Biomedical Signal Processing and Control 14 (2014) 285–290

Contents lists available at ScienceDirect

Biomedical Signal Processing and Control

journal homepage: www.elsevier.com/locate/bspc

Computer modelling of beat-to-beat repolarization heterogeneity in human cardiac ventricles

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ARTICLE INFO

Article history:
Received 12 September 2013
Received in revised form 15 August 2014
Accepted 21 August 2014
Available online 19 September 2014

Keywords:
QRST integral map
Non-dipolarity index
Numerical chest model
Numerical heart model

ABSTRACT

Based on our numerical heart and chest model with stochastically modifiable action potential duration (APD) parameters, the consequences of diminished subepicardial cell-to-cell coupling were studied on beat-to-beat repolarization heterogeneity. Pathological action potential durations and transmural gradient (TG) mean values (M) were assumed in the apical segment of the five-layer heart model, while in the rest of the model the action potential parameters were kept in the normal range. APD mean values and the associated APD standard deviations (SDs) were fitted to experimental data. SD was causally related to APD mean. Repolarization heterogeneity was characterized by QRST integral maps and by the non-dipolarity index (NDI). The TG of −15 model time units (mtu) yielded an NDI of 12%. By sweeping beat-to-beat TG from −15 mtu up to +14 mtu, NDI increased from 12% up to 71%. In healthy heart M is large compared to the SD value; consequently NDI is in the stable <20% range. In arrhythmia patients TG diminishes, M and SD increase, consequently, NDI shows temporally random, increased beat-to-beat fluctuations, suitable for the characterization of repolarization heterogeneity.

1. Introduction

Ventricular tachycardia (VT) and fibrillation (VF) are the most common causes of sudden cardiac death (SCD). In spite of the continuous development of risk assessment methods, still no reliable ECG based marker of arrhythmia prone status does exist according to the scientific statement of the AHA/ACCF/HRS based on hundreds of clinical trials [1].

According to theoretical expectations, parameters casually reflecting the spatial heterogeneity of the elementary myocardial volumes might be the clue of a more efficient risk assessment. Relying on sophisticated experimental observations, Abildskov et al. [2] suggested the use of body surface potential mapping for the characterization of malignant alterations of ventricular repolarization by QRST integral maps. The utility of QRST integral map-based repolarization disparity (RD) detection was proven theoretically by Plonsey [3] and Geselowitz [4]. As QRST integral maps are the surface projections of the ventricular heterogeneity distribution, the desired arrhythmia vulnerability sensitivity should be related to the pathological irregularities of the integral maps. Indeed, Hubley-Kozey et al. [5] proved statistically that a few uncorrelated spatial features of averaged QRST integral maps can identify the arrhythmogenic substrate in the myocardium. Karhunen–Loève (KL) expansion of QRST integral maps proved to be a valuable tool for diagnostic feature extraction. Even the single scalar non-dipolarity index (NDI) computed from KL coefficients could separate high-risk and low-risk population based on time-averaged QRST integral maps [6,7].

Other authors emphasized the utility of beat-to-beat repolarization lability measures [8,9] based on QT parameters (QT variability index) of conventional ECG leads. Within the most recent approaches it is worth mentioning the development of a simple but efficient arrhythmia vulnerability index, based on the averaged sum absolute QRST integrals (SAI QRST) of orthogonal-leads suggested by Tereshchenko et al. [10]. The definition of SAI QRST is related to the NDI, but for the simplicity of clinical measurements the information hidden in the "multipolar" source components is disregarded.

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http://dx.doi.org/10.1016/j.bspc.2014.08.008
1746-8094/

