The Origin of Diastolic Micro-Signals Observed in Defibrillator Recipients might be Qualitatively Explained by a Simple Computational Model

Aldo Casaleggio[1], Paolo Rossi[2], Michele Migliore[3]

[1]Institute of Biophysics, National Research Council, Genova, Italy
[2]Cardiology Division, San Martino Hospital IRCCS, Genova, Italy
[3]Institute of Biophysics, National Research Council, Palermo, Italy

Abstract

In previous studies investigating intracardiac electrograms (Egm) obtained from implantable cardioverter defibrillators (ICD), the presence of Diastolic Micro-Signals (DMS) preceding the initiation of ventricular tachyarrhythmias (VT) has been observed both in coronary artery disease (CAD) and in dilated cardiomyopathy (DCM).

We propose a mechanism, based on a recently published computational model, to qualitatively explain the DMS for the case of ischemic cardiomyopathy.

The model based on a bi-dimensional network of Beeler-Reuter cardiac cell, is able to reproduce all the erratic arrhythmias under the assumptions that the gap-junction conductance are non-linear and fluctuating, and there is a scar in the tissue. Under such hypotheses, an electrical activity may propagate within the scar and, occasionally, it may propagate outside the scar and initiate a premature cardiac beat.

Our hypothesis is that, in ICD recipients with ischemic cardiomyopathy, the DMS reveal the presence of a propagating wavefront within the scar, monitored by the intracardiac electrocatheter which is assumed to be placed in the proximity of the scar lesion.

1. Introduction

In a previous study [1] investigating intracardiac electrograms (Egm) obtained from patients with implantable cardioverter defibrillators (ICD), we observed the presence of diastolic micro-signals (DMS) preceding the initiation of ventricular tachyarrhythmias (VT). The Figure 1 shows an example of DMS. In [1] we considered that such activities could be due to power-line interferences, thus we made spectral analyses of the diastolic signals, and excluded such possibility. Moreover we qualitatively observed the presence of frequent bi-modal power spectrum, that could lead to the hypothesis of multiple mechanisms could be involved in this phenomenon.

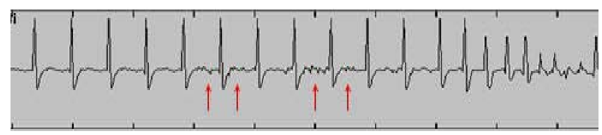

Figure 1: Examples of DMS (indicated by arrows) obtained from a patient with an ICD. VT onset is at the end of the strip.

Further exploring the DMS, we considered the possibility that they could originate from coughing or as a consequence of abdominal contraction. Thus we proposed to the patients, at the periodical follow-ups, to force abdominal contraction or coughing while their activity was recorded by the ICD [2]. In the majority of the trials we could not observe significant DMS, nevertheless in some cases we found some very little DMS. Nevertheless, the DMS likely induced by the abdominal contraction were much less pronounced (almost not significant) than those shown in Figure 1.

The presence of rare and weak diastolic activity (not comparable with those observed immediately before the initiation of a VT and shown in Figure 1), led us to make the hypothesis that DMS might have an intrinsically electrophysiological origin.

The aim of this paper is to propose, for the case of coronary artery disease (CAD) patients, a mechanism that could give a qualitative explanation of the diastolic micro-signals. This mechanism is made possible by a recently published computational model of the cardiac activity [3].

2. Methods

The model focuses on the interaction between cardiac cells: it assumes that all the cardiac cells are equal, while the gap-junction conductance is fluctuating and non-linear in a different way in the different part of the tissue. All the details about the computational model can be found in [3], we simple resume here some aspects of it. As it is shown in the Figure 2, the computational model is a relatively small two-dimensional cardiac tissue, composed of 128×256 cells. The majority of the cells are normal, but a part of them characterize the scar and are assumed to have different conductance properties.

