A Computer Model for Patient Individual Parametrizing of Ventricular Tachycardia Termination Algorithms

Bernhard PFEIFER[a,b,c,1], Robert MODRE-OSPRIAN[a], Peter KASTNER[a], Friedrich HANSER[c], Clemens RISSBACHER[b] and Daniel BAUMGARTEN[c]

[a] *Austrian Institute of Technology, Center for Health & Bioresources, Digital Health Information Systems, Hall in Tirol / Vienna, Austria*

[b] *Landesinstitut für Integrierte Versorgung, Tirol Kliniken GmbH, Bürgerstrasse 15, Innsbruck, Austria*

[c] *Institute of Electrical and Biomedical Engineering, UMIT – Private University for Health Sciences, Medical Informatics and Technology, Eduard Wallnöfer Zentrum 1, Hall in Tirol, Austria*

Abstract. Background: Antitachycardial pacing (ATP) is a painless method for terminating ventricular tachycardias (VT) which would otherwise be treated using a painful high energy shock. However, it is well known that not each VT can be successfully terminated by ATP. Furthermore, ATP can be parametrized in several ways using scan, ramp or scan ramp approaches and can be applied in the right ventricle or in both ventricles (biventricular). In this work, we investigate the therapeutically most convenient ATP protocol based on a computer simulation using a patient individual model. Methods: A patient individual model generated from a 3D/4D data set and a hybrid automaton was used for modeling and simulation of different VT scenarios. On the different VTs (from cycle length 288 ms up to 408 ms) different ATP approaches derived from the ADVANCE-CRT trial were applied in order to determine the effectiveness of these approaches. Results: In this computer simulation study we were able to verify and validate the results from the ADVANCE-CRT trial. Biventricular ATP does not prove to be more effective than RV ATP but has a slight advantage in terminating fast VTs. Conclusions: The availability of a patient individual model and knowledge about the ischemic area and the underlying mechanism of the VTs will allow the use of these models to optimize ATP management.

Keywords. computational cardiology, modeling and simulation, hybrid automaton, ventricular tachycardia, anti tachycardial pacing

1. Introduction

The number of implantable cardioverters/defibrillators (ICD) for primary and secondary prevention is still increasing. Therefore, prevention of inappropriate therapies becomes

[1] Corresponding Author: Bernhard Pfeifer, Austrian Institute of Technology, Center for Health & Bioresources, Digital Health Information Systems, Hall in Tirol / Vienna, Austria, E-Mail: bernhard.pfeifer@ait.ac.at

a more and more important topic. In principal there are two different therapy approaches called painless antitachycardial pacing and cardioversion/shock.

1.1. Arrhythmia Therapy

An ICD has one main goal: rescue the patient from a potentially life-threatening ventricular arrhythmia [1]. Thus, an ICD offers two categories of treatment possibilities, high-energy and antitachycardial pacing therapy (ATP). High-Voltage therapy can be subdivided into shock and cardioversion, which are mainly equivalent with the difference that cardioversion is a triggered shock on the sensed R-wave to terminate ventricular tachycardia (VT), whereas in a ventricular fibrillation (VF) episode no R-wave exists, and, therefore, a high-energy shock is delivered when the capacitor is fully charged to treat the VF episode. The energy delivered through the coils is between 30 up to 40 J. On the contrary, ATP uses pattern stimulation at low-voltage using typically pacemaker (PM) outputs for terminating a detected VT [2].

1) High-Voltage Therapy: For engineers it has been a great challenge to build up a device small enough to be implanted under the skin and being able to deliver a large amount of energy (30 - 40 J) very quickly to terminate a detected VT or VF episode. The voltage of the battery used in these devices is 3.2 V. When an arrhythmia is detected the capacitor as the main high voltage element in an ICD device has to be charged in a very short time.

Clinicians and engineers identified that the type of waveform is crucial in defibrillating the heart effectively as well as lowering the traumatic effects of the involved myocardial tissue [4]. Biphasic waveforms typically use less energy than monophasic waveforms [5], [6], [7], [8]. This type of waveform consists of two phases, where the first phase is positive and the second phase negative, with a very short time delay between the two waveforms due to the reversion of polarity. Furthermore, the duration of the second phase is always shorter or equal to the first phase. Until now it is not completely clear why biphasic waveforms are so effective compared to monophasic ones [9]. Furthermore, it has been reported that triphasic waveforms cause less myocardial injury compared to biphasic waveforms which results in better prognosis [10]. At the present time no vendor supports triphasic waveforms.

