Propagation Velocity Kinetics and Repolarization Alternans in a Sheep Model of Pacing-Induced Atrial Fibrillation

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Abstract

Repolarization alternans, a beat-to-beat alternation in action potential duration, enhances dispersion of repolarization when propagation velocity is involved. In this work, repolarization dynamics and propagation velocity kinetics are studied in a chronic sheep model of pacing-induced atrial fibrillation. Two pacemakers were implanted in four sheep, the first one to deliver pacing protocols and the second one to record a unipolar electrogram. Measuring in vivo in a free-behaving sheep model right atrial CV kinetics and repolarization alternans during electrical remodelling was shown to be feasible. A significant and gradual decrease of propagation velocity and right atrial effective refractory period during the weeks preceding sustained atrial fibrillation was observed. Repolarization alternans and propagation velocity kinetics are promising parameters for in vivo assessment of atrial fibrillation susceptibility.

1. Introduction

Atrial fibrillation (AF) is the most common arrhythmia and is frequently responsible for morbid and fatal complications. This study investigates the potential of original electrophysiological parameters (i.e. repolarization alternans and propagation velocity kinetics) in predicting AF susceptibility in a pacing-induced sheep model of sustained AF.

It has been shown experimentally that sustained AF requires a critical amount of dispersion of repolarization [1] and a critical slowing down of propagation velocity [2]. Repolarization alternans, a beat-to-beat alternation in action potential duration, enhances dynamically the dispersion of repolarization when propagation velocity is involved [3]. Moreover, atrial cells are especially prone to repolarization alternans because of the absence of T-tubules [4]. However, it is unknown whether repolarization alternans plays a role in sustaining AF and whether the involvement of propagation velocity restitution at slow heart rates decreases atrial repolarization alternans threshold.

We hypothesize that the increased susceptibility to AF that takes place during the time course of pacing-induced electro-anatomical remodelling is associated with :
1. a gradual reduction in atrial repolarization alternans threshold;
2. a gradual reduction in atrial propagation velocity.

In this paper, we report on the feasibility of studying atrial repolarization alternans and propagation velocity kinetics in a chronic free-behaving sheep model of pacing-induced AF. First we describe the experimental procedure and the parameter extraction approach we used. Then, we present some results on the evolution of propagation velocity kinetics with respect to the induction of AF. We also present preliminary observations of repolarization wave alternation at high pacing rates.

2. Methods

Two pacemakers (Vitatron^{TM}), each with a single lead screwed into the right atrium (figure 1 (a)) were implanted in four sheep. The first pacemaker was used to record a broadband (sampling frequency 800 Hz, 0.4 Hz high pass filter) unipolar atrial electrogram (EGM). Figure 1 (b) shows a typical intracavitar EGM. The pacemaker impulse (I) is followed by right atrial depolarization (R_a) and repolarization (T_a), and far-field ventricular depolarization (R_v). An EGM and a subcutaneous ECG were recorded with a Holter device and transmitted to a computer by Bluetooth. The second pacemaker was used to deliver long term intermittent burst pacing and electrophysiological protocols.

2.1. Signal analysis

In order to extract the different parameters (repolarization alternans threshold and propagation velocity), identification of timing of each event must first be extracted from EGM signals. These different types of event are

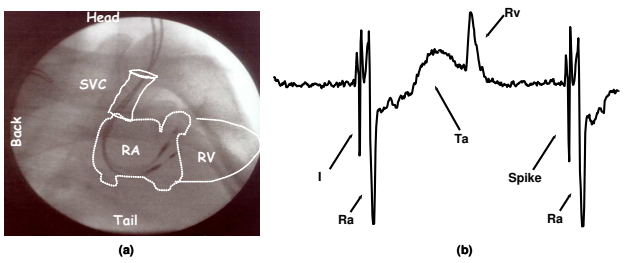

Figure 1. (a) X-ray view of the pacemaker's leads screwed in the right atrium. (b) Typical right atrial EGM with pacemaker impulse (I), atrial depolarization (R_a), atrial T wave (T_a) and far-field ventricular depolarization (R_v)

pacemaker impulse, atrial depolarization and repolarization waves, and far-field ventricular depolarization wave.