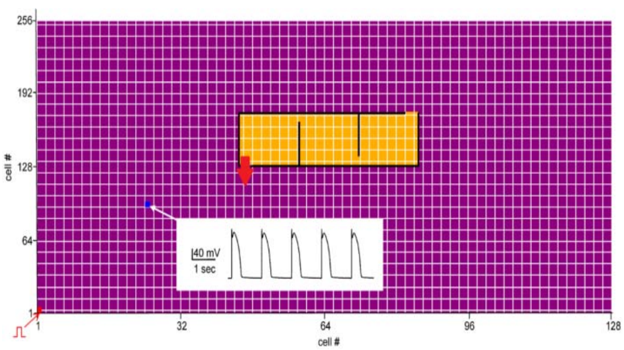

Figure 2: Schematic representation of the full 128×256 cell network; individual cells are represented with small purple (normal) or yellow (scar) rectangles; the black lines identify the contour of the lesion, composed by non-conducting cells (i.e. g=0; g=gap-junction conductance). The red arrow indicates a unidirectional block determining the exit door of the scar. Physiological input signals were modeled by periodically stimulating with a short current pulse cell(1,1) (bottom left of the network, shown in red). The action potentials of the white insert, shows a typical membrane potential of cell(25,100) under physiological conditions (i.e. no ischemic area).

Each single cardiac cell is approximated using the Beeler-Reuter model which is the simplest realistic electrophysiology model for a single ventricular canine myocyte. It describes the cell activity on the basis of 4 trans-membrane currents: a sodium current, two potassium currents, and a calcium current which is responsible for the plateau potential occurring during a cell's depolarization. The propagation is purely electrical: a spiking cell transfer via gap-junction conductance the current to its neighboring cells which, when activated, generate spikes and propagate in turn. In practice we solve a set of 4 (differential equation per cell) x 128 x 256 coupled differential equations. All these cardiac cells interact among each other with a linear gap-junctions conductance. A subset of the two-dimensional cardiac tissue (about 1800 cardiac cells with dimension of 40 x 45 cells) has different interaction properties and it represents the scar. The scar is assumed to have a non conducting contour (black line in Figure 2) with two doors connected to the normal tissue. One of the two doors has a uni-directional block that allows the propagation only from inside the scar to outside it (large red arrows in Figure 2). Moreover the gap junctions conductance of the cardiac cells inside the scar (yellow portion of Figure 2) is fluctuating with time. The uni-directional block can be obtained modifying the geometry and the conductance properties of the cardiac cells [4].

All simulations were carried out with the NEURON simulation environment (v7.3) on a parallel BlueGene/Q IBM supercomputer (CINECA, Bologna, Italy). A typical 130 sec simulation required about 3 hours using 1024 processors.

Model and simulation files are available for public download on the ModelDB section of the Senselab suite (http://senselab.med.yale.edu/ModelDB/ , acc.n.150691).

3. Results

3.1. Simulated arrhythmias

In [3] we showed that the mathematical model described above can generate all the types of principal arrhythmias that are observed in the clinical practice. Of course, since we are considering a two-dimensional tissue, the arrhythmia cannot be identified on the basis of the signal morphology, rather on the basis of its interval between action potentials. This is what we have verified, and the Figure 3 shows slices of simulations where different types of arrhythmias can be simulated taking into consideration the inter-spike interval of the action potential of the cell(25,100) shown in blue in Figure 2.

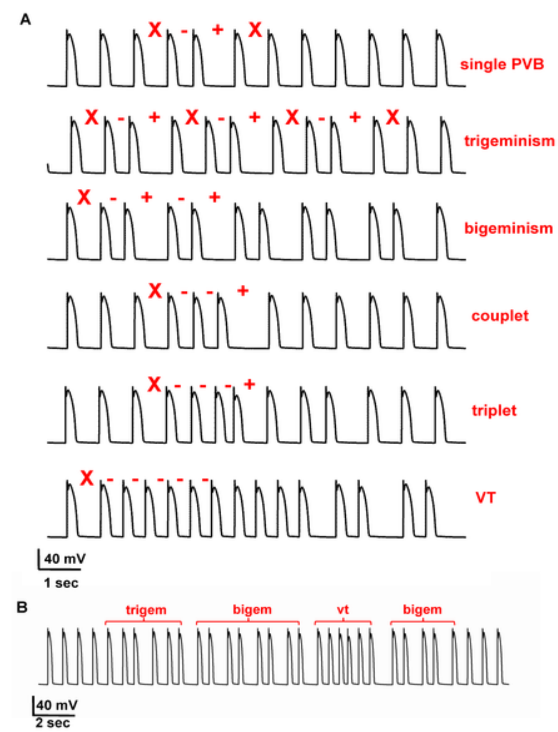

Figure 3: Plot of selected excerpts of single cell recordings (cell(25,100)) from simulations using different values for the average and variance of the gap junctions conductance in the ischemic area. Panel (A) shows simulations of the different types of arrhythmias, while panel (B) shows a simulation with the combination of different types of cardiac arrhythmias in a single strip. The markers "X, "-" and "+" indicates normal, short and long inter-beat intervals respectively.