2) Antitachycardia Pacing (ATP): The theory behind ATP is simple: one or a defined number of low voltage stimulation pulses with a rate faster than the tachycardia is applied to break the self-preserving excitation loop. For enabling such a loop causing a VT a closed loop reentrant circuit with a fast and a slow pathway must be present. When the depolarization wave is entering the system the loop splits, which means, that the depolarization wave travels through both branches. When the slowly traveling electrical spreading reaches the end of the loop the fast pathway is not refractory anymore. This means that the signal coming from the slower pathway can travel up the fast pathway. This creates a circular pathway with the electricity traveling faster and faster trough the loop [1], [2]. For terminating ventricular arrhythmia using ATP, the arrhythmia must have a reentrant mechanism. Some clinicians see a disadvantage in ATP due to the large number of parametrizing aspects which can only be programmed patient individually when understanding the complete underlying reasons for the arrhythmia. Nevertheless, ATP does offer some powerful advantages as enabling a painless treatment, setting up of the ATP parameters is quite simple, many hemodynamically stable VTs can be terminated and ATP also reduces the drain of the battery which increases longevity of the ICD. Even if a fast VT (FVT) with a frequency higher than 220 bpm falls into the VF therapy zone,

ATP while or before charge is possible; several studies showed that also in these high rate zones ATP can be successful [2]. Another important aspect is that ICD shocks may contribute in increasing mortality, because a shock might damage the myocardium. The partial damage of myocardium could be seen using troponin as marker, but it is impossible to determine whether the troponin levels are elevated due to the shock or myocardial ischemia [11], [12]. Furthermore, adverse effects of patients having felt painful ICD shocks could also be a result of psychological effects including anxiety and depression, both known to be associated with a worse prognosis in such patient cohorts.

1.2. Clinical Trials

1) PainFree Trial: The PainFree Trial [14] was a prospective, randomized, multi-centric trial with the aim to show the effectiveness and safety as well as the quality of life of patients of antitachycardial-pacing (ATP) during fast ventricular tachycardias (VT) compared to defibrillation therapy. The selected patient cohort for this study consisted of standard implantable cardioverter defibrillator (ICD) indications except those not featuring a basis for stable monomorphic VTs. In total 634 ICD patients were randomized into two groups, which differed in the applied therapy (empirical ATP n=313 patients, shock n=321 patients). A fast-ventricular tachycardia (FVT) was programmed to be detected when a minimum of 18 out of 24 intervals of the heart frequency was between 188 bpm and 250 bpm and during the last 8 intervals the frequency had never been higher than 250 bpm. The initial therapy based on the group the patient was randomized with ATP (a train composed of 8 stimuli with a burst cycle length of 88% or shock (10 joule above the defibrillation threshold). In case that the ATP was unable to stop the VT, a shock was applied to stop the event. In both groups the therapy was extended to maximum shock in case that the first applied shock was ineffective. VTs with a frequency below 188 bpm were therapied with ATP (3 bursts with 8 stimuli per burst and a cycle length of 88%). The mean follow-up time was 11 months. During the study 4230 spontaneous episodes, which were classified as ventricular arrhythmias, were recorded. For 1873 episodes a complete set of electrocardiographic (ECG) data was available. For the evaluable data in 98 patients 431 FVT were recorded.

2) ADVANCE-CRT Trial: The ADVANCE-CRT trial [15] was a prospective, randomized, controlled, multicentric trial with the objective to test the efficiency and safety of biventricular (BiV) ATP compared to conventional right ventricular ATP treatment in terminating ventricular tachycardias (VT). 526 patients were enrolled in this study and were randomized into a BiV treatment group (n=266) and a RV only treatment group (n=260). Both ATP groups were parametrized to treat a VT with a burst consisting of 8 stimuli and a basis cycle length (BCL) of 88%. The follow up time was 12 month and each 3 month a follow up was performed to collect the clinically relevant data. If an episode occurred an additional follow up was performed. During this period 1077 ventricular episodes in 180 patients were recorded. From these 1077 episodes 634 episodes were real ventricular events, 32% were falling into the fast VT zone and 11% of these episodes were classified as ventricular fibrillation (VF). The success rates of the different ATP approaches are summarized in Table I.

Table 1. Results obtained from statistical analysis of ADVANCE-CRT trial.

Zone	BiV	RV	p
FVT + VT	65%	68%	0.59
VT	62%	71%	0.25
FVT	71%	61%	0.34

Although there was no statistical significant result, the tendency of lower acceleration probability during FVTs in the BiV group could be found (BiV 3,5%, RV 10,2%, p=0.163). Furthermore, in the BiV group no syncope's or presyncope's during the therapy (p=0.016) were recorded. In addition, the effectivity of BiV therapy during VFTs in combination with coronary heart disease was significantly higher (p=0.032). If no coronary heart disease was present, then subsequently BiV as well as RV ATP therapy was equally effective. The main conclusion of the trial is that no significant difference between the two ATP approaches could be observed and BiV ATP is safe for patients.

