Available online at www.sciencedirect.com

ScienceDirect

Journal of Electrocardiology xx (2017) xxx – xxx

JOURNAL OF Electrocardiology

www.jecgonline.com

Ventricular repolarization duration and dispersion adaptation after atropine induced rapid heart rate increase in healthy adults

Lennart Bergfeldt,* Gunilla Lundahl, Gabriel Bergqvist, Farzad Vahedi, Lennart Gransberg

Dept. of Molecular & Clinical Medicine/Cardiology, Institute of Medicine, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden
Dept. of Cardiology, Sahlgrenska University Hospital, Gothenburg, Sweden

Abstract

Background: Proper adaptation of ventricular repolarization (VR) to rapid heart rate (HR) increase is crucial for cardiac electro-mechanical function. The pattern and temporal aspects of this adaptation and its components (duration and dispersion) during normal conduction are, however, incompletely known in humans and were the topic of this study.

Methods & results: The VR duration (QT & QTpeak) and dispersion (Tamplitude, Tarea & ventricular gradient; VG) responses were studied by continuous vectorcardiogram after a bolus injection of atropine 0.04 mg/kg b.w. in 31 healthy young adults (16 men). The primary measure (T90 End) was the time to reach 90% change from baseline to end value 300 s later.

Mean (SD) of T90 End was 23 (9) s for a 41% RR decrease, 130 (35) s for a 16% QTend decrease and 110 (36) s for a 19% QTpeak decrease; the response was single-exponential for these measures. For 35–43% decreases of Tamplitude, Tarea & VG, mean (SD) of T90 End were 21 (10), 38 (20) and 40 (23) s and the response pattern was double-exponential with varying overshoot.

Conclusions: VR duration and dispersion responses to a very rapid HR increase during normal conduction differed substantially. In contrast to the well-known single-exponential delay in VR duration adaptation the responses of VR dispersion measures were double-exponential and much more rapid. We describe a new and completely non-invasive phenotypic characterization of different components of VR adaptation.

Keywords: Ventricular repolarization; Restitution; Hysteresis; Atropine; Vectorcardiography

Introduction

The duration of ventricular repolarization (VR) depends on the preceding diastolic interval, a phenomenon known as electrical restitution. Electrical restitution characteristically shows hysteresis, a delay which builds not only on one but on hundreds of preceding diastolic intervals, a phenomenon also referred to as ultra-rapid cardiac memory [1]. The physiologic advantage of hysteresis is a gradual change of the relation between systolic ejection and ventricular filling time and optimization of the time for coronary perfusion. Hysteresis also dampens fluctuations in VR duration and thereby reduces the risk for oscillations (alternans) that may predispose for life-threatening arrhythmias [2].

Knowledge about the physiology and pathophysiology of electrical restitution and its hysteresis therefore has both theoretical and clinical interest, and can create a foundation for how to assess and reduce the risk for life-threatening arrhythmias. Present knowledge of these phenomena is based on pacing studies, a method suitable for research but with limited applicability in clinical routine for practical and ethical reasons and with protocol dependent results [3].

Furthermore, although prolongation of VR duration is mechanistically linked to triggering of ventricular arrhythmia by a premature beat (due to early or late after depolarizations), the sustenance of such arrhythmias is presumably dependent on VR dispersion [4]. Adaptation of VR dispersion has been studied during ventricular pacing [5,6], but neither its response during increasing HR and normal ventricular conduction, nor its relation to VR duration. Global VR dispersion can be evaluated non-invasively by vectorcardiography (VCG) measuring e.g. Tarea, the ventricular gradient (VG), and Tamplitude. The aim of this study was therefore to define the pattern and temporal aspects of the adaptation of VR duration and global VR dispersion during normal ventricular conduction in response to a rapid HR increase induced by a bolus injection of atropine in adult healthy subjects. Although a delay of the VR duration response would be expected from

* Corresponding author at: Dept. of Cardiology, Sahlgrenska University Hospital, S-413 45, Gothenburg, Sweden.
E-mail address: lennart.bergfeldt@hjl.gu.se

http://dx.doi.org/10.1016/j.jelectrocard.2017.03.014
0022-0736/

previous research, the VR dispersion response and its relation to that of duration would be important whatever the result.

Methods

This study is based on a de novo beat-to-beat analysis of the atropine part of the protocol of a prior study of the signal-averaged repolarization response to pharmacologically induced autonomic nervous system (ANS) modulation [7]. Restitution curves are created by plotting VR duration measures against the preceding diastolic interval. We focused, however, on defining the response pattern and within what time-frame measures of VR duration and dispersion adapt to a rapid decrease in RR intervals (HR increase) in young adult healthy men and women, i.e. a phenotypic characterization of VR adaptation during a rapid HR increase and during normal ventricular conduction.