3.2. Suggested DMS explanation

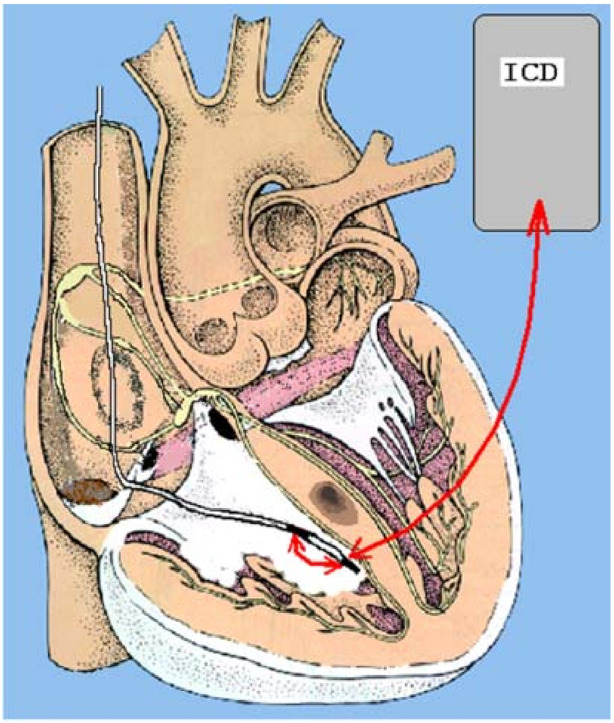

Figure 4: schematic of the heart of a patient with an ICD and a scar in the septum (indicated as a grey-brown large spot).

The suggested hypothesis is simply explained in the Figure 4. The electrocatheter is assumed to be placed in the proximity of the scar (indicated by the brown-grey area in the septum). Under this hypothesis the electrocatheter can be able to record a cardiac activity within the scar. Our hypothesis is that, at a certain time for some unknown reason (by effect of electrophysiological changes due to metabolism or to the autonomous nervous system or other origin) the gap junction conductance within the scar might slightly change its average value, allowing the initiation of a propagating wave within the scar itself. Such activity is triggered by the physiological wave-front propagation in the healthy tissue, but it propagates within the scar (independently from the outside activity), thus it can propagate also during the cardiac diastole, and it might be revealed by the electrocatheter recordings. Such activity could identify with the diastolic micro-signals that we observed from ICD recordings.

4. Discussion

In this discussion we like to build up the following points: (i) the electrophysiological model on which is based the computational model; (ii) the mechanism underlying a unidirectional block across the scar; (iii) limitations of the work.

4.1. Electrophysiological model

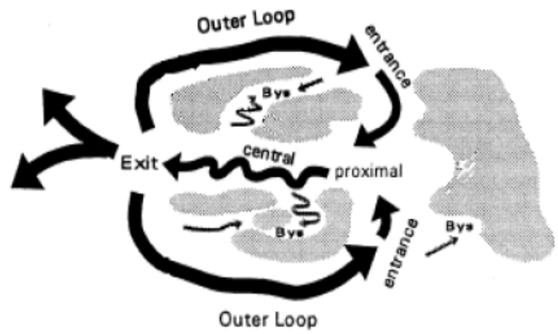

Figure 5: Electrophysiological model of the scar.

The Figure 5, obtained from the paper by Stevenson and co-workers [5], shows the schematic of the re-entry mechanism that might originate in the presence of a scar. The idea is to have an entrance and an exit door across the border of the scar and a slower propagation of the front-wave within the scar. It is also needed that the “exit door” is characterized by the presence of a unidirectional block allowing the front-wave propagation to go across only in one direction (from inside to outside the scar). Other authors proved this electrophysiological model of reentry in animal [6].

4.2. Gap-junction conductance and block

The Kucera group [4] investigated the possibility to generate unidirectional blocks in the cardiac tissue, showing that an unidirectional block can occur when the propagation flows from a narrow strand toward a wider cell network. Moreover the presence of different gap-junction conductance in the narrow strand and in the wider network, may facilitate the formation of the block. Thus a unidirectional block can be generated as a consequence of the geometry of the exit door together with disturbed properties of the gap-junction conductance in that region. Such condition is an assumption of the computational model to have the exit door.