The pacemaker impulse constitutes the highest frequency component of the EGM. The impulse detection is carried out as follows :

1. application of a highpass filter to the EGM signal. A Chebyshev filter was used (cutoff frequency 180 Hz);
2. application of a threshold ($\alpha = 85\%$ of the maximal amplitude of the filtered signal);
3. identification of pacemaker impulses as local maxima.

Atrial depolarization waves were then identified as the local minima (window length of 50 ms) following the pacemaker impulse. A template matching approach was used to identify the timing of T waves. In order to reduce noise and artifacts, a fourth order polynomial was fitted on each T wave segment. A threshold (85 $\%$ of maximal amplitude) was applied to the subcutaneous ECG to detect the far-field ventricular depolarizations. They were then identified by the local maxima.

2.2. Experimental procedure

Three different pacing protocols, named S1S1, S1S2 and burst pacing, were used in the experimental procedure. The first two are measurement protocols and the last one is used for AF induction.

The S1S1 protocol was used to determine of atrial repolarization alternans threshold. It consists of sequences of 400 beats applied to the sheep's right atrium. From one sequence to the next, the coupling interval is decremented by 10 millisecond (ms) steps, starting at 400 ms. This protocol stops when some stimulus fails to depolarize the right atrium.

The S1S2 protocol was used to determine restitution of atrial activation time. This protocol consists of sequences of 20 beats at 400 ms cycle length (S1) followed by delivery of a premature beat (S2). From one sequence to the next, the time interval between the last S1 beat and the S2, defined as S1S2 interval, is decremented by 10 ms steps (from 400 ms to 30 ms). The time interval between the S2 impulse (I) and the following atrial depolarization (R_a) for each S1S2 interval was measured. The atrial effective refractory period was defined as the longest S1S2 interval that failed to depolarize the atrial tissue.

The pacing protocol leading to sustained AF consists in intermittent sequences of burst pacing of 5-sec duration followed by 2-sec rest period. The pacing interval was programmed at 10 ms above the atrial effective refractory period.

The experimental procedure was the following :

1. measurement protocols (S1S1 and S1S2);
2. two weeks of burst pacing protocol (induction of electro-anatomical remodeling);
3. measurement protocols (S1S1 and S1S2).

Measurements of atrial effective refractory period and propagation velocity made before burst pacing activation were taken as baseline conditions. Steps 2 and 3 were repeated until the sheep developed sustained AF.

3. Results

None of the four implanted sheep developed non-sustained AF at baseline (before burst pacing protocol activation), in spite of aggressive pacing rates during measurement protocols (S1S1 and S1S2).

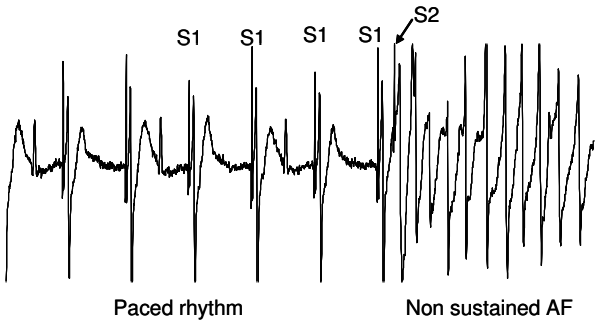

Figure 2. Non-sustained AF induced during the S1S2 protocol. AF started at a S1S2 interval = 100 ms

The burst pacing protocol was activated in two sheep in which sustained AF was successfully induced after respectively four and six weeks. Interestingly, both sheep developed non-sustained AF after 2 weeks of burst pacing during S1S2 protocol for coupling intervals between 140 ms and atrial effective refractory period ($\sim$ 110 ms) as shown in figure 2.