Study subjects

Thirty-one healthy male (16) and female (15) volunteers were recruited based on the following criteria: 20–45 years of age, body mass index 19–27 kg/m^2, no acute or chronic illness, no family history of sudden cardiac death, no concomitant medication except for contraceptives, no history of drug addiction, alcohol or anabolic steroid abuse or habitual use of tobacco, and no relation to the study investigators. Normal physical findings, resting ECG and laboratory assessments including electrolytes were also required.

The study was performed following the principles of the Declaration of Helsinki, was approved by the regional ethics committee and written informed consent was obtained from all participants.

Procedure and protocol

The study was performed in a hospital setting. The subjects rested in the supine position in a hospital bed and VCG recording electrodes were applied. A peripheral venous cannula was inserted. During continuous VCG recording parasympathetic inhibition was achieved by administering atropine (0.04 mg/kg b.w.) i.v. over 30 s; VR adaptation was followed at least 5 min. No blood samples were collected.

Data acquisition and analysis

Recording procedure

A CoroNet II system (Ortivus AB, Danderyd, Sweden) was connected to 8 electrodes positioned according to a Frank orthogonal lead system (X, Y, and Z) modified for the supine position. Signals were sampled at 500 Hz with an amplifier bandwidth of 0.03–170 Hz. Time points (fiducial points) for P-, QRS- and T-waves were identified from the vector magnitude and direction derived from the X, Y, and Z lead recordings except for Tend, which was derived from the magnitude alone. The methodology follows the same principles as described previously using customized software [7,8]. See Supplement for methodological details pertaining to this and subsequent sections in Methods.

Beat-to-beat dynamics – RR and VR measures

The instantaneous changes in HR were measured from all consecutive RR intervals. VR duration was assessed from 2 measures, QTend and QTpeak (QTp). In this context the QTp response pattern was used to validate the QTend (abbreviated as QT in the following text) response pattern on the assumption that they followed each other. Initially, we sought to study four VR dispersion measures: Tpeak-end interval (describing the time from the earliest to the latest complete repolarization of any part of the in situ heart) [9,10], Tarea reflecting global VR dispersion, ventricular gradient (VG) reflecting dispersion of action potential morphology, and Tamplitude [11–14]. The T wave end (Tend) was defined using the tangent method because after atropine there was a transient phase with partial merging of the T and P waves and also T wave flattening (as expected during HR increase) making it impossible to otherwise define Tend. The QT interval subsequently shortened and T- and P-wave merging disappeared. Fig. 1 shows for one participant how the T-wave amplitude changed and the relation between Tend and the P-wave onset at 9 time points during 5 min after the onset of the atropine effect (see Supplement).

Defining the reaction start-point

The start-point of the RR (and VR) responses to atropine was set to the intersection of an exponential curve of the type [*Baseline + (Change from Baseline to End)*(1 – e^{-kt})*] fitted to the RR values. The RR baseline value was calculated as the average of the preceding 90 s. The start-point for the RR response to atropine was used as time "0" for all other measures.

Curve-fitting to RR and VR responses

The best fit (red in figures) of the exponential curve to the raw data (blue in figures) of RR and VR values was identified and selected by minimizing the square-sum of difference using the generalized reduced gradient (GRG2) nonlinear optimization solution (as implemented in Microsoft Excel's Problem Solver) [15]. Fig. 2 a–d illustrates that two different response patterns were observed: One pattern was single-exponential with an initial rapid response turning gradually into a new although not entirely stable level as shown for RR and QT intervals (Fig. 2 a & b). The second pattern was double-exponential with a similar rapid initial response followed by an overshoot before returning slowly to a level closer to the baseline. In some participants there were oscillations before reaching the End value and in some there was a slow drifting towards the End value 300 s after onset. This response pattern is exemplified for Tamplitude and Tarea (Fig. 2 c & d) (see Supplement).

Descriptors of dynamical changes

The amount of change in the equation was defined by the difference between the baseline and the End value 300 s later (from here: ΔEnd). The ΔEnd measure was a point-value because our VR measures did not always reach a steady-state level.

Because participants had different baseline and End values, "normalized" graphs or curves describing the dynamical changes were constructed before measuring the temporal aspects of all 7 measures (RR, QT, QTp and Tp-e intervals, Tarea, VG, and Tamplitude) as exemplified in Fig. 2