Since the model simply requires the presence of the unidirectional block in order to originate an “exit-door”, the above comment could be enough. Nevertheless we like to expand a bit the topic related to gap junction formation and arrhythmia. It is well known that gap junctions are formed by 8 connexins, and that in cardiac myocites the large majority of connexins are the Cx43, but there are also Cx45 and Cx40 [7 and reference therein]. It is also known that gap junctions made with different connexins (combination of Cx43 and Cx45, named heterotypic gap-junctions) have a rectifying conductance property with respect to the junctional potential at the steady state [7]. Although the kinetics of heterotypic gap junctions is slow compared to the cardiac rate (and the rectifying behavior cannot occur in the interbeat interval), it is interesting to observe that, in the literature, disturbed Cx 43 gap junction distribution correlates with the location of reentrant circuits in the epicardial border zone of healing canine infarcts that cause ventricular tachycardia [6], while another study found an heterogeneous loss of Cx 43 protein in ischemic dog hearts [8] (possibly leading to a greater probability to build heterotypic gap-junction).

Finally, using microelectrode arrays in cultured strands of foetal murine ventricular myocytes with predefined contents of Cx 43 knockout, it has been obtained a nonlinear behavior of conduction and of block (including uni-directional block) [9].

It is our opinion that these aspects require further experimental investigations.

4.3. Limitations

This study is at its initial stage and it has a few limitations. The most important one is that we consider a model of a flat surface to speculate on the behavior that such model might have on a three-dimensional complex structure such as the heart. For more accurate predictions further steps are needed, the first of which will be the implementation of the model with a paraboloid shape (or a surface resembling with a geometry similar to a cardiac ventricle) in order to simulate the pseudo-ecg and compare it with the real EGMs that we have measured in patients. This work is in progress.

5. Conclusion

In summary, our results demonstrates that, qualitatively, we can think that DMS has an electrophysiological origin that could be reasonably explained by a computational model.

Acknowledgements

We thank the CINECA consortium (Bologna, Italy) for access to their Fermi IBM BG/Q supercomputer system under grants HP10BGQGH0 and HP10BUD4WT.

References

[1] Casaleggio A, Guidotto T, Malavasi V, Rossi P. Diastolic Heart Activity Inspection from Intracardiac Electrogram Analysis. Computing in Cardiology 2010; 37: 737-740.

[2] Casaleggio A, Rossi P. Diastolic micro-signals preceding ventricular tachyarrhythmias: evaluation of potential association with muscle activity. **In** Buchner T, Gierałtowski J, Petelczyc M, Podziemski PM, Żebrowski JJ, Cieslak K, Furgata A, Machowska AM eds. ESGCO 2012: O17.1-4, ISBN 978-83-934693-0-7.

[3] Casaleggio A, Hines ML, Migliore M. Computational Model of Erratic Arrhythmias in a Cardiac Cell Network: The Role of Gap Junctions. PLoS ONE 2014; 9: e100288.

[4] Kondratyev AA, JGC, Munteanu A, Rohr S and Kucera JP. Dynamic changes of cardiac conduction during rapid pacing. Am J Physiol Heart Circ Physiol 2007;292: H1796–H811,.

[5] Stevenson WG, Friedman PL, Sager PT, Saxon LA, et al. Exploring Postinfarction Reentrant Ventricular Tachycardia With Entrainment Mapping. JACC 1997;29:1180–9.

[6] Peters NS, Coromilas J, Severs NJ and Wit AL. Disturbed Connexin43 Gap Junction Distribution Correlates With the Location of Reentrant Circuits in the Epicardial Border Zone of Healing Canine Infarcts That Cause Ventricular Tachycardia. Circulation 1997;95:988-96.

[7] Desplantez T, Halliday D, Dupont E, Weingart R. Cardiac connexins Cx43 and Cx45: formation of diverse gap junction channels with diverse electrical properties. Pflugers Arch - Eur J Physiol 2004;448:363–75.

[8] Huang XD, Sandusky GE, Zipes DP. Heterogeneous loss of connexin43 protein in ischemic dog hearts. J Cardiovasc Electrophysiol 1999;10:79-91.

[9] Prudat Y, Kucera JP. Nonlinear behaviour of conduction and block in cardiac tissue with heterogeneous expression of connexin 43. J Molec and Cell Cardiol 2014;76:46–54.

Address for correspondence.

Aldo Casaleggio
Institute of Biophysics, National Research Council
Via De Marini 6, 16149, Genova, Italy
aldo.casaleggio@cnr.it