Proceedings Paper:
Benson, AP, Hayes-Gill, B, Holden, AV et al. (2016) Self-terminating re-entrant cardiac arrhythmias: quantitative characterization. In: Computing in Cardiology. Computing in Cardiology, 06-09 Sep 2015, Nice, France. Computing in Cardiology/IEEE, pp. 641-644. ISBN: 978-1-5090-0685-4. ISSN: 2325-8861. EISSN: 2325-887X.

https://doi.org/10.1109/CIC.2015.7410992

Self-terminating re-entrant cardiac arrhythmias: quantitative characterization

Alan P Benson[1], Barrie Hayes-Gill[2], Arun V Holden[1], Rosa Matthews[1], Aneela Naz[1], Stephen Page[3], Eleftheria Pervolaraki[1], Edward Spofford[4], Muzahir Tayebjee[3]

[1]University of Leeds, Leeds, UK
[2]University of Nottingham, Nottingham , UK
[3]Leeds Teaching Hospitals NHS Trust, Leeds, UK
[4]University of Liverpool, Liverpool, UK

Abstract

Atrial and ventricular tachyarrhythmia are often sustained by re-entrant propagation, and explained by deterministic models. A quantitative, stochastic description of self-termination provides an alternative to the current paradigm for re-entrant tachyarrhythmia - that of triggers and a substrate, modelled by parametrically heterogeneous deterministic partial differential equations

Atrial and ventricular data was from recordings obtained during routine clinical monitoring and treatment, either noninvasively or invasively. Atrial and ventricular tachycardia are characterised by their initiation times and durations, re-presented as instantaneous rates, whose means estimate transition probabilities/s for onset and termination. These estimated probabilities range from10^{-9} to 10^{-1}/s .

1. Introduction

Atrial and ventricular tachyarrhythmia are often sustained by re-entrant propagation [1,2,3]. Episodes of paroxysmal atrial fibrillation are by definition self-terminating, and ~20% episodes of recorded endogenous or induced ventricular fibrillation self- terminate before they are defibrillated. A quantitative, stochastic description of self-termination provides an alternative to the current paradigm for re-entrant tachyarrhythmia - that of a system of triggers and a substrate, both modelled together by parametrically heterogeneous deterministic partial differential equations [4]. The persistence/lifetime of multiple re-entrant activity in simple excitable media has been modelled by stochastic birth and death process models for re-entry sources [5].

2. Methods

We assume normal sinus rhythm NSR and re-entrant tachycardia are clearly distinguishable, over time scales from seconds to tens of years, and in an individual can be modelled stochastically by the transition probabilities/unit time of the initiation α and termination β of a tachyarrhythmia. All re-entrant tachyarrhythmia begin with the break of a wavefront. As NSR has a cycle length of ~ a second, and computational electrophysiological models of arrhythmia can lead to estimation of the probability/cycle of a wavebreak leading to a re-entrant arrhythmia, the transition probabilities are /s. The transition probabilities α, β can be estimated from longitudinal recordings in an individual, from the mean rate of episodes α and their mean duration $\tau = (1/(\alpha+\beta))$.

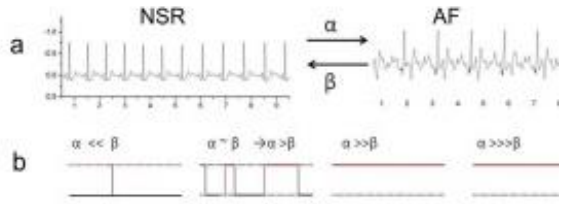

Figure 1. Transitions (a) between NSR and re-entrant tachycardia, illustrated for AF, with transition probabilities/s α and β; (b) model for NSR, paroxysmal, persistent and permanent AF.

All data was from recordings obtained during routine clinical monitoring and treatment, after informed consent. Paper recordings were digitized by GraphClick (www.arizona-software.ch), and all graphical analysis was in Origin Pro (www.originlab.com).

2.1. Atrial fibrillation

6 patients with implanted pacemakers who had developed AF were selected from the pacemaker clinic. The time of onset (date, hour, minute) and duration (hours, minutes, seconds) of episodes of AT/AF were extracted from the arrhythmia episode list.

2.2. Induced ventricular fibrillation

The deliberate induction of VF, by high frequency stimulation/excitation on the T wave, to test an implanted ICD, provides an opportunity to characterize VF which will then be automatically terminated after 15 s by the ICD. Endocardial recordings exported from the ICD, or concurrent ECG recordings, were quantified by their rates. In this pilot the induced VF self-terminated within this 15 s window in 1 out of the 10 cases.