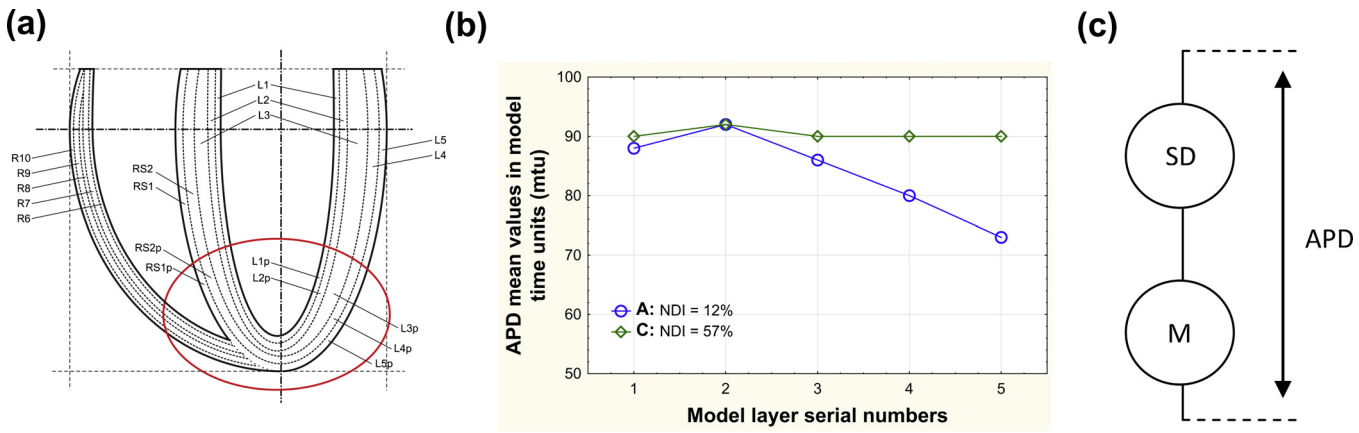

Fig. 1. (a) A schematic representation of the "layered" structure and geometry of the left and right ventricles. The ellipse at the apex contains the pathologically modulated area of the model. The labels of the layers can be interpreted as follows: initial capital letters 'L' and 'R' mark the left and right ventricles respectively, while 'RS' refers to the septum. The numbers represent the serial number of each layer. Small letters of 'p' at the end of the label indicate the pathological modulation of the model action potentials (MoAPs) related to the layer. (b) Mean value (M) of the APD profile of a healthy subject (profile A) and a failing heart patient (profile C) vs. the serial number of the model layers. The simplified graph is based on the experimental data of Glukhov et al. [12]. (c) Schematic representation of our APD model consisting of a constant component (M) and an additive Gaussian random component with standard deviation (SD).

The novelty in our approach published earlier was the use of beat-to-beat QRST integral map analysis instead of time-averaged QRST integral maps. This method allowed theoretically sound characterization of the stochastically changing spatio-temporal RD irregularities (lability) throughout a long train (typically 300) of cardiac cycles [11]. We could demonstrate that QRST integral maps, or even the extracted NDIs, computed from the KL coefficients of the QRST integral maps; characterize sensitively the spatio-temporal variability of the subsequent maps. According to our learning groups, NDI plots separated efficiently the group of implanted cardioverter (ICD) patients with documented malignant arrhythmia vulnerability from healthy subjects. In the arrhythmia group the beat-to-beat time series of the NDI values were uncorrelated and the corresponding NDI amplitude histograms showed skewed lognormal distributions, in certain cases with extreme NDI values going up to 90%. In healthy subjects the sequences of NDI values were correlated and the amplitudes remained typically in the range of (10%–20%) with slight quasi-periodic components, partly due to the respiration related positional heart changes.

In this study we attempted to link the observed normal and pathological QRST integral (and NDI) behaviour, to mesoscopic (intramural) and even to microscopic experimental findings. To this end, numerical chest and multi-element heart models were used. In the heart model, APD mean values of the different myocardial layers were approximated based on the recent optical mapping results of stained subepicardial, midmyocardial, and subendocardial sections taken from healthy and failing human hearts (Glukhov et al. [12]). The beat-to-beat APD variability estimates were taken from isolated cellular measurements of Zaniboni et al. and others [13,14]. Because in our previous study we demonstrated that the sources of measurable body surface QRST integral map variability are located mostly in the apical part of the heart, for the sake of modelling simplicity, the mesoscopic model action potential (MoAP) modulation was confined to the apical region [15].

2. Materials and methods

2.1. Numerical modelling of the heart

Details of the simplified computer model of the human cardiac ventricles were described previously by Szathmáry and Osvald [16]. The model was defined in a 3-dimensional matrix consisting of 1 mm^3 cubic elements. The local functional properties of the elementary volumes were represented by simplified model action potentials (MoAPs). The overall geometry of cardiac ventricles was defined analytically by segments of ellipsoids representing their inner (endocardial) and outer (epicardial) surfaces. The parameters of the ellipsoids were derived from the gross dimensions of the right and left ventricles (RV and LV), given as input data of the model. To simulate the fine structure of physiological repolarization heterogeneity, ventricular walls were sliced into 5 layers, paralleling with the inner and outer surfaces (Fig. 1(a)). The different fibre directions from the endo- to epicardial myocardium were not taken into account. The MoAP characteristics of model elements may be defined differently depending on their localization in respective layers.

In the reference model, simulating the normal activation, the gross dimensions of ventricles and the parameters of activation were derived from data published by Durrer et al. [17] and Hutchins et al. [18]. Ventricular depolarization was started from predetermined elements on the inner endocardial surface of both ventricles, corresponding to regions of earliest activation. The spread of activation in the most inner layer, representing the Purkinje mesh, was three times faster than in the remaining layers of the walls. After depolarizing of model elements their consecutive repolarization is governed by their action potential length and shape. The MoAP differences in respective layers cause a physiological transmural dispersion of cardiac action potential durations [19]. The activation and repolarization of the reference model, defined in this way correspond well to the generally accepted normal patterns of human heart activation.

The model allows a layer-by-layer modulation of ventricular wall AP parameters simultaneously in the whole ventricular myocardium or in a spatially limited region. An example is shown in Fig. 1(a), where the apical part (surrounded by the ellipse) has different APD profiles as it is shown in Fig. 1(b). In this study the apical segment of the myocardium has pathological APD profile [12]. In general, the geometry of local heterogeneities is always defined analytically by subsidiary ellipsoids.

The spread of the activation wave front is simulated by a cellular automaton. In each step of simulation the elementary dipole moments are computed as the potential differences between the adjacent cubic elements. Finally, the whole model of the cardiac ventricles' myocardium is divided into 33 volume segments. In each segment the dipole moments from all corresponding elements are summarized in its gravity centre, so finally a multiple-dipole equivalent cardiac generator is created.