3.1. Propagation velocity kinetics

Activation time restitution was determined in both burst-paced sheep on a 2-week basis. For long S1S2 intervals, activation time remained stable; an increase was noted

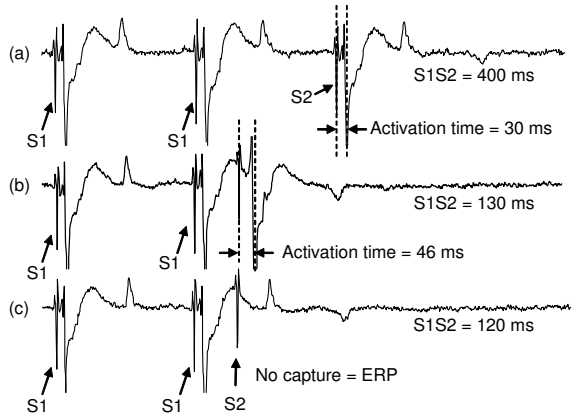

Figure 3. Illustration of the slowing of propagation velocity with shortened S1S2 intervals. (a) Normal activation time for long a S1S2 interval (400 ms). (b) Increase in activation time near effective refractory period (130 ms). (c) Effective refractory period (no atrial capture at 120 ms).

(corresponding to a slowing of propagation velocity) as the S1S2 interval approached atrial effective refractory period (figure 3). Figure 4 shows a representative example of activation time restitution kinetics at baseline (i.e. before burst pacing activation) and after 15 and 30 days of burst pacing before sustained AF was induced. Each activation time curve was fitted by an exponential function using a minimum least-squares approach :

$$y = a \cdot \exp\left(-\frac{x}{\tau}\right) + c$$

where x is the S1S2 interval and y is the corresponding activation time. The amplitude a, the offset c and the time constant τ are the parameters to be estimated.

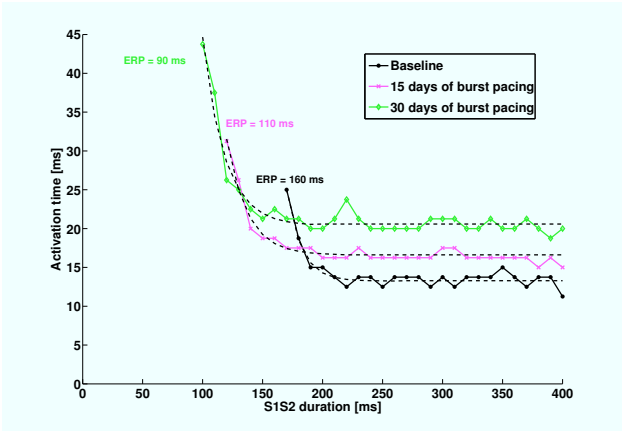

Figure 4. Evolution of activation time curve during the time course of burst pacing

The offset c, corresponding to the activation time at rest (400 ms cycle length), increased progressively during the time curse of rapid pacing from 13 ms at baseline to 17 ms and 21 ms after 15 days and 30 days of burst pacing, respectively. Also the amplitude a increased with burst pacing, which illustrates the slowing of propagation velocity for coupling intervals close to the effective refractory period starting at a value of 25 ms at baseline, and increasing to 30 ms and 44 ms after 15 and 30 days of burst pacing, respectively. The corresponding propagation velocities for both burst-paced sheep are summarized in table 3.1. No significant evolution in the time constant τ was observed with burst pacing.

	PVel at rest		PVel near ERP	
Sheep	# 1	# 2	# 1	# 2
Baseline	101 cm/s	110 cm/s	51 cm/s	63 cm/s
2 weeks	88 cm/s	92 cm/s	44 cm/s	50 cm/s
4 weeks	66 cm/s	AF	33 cm/s	AF
6 weeks	AF	AF	AF	AF

Table 1. Propagation velocity (PVel) measured for both burst paced sheep, at rest and near effective refractory period, from baseline to sustained AF.