2.3. Idiopathic ventricular fibrillation

Episodes of idiopathic ventricular fibrillation were recorded either noninvasively (ECG), or invasively (endocardial recordings during electro-anatomical mapping and ablation procedures).

2.4. Putative foetal ventricular fibrillation

The foetal ECG [6,7] was extracted from maternal recordings (non-invasive monitoring of uterine electrical activity) from a Monica AN24 *via* electrodes placed on the abdomen. Episodes of foetal tachycardia were initially located using Monica software, and then the raw V(t) exported for graphical analysis.

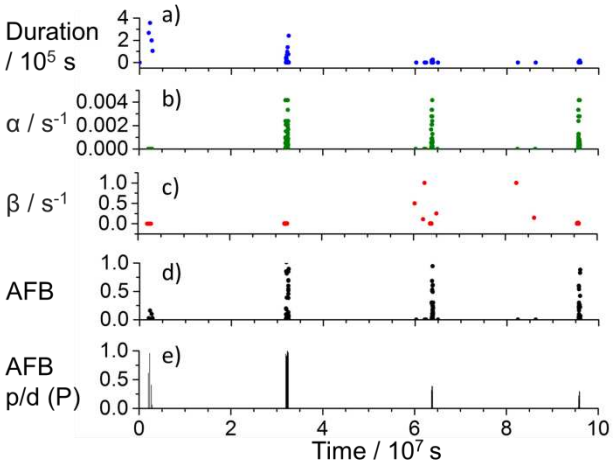

Figure 2. Longitudinal AF characteristics over ~40 lunar months in one patient (a) duration of episode; (b), (c) instantaneous rates α_i,β_i estimated from (a); (d) instantaneous AF burden estimated from (b) and (c) by AFB= $\alpha_i/(\alpha_i+\beta_i)$ (d) AF burden as fraction of day spent in AF estimated from raw occurrence time, duration data from AF episode list..

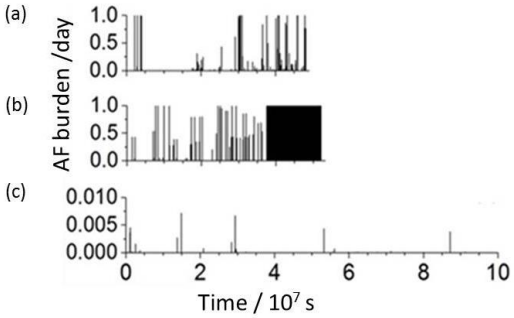

Figure 3. Time evolution AF burden/day obtained from pacemaker recordings lasting up to ~40 lunar months. Note 100-fold scale change in AFB for (d).

3. Results

Data is analyzed in terms of episode timing and duration, instantaneous rates α_i, β_i and their probability/s, the means $<\alpha>$, $<\beta>$.

3.1. Atrial fibrillation

AF episode durations were from a few s to months, so were predominantly in the paroxysmal (<7 days) to persistent (>7 days, <a year) range). The AF burden (Fig.2d) calculated from the instantaneous rates α_i, β_i (Fig 2b,c) is consistent with the AF burden estimated directly from the AF episode list (Fig 2e). The 6 patients in this pilot exhibited 730 episodes of AF; only one AF episode lasted more than a lunar month (Fig. 3b). In some the (averaged) AF burden increases monotonically with time, in most the averaged burden was intermittent, in short bursts lasting days, of episodes lasting 10^2 - 10^5 s (Table 1). Intervals < 10^5 s between episodes were exponentially distributed, intervals > 10^5 s were more frequent and regular than expected for an exponential with the same overall mean rate.

3.2. Induced ventricular fibrillation

Although VT is a common cause of death, recordings of spontaneous or endogenously triggered episodes of VT and VF in patients are sparse. The testing of an implanted cardiac defibrillator (ICD) provides an opportunity for observing the onset and first ~15 s of the VT before it is eliminated by a shock. Deliberately allowing the VT to persist for longer is unacceptable as the defibrillation threshold begins to increase after more than 15s, presumably due to activity dependent changes in ion distribution and excitability. These induced VTs have not been initiated or sustained by the same mechanisms as clinical VT/VF, but allow quantitative observations on the process of onset and any self-termination.

