ELECTRO-ANATOMICAL CHARACTERIZATION BY CARDIAC ELECTRIC NEAR-FIELDS

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Pathways, contours of wavefronts and velocity of cardiac conduction are the essential parameters to study normal and abnormal excitation spread. Apart from very elaborated endocardial multi-electrode mapping systems used to compute the patterns of activation we propose to measure the electric field intracardially in the close vicinity of the cardiac tissue. Specifically in regions of complex structures of conduction like in the atrium by this method we can obtain parameters of the very local process of excitation spread. We studied the case of continuous anisotrope conduction, complex propagation in fibrotic tissue as well as the case of branching structures in macroscopic-dimensions. Electrophysiologic experiments, structural analysis of the tissue and computer models of excitation spread were put together to clarify how gross-anatomy and micro-architecture of heart tissue affects the behavior of the near-field during depolarization. The power of computer-models to define clearly structures (unpredictable in real tissue during the experiment) enabled us to classify and differentiate effects of cardiac structure on extracellular potentials and near-fields. In the future field-sensors could be built in catheders as a navigation-tool identifying complex pathways of conduction or to asses conduction patterns modified by intracardiac ablation procedures.

Keywords - electrophysiology, computer-model, cardiac micro-structure

I. INTRODUCTION

The prevalence of atrial fibrillation, a life-threatening arrhytmia doubles with each decade of age over 50 years [1]. One of the reasons might be the fact that cardiac microstructure is modified by the ageing process. Cardiac myocytes are being replaced by connective tissue and previously well electrically connected muscle fibres become separated. This structural remodelling may lead to a zig-zag course of activation [2] and to fibrillation [3]. Therefore the role of macro- and microstructure of the myocardium will be increasingly the focus in basic research of arrhythmias. In this work we present a way to study excitation spread in cardiac tissue with respect to structure, namely electro-anatomical characterisation by means of the electric near-field E_n.

We define the cardiac-near-field E_n as an expression of the distribution of extra-cellular potentials Φ_e in a plane parallel and at close to the tissue surface (< 100 µm). The detection of E_n requires high-resolution measurements in time and space [4],[5]. With 4-electrode-arrangements of Laplace type a two-dimensional representation of E_n in the surrounding volume conductor can be measured. The time-course of E_n during depolarisation describes vector-loops of large varieties in morphology, which are not yet clarified completely.

The goal of this work is to elucitate the role of structure on near-field behaviour during excitation spread using a multidisciplinary approach. Near-field sensors could help in the future to navigate intracardiac catheders, to measure conduction paths and velocity with high resolution and to give information about zones of electrical uncoupling in the heart.

II. METHODOLOGY

A. *Electrophysiological experiments*

Pieces of heart tissue were obtained from isolated Rabbit hearts, dissected, placed in a tissue bath and superfused with Tyrode's solution at 37°C. The preparation was paced by an isolated current-pulse source with 1 Hz, 1 ms and 1,5 times the threshold level of excitability in amplitude.

We studied three types of cardiac activation: (a) continuous anisotrope conduction, (b) discontinuous conduction in complex structured tissue and (c) conduction in branching structures. For each of these cases we selected a specific model of tissue. Continuous conduction was shown in Papillary muscles of Rabbit hearts, complex structures formed by connective tissue were studied on a Papillary muscle of an explanted human heart and the effects of branching structures were demonstrated with atrial preparations of Crista-Terminalis and Pectinate muscles from the Rabbit heart.

B. *Signal recording*

Extracellular potentials Φ_e were recorded by means of multi-electrode arrays with different configurations and numbers of electrodes (4 and 25) and spacing between the electrodes (from 50 µm to 400 µm). The arrays were positioned by means of a micro-manipulator as close as possible (20-100 µm) to the surface of the heart, but in a non-contact manner. The signals were digitized with 200 kHz and 14-bits resolution each channel by means of a VXI-based data-acquisition system developed recently [4].