1.3. Modeling Approaches

In the past several research groups have worked on modeling and simulation in the field of implantable pacemakers and cardioverters. Volosin et al. [16] generated a model to test the effectivity of different shock reduction strategies. The model consisted of deterministic and probabilistic decision tables. To test the model several ICD data sets from the Sudden Cardiac Death Heart Failure Trial (SCD-HeFT) [17] were taken and used for model verification. Several groups [18-23] generated simulation models to find electrode positions for reducing the defibrillation threshold. One key result of these computer simulations was that transvenous systems had lowest DFT in comparison to other epicardial approaches.

2. Methods

The goal of this computer simulation study was to show how effective RV and BiV ATP approaches are to terminate VTs. Furthermore, by incorporating knowledge about the reentry pathway and about the ischemic areas in the ventricles, it is possible with the proposed computer model to adapt the ATP program patient individually. A patient individual computer model is needed to perform the simulation task. The 3D/4D cardiac data were obtained from a cine gated, T1 flash, non-contrasted short-axis MRI dataset. The slice thickness was selected to be 6 mm. The myocardial structure was segmented using a 3D cellular automaton approach developed in-house. The segmented cells were then used and parametrized by incorporating them into a hybrid automaton (HA) system.

In principal, a hybrid automaton (HA) is an enhancement of the finite state automaton, working in a cellular automaton system. In a HA system discrete as well as continuous components are interacting. The definition of a HA system is following: A=(X, G, init, inv, flow, jump, event). X represents a finite amount of variables of functionals, G is a graph with G=(V, E) with V , representing control modes and E control switches, init represents the node-labeling function for the control nodes as initial constraint, inv represents the node- labeling function for the control nodes as invariant, jump holds the "firing" condition, and event holds a set of events, respectively [24-26].

For the implementation of the hybrid automaton, which is shown in fig 1, simulation model an adapted version of the framework from Pfeifer et al. [27] was used. The modification of the system was performed in that way that for cells behavior a Beeler-Reuter model was implemented by using a multicore processor system [28]. Figure 1 shows the control nodes and the transitions between the nodes for simulating an action potential. The transition values were defined as Vt=-60 mV, Vp=27 mV, Vq=0 mV, Vr=-83 mV. A detailed description can be found in [29].

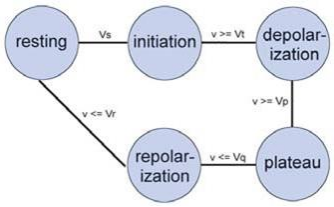

Figure 1. Definition of the control nodes and the possible transitions as well as the transition conditions.

For the electrophysiological part of the hybrid automaton system the Cell Electrophysiology Simulation Environment (CESE) [30] was used. CESE provides simulation of action potentials, ion-models and changes in ion concentrations.

2.1. Generation of VTs

For generating ventricular tachycardias, the model was adapted by incorporating disordered electrical excitation, which is also present in patients with myocardial infarction or ischemic areas. Figure 2 shows the modeled reentry pathway that which was integrated at different positions for simulating RV and BiV ATP protocols in order to terminate the arrhythmic event. Each cell represents one cardiac cell incorporating a HA system.

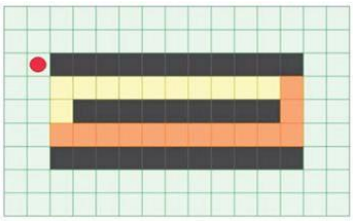

Figure 2. Reentry pathway integrated into the ventricular model for generating stable VTs. The red circle represents e.g. a stimulation or ventricular extrasystole (VES), green marked cells indicates healthy myocardial cells, a black square represents a necrotic cell, and light orange and orange areas reflect represent cells with different excitation speeds (slow and fast pathway).

2.2. ATP Stimulation Protocol

The focus of interest in the ADVANCE-CRT trial was to find out if ATP stimulation protocols using the scan, ramp and scan ramp method is more effective in the BiV group

compared to the RV group; see [15]. Therefore, in this computer model the parameters scan, ramp, and scan+ramp were used analogously to the ADVANCE-CRT trial and the rhythm was simulated for 8000 ms to find out whether the sinus rhythm could be restored or not. The number of stimuli was defined to be five per burst, and the number of bursts was defined to be three. The burst cycle length (BCL) was derived from a typical clinical setting as used in the ADVANCE-CRT trial as well and is also known e.g. from the PainFree II trial. The values for BCL were 82% and 88%. The simulated ventricular tachycardias ranged from slow tachycardia with 147 bpm, a common tachycardia rate with 176 [bpm] up to fast and hemodynamically non-stable tachycardia rate with 208 bpm. The reentry pathway was modeled at the free lateral wall and close to the apex for simulating pathways near the lead as well as far pathway lead location. Then the hybrid automaton system is simulated according to this parametrization.