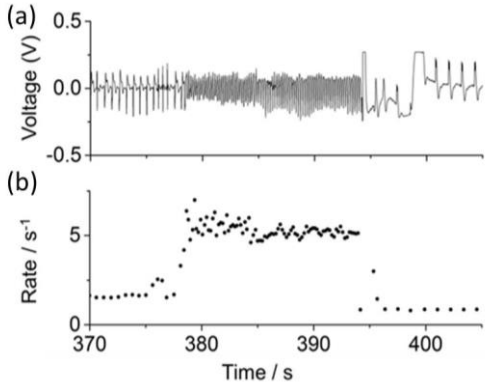

Figure 4. (a) Endocardial recording from ICD during induction of VT/VF and automatic defibrillation, (b) instantaneous rate, as reciprocal of preceding interval between local minima.

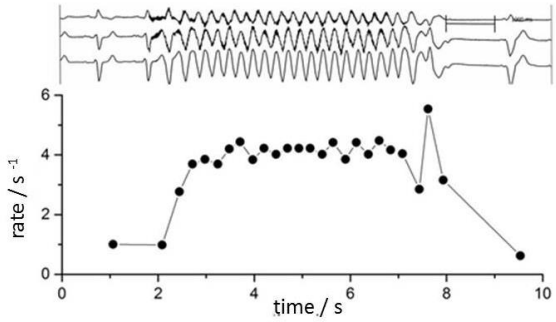

Figure 5. VT triggered and driven by 50 Hz pacing, self-terminated 2.5s after pacing turned off

Figure 4 presents direct endocardial recordings obtained from an ICD during the induction of VF and its termination by a defibrillating shock, sampled at 1kHz. During the onset of VF there is an increase in rate (estimated simply by the reciprocal of the interval between successive troughs); during the first 5s of VF the rate is irregular, during the last 10s there is a suggestion of a periodic rate modulation. Figure 5 presents ECG recordings from another patient during another induced fibrillation; in this case the VF self-terminated. There is also a suggestion of modulation of the rate during the last 5 s of VF. The period of this "suggestive modulation" is 3-5 that of the VT period.

3.3. Putative foetal ventricular fibrillation

The *in utero* human foetal ECG (fECG) can be recorded noninvasively *via* electrodes on the mother's abdominal surface from about 12 weeks gestational age (WGA). The fECG has a small (<~50 μV) amplitude but foetal QRS complexes are clearly identifiable, and foetal RR intervals can be automatically extracted, and foetal bradycardia and tachycardia readily identified.

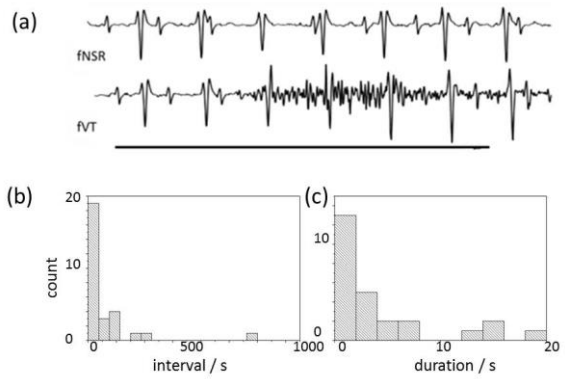

Figure 6. (a) Single channel Monica Healthcare AN24 fetal monitor recording showing of maternal and foetal ECG, with episodes of normal sinus rhythm and a brief episode of putative self-terminating foetal tachycardia (b) intervals between and (c) durations of putative episodes, in a single two hour recording.

In some pregnancies short intermittent bursts of high frequency activity are observed, as illustrated in Figure 6: these resemble magneto-cardiographic recordings of foetal tachycardia [6], their amplitude on all four channels of the monitor, and changes in these amplitude with foetal position, are both similar to those of preceding and subsequent foetal QRS complexes. However, there is no direct evidence that these "putative foetal VTs" are produced by activity in the foetal heart: they look and behave as if they could be. Their durations and the intervals between their occurrence are both approximately exponential (Fig 6b,c). Self-terminating VTs with durations < 10 s have been modelled in 1-D and 3-D models of the 24 week gestational age foetal human ventricle.

3.4. Idiopathic ventricular fibrillation

Spontaneous VTs, including fibrillation, are extremely rare in the general population, even from patients in intensive or Coronary Care Units they occur in < 0.05% but ~20% of those that occur and are recorded on an ECG self-terminate before any intervention [8,9]. Spontaneous VTs are commoner in some channelopathies e.g. the long QT syndromes, or Brugada's syndrome, and in clinic and Holter recordings provide examples of self-terminating VTs that last up to ~30s. Even in the LQT storm illustrated in Fig 6 there are insufficient episodes for an estimate of mean α,β analysis to be useful, so quantification is limited to mean instantaneous α_i and mean duration (Table 1).