C. *Tissue gross-anatomy and micro-structure*

During the experiment the gross-anatomy of the tissue as well as the positions of recording and pacing electrodes were

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Abstract

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recorded digitally via microscope camera (Sony AVC/D7CE) and stored on PC. After the experiment the tissue was fixed with a mixture of paraformaldehyde-glutaraldehyde and embedded in paraffin. Sections of 10 µm thickness were made parallel to the endocardial surface. Fiber architecture and distribution of connective tissue were analyzed with light microscopic techniques and, for more detailed information, with an electron scanning microscope.

D. *Computer* simulation:

A monodomain computer model was developed consisting of a two-dimensional sheet of excitable tissue surrounded with an unbounded volume conductor [6]. Networks of up to 450000 excitable elements 15 µm in size were build up to compute the response on pacing currents during 15000 time steps of 2 µs. Extracellular potentials as well as electric fields could be predicted at given sites in the volume conductor. We used membrane-kinetic models of Luo-Rudy-I. A detailed description of the model is given in [6]. Continuous and anisotrope conduction was simulated by different coupling resistances longitudinally and transverse to the fiber axis. Discontinuous conduction induced by electrically uncoupled obstacles was studied by introducing a rectangular zone (60x800 µm) of non-excitable elements uncoupled along the border to the surrounding excitable tissue. Bifurcation of conducting structures was simulated by building a coupling matrix from the video image of complex atrial tissue showing the complex net of gross anatomy of Crista Terminalis and pectinate muscles. The contours of the conducting structures as well as the change of fiber direction was put in interactively by overlaying video image and coupling matrix. The simulations were run on a PC (2xPentium III, 800MHz) using MatLab.

III. Results

A. Field during continuous conduction:

In the experiments propagation parallel to the fiber orientation (longitudinal propagation LP) resulted in smooth biphasic signals of Φ_e with amplitudes usually between a 5 and 20 mV peak-to-peak, peak values of E_n from 20 to 80 V/m and conduction velocities v of a 0.5-0.8 m/s depending on the specific region and tissue part of the ventricle. E_n described an open vector-loop of "narrow"-morphology pointing opposite to the direction of excitation spread. If the direction of propagation was changed Φ_e as well as E_n decreased substantially, the morphology of the loops became irregular and fractionation of Φ_e and $d\Phi_e/dt$ indicated the change from continuous to discontinuous conduction.

During LP at a distance of 30 µm from the tissue we computed Φ_e, E_n and the conduction velocity v and obtained values of 27.5 mV, 164 V/m and 0.72 m/s. The loop-morphology of E_n changed from a straight line to an open vector loop depending on probe orientation and curvature of the wavefront. Propagation transverse to the fiber orientation (TP) resulted in 6.3 mV, 79 V/m and 0.24 m/s.

B. Fields during discontinuous conduction

Measurements in ventricular preparations generally showed discontinuous conduction if direction was changed from parallel towards perpendicular to the fiber orientation or at sites of substantial amount of connective tissue. We studied a Papillary muscle from an explanted human heart with interdigitized formations of connective tissue 20 to 100 µm broad and some hundreds microns long, which separated groups of fibers in the side-to-side apposition. A change in direction of propagation from 0 to 105° related to the fiber orientation caused a decrease of Φ_e from 13 to 6 mV, of $d\Phi_e/dt$ from 30 to 7 V/s and of the peak values of E_n from 50 to 17 V/m. The degree of fractionation expressed by the number of negative peaks of $d\Phi_e/dt$ exceeding 20% of the largest peak increased from 1 to 4. The variety of vector-loop morphology increased during complex propagation, at some sites twisted and double loop formations of E_n were seen.
Tue to the immense complexity of connecting structures in tissue mentioned above we decided to step back in computer simulation and to study how a single obstacle of size comparable to connective tissue structures would affect the cardiac near field. During LP we found changes in the vicinity of the obstacle in front, behind and aside of it and related to the undisturbed case. E_n decreased from 164 V/m to 87 / 92 / 122 V/m, the peak-to-peak amplitude of Φ_e from 27.5 mV to 19/ 21/ 19 mV. The apparent conduction velocity v changed from 0.72 m/s to 1.7/0.23/ 0.6 m/s. During TP E_n decreased from 79 V/m to 59/65/65 V/m, Φ_e from 6.3 mV to 5.3/6.0/4.5 mV. The estimation of local conduction requires further analysis due to major distortions of the signals.