3. Results

Each simulated VT episode and the ATP treatment of the ventricular event was simulated for 8000 ms with an intervall of 0.5 ms. The computational time was about 1 hour and 30 minutes for each simulation.

The total simulation was performed over 30000 ms in order to guarantee that the generated VT are sustained VTs. Figure 3 shows the intracardial electrogram with a cycle length of 340 ms.

For the generation of the different VTs using a reentry, the HA was modified to work with pathologic cells. It could be demonstrated that the closer the cycle length of the VT came to the shortest possible cycle length of the myocardial cell the harder it is to terminate the VT using ATP. Further, the more similar the properties of the reentry pathway the more difficult to terminate the VT using any ATP protocol.

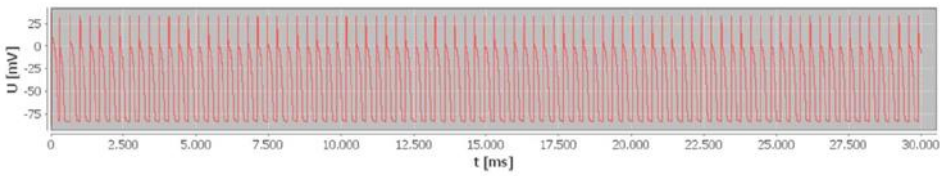

Figure 3. Simulated sustained ventricular tachycardia with a cylcle length of 340 [ms]. The reentry pathway was modeled near the apex.

Eight different VTs were generated. Each of the simulated VT considered different properties regarding cycle lengths and origins of the modeled reentry pathway. Table II shows which ATP program was able to terminate the underlying VT. In the simulated series 96 VTs were generated from which it was possible to terminate 72 episodes with ATPs. Summarized, using the scan protocol 19 of 32 (59%) episodes, with ramp protocol 26 of 32 (82%) episodes and with scan+ramp 27 of 32 (85%) VTs could be terminated. The most effective form of therapy was the RV scan protocol with a programmed cycle length of 88%. The biventricular ATP treatment with ramp+scan protocol and a cycle length of 88% was the second-best approach in the simulation.

Neither right ventricular nor biventricular pacing could be figured out to be more effective as investigated in this simulation study. These findings are in good accordance with the ADVANCE-CRT [15] trial and thus confirm the feasibility and reproducibility of our computer model. Nevertheless, in the simulation it could be found that the ramp protocol should be preferred when using biventricular ATP, but it must be clearly stated, that this behavior maybe occurs because of this special modeled and used reentry mechanism. The result could be different when changing the underlying ischemic area or necrosis. More simulations with different properties are necessary to answer this topic.

Table 2. Results of the simulation of the different ATP attempts on slow up to fast VTs. Symbol 'x' indicates a successful ATP attempt thus stopping the running VT in the patient individual ventricular model.

ATP	BCL	Type	408ms	408ms	408ms	408ms	340ms	340ms	288ms	288ms
			P1	P2	P1	P2	P1	P2	P1	P2
scan	82	RV			x		x		x	x
		BiV			x		x		x	x
	88	RV		x	x	x	x			x
		BiV		x	x		x	x	x	x
ramp	82	RV		x	x	x	x	x	x	x
		BiV		x	x	x	x	x	x	x
	88	RV	x		x	x	x	x		x
		BiV	x		x	x	x	x		x
scan+ramp	82	RV		x	x	x	x	x	x	x
		BiV		x	x	x	x	x	x	x
	88	RV	x		x	x	x	x	x	x
		BiV	x		x	x		x	x	x

4. Discussion & Outlook

In this simulation study different VTs were generated and virtually therapied using different ATP protocols that were also used the same way in the ADVANCE-CRT trial. The focus of this work was to show that our computer model can simulate different VTs by incorporating reentry pathways. The success rate of the applied ATP therapy protocols derived from the Painfree-II as well as from the ADVANCE-CRT trial were comparable to those studies, which allows to state that this approach is an indirect validation of the model, but of course more simulations and trial data are necessary for detailed confirmation.

The obtained results of our simulations showed that not all ATP configurations were equally effective and that there is a difference between the VT scenarios. This seems to be intuitively clear, but it is not completely understood why and what the underlying reasons are. Therefore, a perfect parameter set for ATP treatment does not exist, and the optimization is more like an iterative approach.

In this study the reentry pathway was modelled using one well-defined pathway, but for future studies different pathway sizes, ischemic areas and/or multiple pathways would be of interest. If those areas could be obtained with high accuracy for each individual patient it might be possible with these models to simulate the behavior of the dominant and other possible VTs and their optimal ATP device therapy using our models. This could lead to prevention from high energy therapy and therefore might increase the patient's quality of life.

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