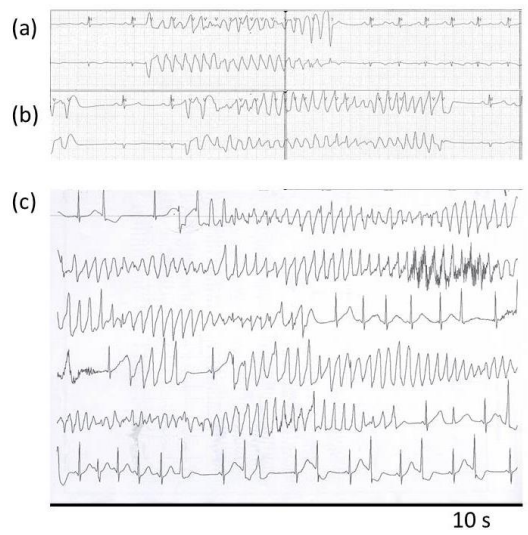

Figure 7. Endogenous episodes of self-terminating VT. (a), (b) Separate episodes of STVT in two different patients (c) continuous recording of torsade storm in a patient with LQT syndrome.

4. Conclusions

Table 1. Quantitative characteristics of re-entrant arrhythmias.

Arrhythmia episodes	n	<duration> s	<α> s^{-1}	<β> s^{-1}
Atrial fibrillation	540	14885	0.003	0.02
Foetal"STVT"	31	9.5	0.004	
EndogenousSTVT	6	5-23	0.03	

Current clinical recordings, noninvasively, from the body surface as ECGs, or invasively, from endocardial electrodes, provide data that can provide quantitative constraints on model of arrhythmogenesis. Infrequent but not uncommon events, such as spontaneous tachyarrhythmias, can be quantified in terms of their rates of occurrence and duration, or probabilities/s of initiation and termination. These probabilities can be related to mechanistic models for the initiation, persistence and termination of reentrant arrhythmia. "w"

The transition probability estimates illustrated in this case studies, when extended to larger patient populations, can be related to probability estimates of AF incidence and burden from population studies that show variation with age, with gender, ethnicity and provide a measure of the effect of remodelling . They can be related, via birth and death models for rotor phase singularities, to pharmacologically addressable electro-physiological parameters.

A few cases of induced fibrillation show an apparent periodic modulation of rate during the last 5-10 s of fibrillation. Such a modulation has been demonstrated in numerical studies [10] and identified as due to a meander induced Doppler shift..

Self-terminating tachyarrhythmia have been observed in atria and the ventricles, in the general population and in patients with specific cardiac pathologies, and in the developing foetal heart.

References

[1] Pandit SV, Jalife J. Rotors and the dynamics of cardiac fibrillation Circ Res. 2013 Mar 1;112(5):849-62.

[2] Nattel S, Burstein B, Dobrev D. Atrial remodeling and atrial fibrillation: mechanisms and implications. Circ Arrhythm Electrophysiol 2008;1(1):62-73.

[3] Prystowsky EN, Padanilam BJ, Joshi S, Fogel R Ventricular arrhythmias in the absence of structural heart disease. J Am Coll Cardiol. 2012 May 15;59(20):1733-44.

[4] Cherry EM, Fenton FH, Gilmour RF Jr. Mechanisms of ventricular arrhythmias: a dynamical systems based perspective. Am J Physiol Heart Circ Physiol 2012 302(12) H2451-63.

[5] Gil L, Lega J, Meunier JL.Statistical properties of defect mediated turbulence 1990 Phys Rev A 41: 11381141

[6] Strasburger JF & Wakai RT Fetal cardiac arrhythmia detection and in utero therapy Nature Reviews Cardiology 2010 7, 277-290.

[7] Pervolaraki E, Anderson RA, Benson AP, Hayes-Gill B, Holden AV, et al. Antenatal architecture and activity of the human heart. Interface Focus 2013 3 (2) 20120065.

[8] Clayton RH, Murray A, Higham PD, Campbell RWF. 1993. Lancet 341 93- 5.

[9] Cisru G, Brembill-Perrott B, Pauriah M, Zinzius PY, Sellal JM, Schwartz J,Sadoul N. Cycle length characteristics differentiating non-sustained from self-terminating ventricular fibrillation in Brugada syndrome. 2013. Europace 15 1313-1318.

[10] Panfilov AV, Holden AV. Computer simulation of re-entry sources in myocardium in two and three dimensions. J 1993. J theoretical biology 161, 271-286.,

Address for correspondence.

Arun V Holden
Multidisciplinary Cardiovascular Research Centre
& School of Biomedical Sciences
University of Leeds, Leeds LS2 9JT, UK
a.v.holden@leeds.ac.uk