation with insertion site of needle electrodes (black dots) and pacing site via epicardial pacing wire (Π). **Right:** In vitro preparation with the wedge preparation (inner rectangular box) and the cannulated second diagonal branch of the left anterior descending vessel (small arrow). Again, the sites of the needle electrodes (black dots) and the pacing site (Π) are indicated. The wedge lies in the tissue bath (outer rectangular box), which is also perfused with Tyrode solution (large arrows).

In vitro experimental setup

After completing the in vivo measurements, each heart was excised and immediately placed in Tyrode solution (NaCl: 129 mM, KCl: 4.0 mM, CaCl2: 2 mM, MgCl2: 1 mM, NaHCO3: 14 mM, NaH2PO4: 1 mM, glucose: 12 mM, pH: 7,4) with a temperature of 37°C. A transmural rectangular preparation (2.5 × 2.5 cm) was dissected from the left ventricle, with the 2 needle electrodes placed in vivo left in place. The preparation was cannulated via the second diagonal branch of the native left anterior descending artery and continuously perfused with warmed (37°C) Tyrode solution by a roller pump providing a constant pressure of 40 mm Hg (Julabo, Labortechnik GmbH, Seelbach, Germany). Leaking collaterals were ligated. Finally, the preparation was placed in a tissue bath, superfused continuously with warmed (37°C) Tyrode solution by a second pump (Haake, Karlsruhe, Germany), and allowed to equilibrate during constant pacing at a cycle length (CL) of 850 ms for 45 min. Pacing was performed through 2 pacing wires that were placed on the epicardium (Figure 1). The time interval from excision of the heart to cannulation and perfusion of the artery was <2 min in all experiments. After completing the in vitro measurements, homogeneity of arterial perfusion was confirmed by administration of Lisamin-Green into the coronary circulation after prolonged periods of perfusion.

Needle electrodes and ERP measurements

Two custom-made, high-resolution needle electrodes were used to measure local ERPs throughout the ventricular wall. Each needle was 13 mm in length and 1.5 mm in diameter, containing 8 bipolar electrodes. Bipolar recordings could be obtained from intramural sites 1.0, 2.5, 4.0, 5.5, 7.0, 8.5, 10.0, and 11.5 mm in depth. Using the extrastimulus tech-

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