C. Fields near structural branching sites

Potentials and near-fields at junction sites of CT with pectinate muscles were measured. Peak-to-peak amplitudes of Φ_e, $d\Phi_e/dt$ and E_n were 8 mV, 18 V/s and 49 V/m. A secondary delayed signal was represented with a second peak in $d\Phi_e/dt$ of 4 V/s and a second loop in E_n of 19 V/m magnitude, pointing in a different direction as the main loop.

In a first approximation of complexity we modeled the gross-anatomy of Crista Terminalis and Pectinate muscles by taking the contours of its gross-anatomy, by introducing a zone of junction with higher coupling resistances and by fitting approximately the preferential axis of anisotropy to the contours of the Pectinate muscles. We obtained changes in front and behind the transitional zone similar to those observed in obstacles. E_n decreased from 176 to 123 V/m, the amplitude of Φ_e from 24 to 14 mV. Vector loops of E_n were perpendicular to the isochrones and changed the direction with fiber orientation of the tissue.

IV. DISCUSSION

Experimentally we found that even preparations thought to be coupled very well do not represent perfectly continuous conduction during transverse propagation. Small distortions of or double peaks of $d\Phi_e/dt$ can often be seen and the change in vector-loop morphology indicates complex wavefronts at a microscopic size scale. The only model of ideal anisotrope and continuous conduction can be provided by computer simulation. From these computations we found that appropriate measurement of E_n is unlikely with interelectrode distances larger than the thickness of the depolarization wave (a 300 µm) and what the causes for opening and bending of the vector loops of E_n. are.

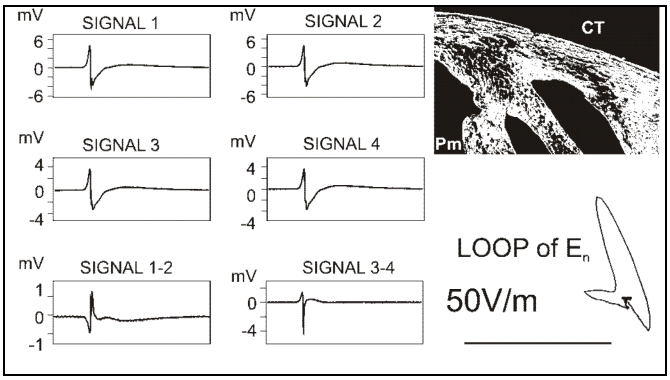

Fig.1. Extracellular unipolar (1-4) and bipolar signals (1-2, 3-4) from a four-electrode array placed near the junction of Crista Terminalis (CT) with Pectinate muscle (Pm). The micrograph depicts the gross-anatomy of this region as well as the connective tissue. Small distotions in the signals, double peaks in the bipolar signals as well as the two-loop morphology of E_n indicates two propagation processes running in different directions.

Tue to the complexity of coupling structures and the fractionation of signals during TP, local conduction velocity can only be estimated by averaging procedures from maps of local activation times within a small area. The increased complexity might rather be characterized by analyzing the degree of fractionation from $d\Phi_e/dt$ than by the diversity of vector-loops of E_n . Distinct obstacles of conduction could be identified if vector-loops behave like in the computer simulation.

In the vicinity of branching tissue structures the near-field may be represented in two distinct vector-loops if there is a sufficient delay between the two signals. Otherwise superposition of potentials would overlap the two signals and hide the directional diversity of the two processes.

The modification of the two-dimensional coupling matrix corresponding to the digitized image of a piece of tissue and to the pattern of fiber orientation can be seen just as a first approach to implement the microarchitecture of tissue. The implementation of connective tissue like it is distributed in real specimens at junction sites remains work to be done in the future.

V. CONCLUSION

Cardiac near-fields reflect structure of conduction. In the future near-fields could be used to navigate intracardiac catheders exploring abnormal conduction pathways to detect the origin of the arrhythmogenic substrate. The requirements on adequate sensors and instruments are very high. To clarify which intracardiac structures can be identified by this method, a multidisciplinary approach using in-vitro-experiments, histological studies and computer-models is indispensable.

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