Atrial effective refractory periods also showed a gradual decrease during the time course of burst pacing (figure 4). Table 2 summarizes the values of atrial affective refractory period.

Sheep	# 1	# 2	# 3	# 4
Baseline	150 ms	160 ms	150 ms	160 ms
2 weeks	NA	110 ms	120 ms	NA
4 weeks	NA	90 ms	AF	NA
6 weeks	NA	AF	AF	NA

Table 2. Atrial effective refractory periods measured on four sheep, from baseline to sustained AF

3.2. Atrial repolarization alternans

In two of the four implanted sheep, we were able to reliably identify alternans of atrial repolarization which was observed during S1S1 protocol at coupling intervals near atrial effective refractory period. Figure 5 shows a representative example. The top row shows a bipolar subcutaneous ECG derivation with 4/1 atrioventricular block. The bottom row shows the intracavitary EGM. Note the alternation of atrial repolarization (T_a), while the far field ventricular depolarization takes place every 4 atrial beats. In general, atrial repolarization alternans and its threshold could not be reliably established during the time course of burst pacing because of 2/1 atrioventricular block at most rapid pacing rates.

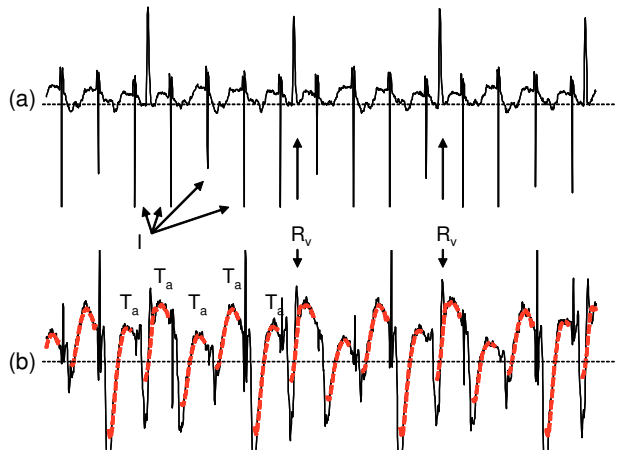

Figure 5. Example of atrial repolarization alternans during an S1S1 protocol. (a) Subcutaneous ECG during a four-to-one atrioventricular block. The atrial EGM clearly shows the beat-to-beat alternation in the repolarization wave amplitude (T_a). The S1S1 cycle length is 140 ms.

4. Discussion and conclusions

We report here for the first time the observation of right atrial repolarization alternans in a free-behaving sheep model of pacing-induced AF. Importantly, atrial repolarization alternans was observed near atrial effective refractory period; its threshold, however, could not be reliably determined during pacing-induced electro-anatomical remodeling because of far field ventricular interference. Also other important changes took place including:
1. a gradual decrease in atrial effective refractory period;
2. a progressive decrease in propagation velocity at any pacing rates, with a marked slowing near atrial effective refractory period.

Allessie et al. [5] reported in a similar model the lack of any increase in dispersion of refractory periods with increasing susceptibility to AF. Their measurements, however, were made during steady state conditions, i.e. with delivery of a single premature beat to determine atrial effective refractory periods. Our findings extend to the whole heart previous works performed in single cells showing the susceptibility of atrial cells to repolarization alternans (Huser et al [4]). Therefore, repolarization alternans might enhance dispersion of refractory periods only at pacing rates near atrial refractory periods. Interestingly, Qu et al. [3] showed in simulated tissues that propagation velocity had to be engaged for discordant alternans to take place. Only discordant alternans, where islands of action portential duration were out of phase, increased dispersion of repolarization. In the present study, propagation velocity declined gradually during the time course of electro-anatomical remodeling, with a steep slowing near atrial refractory period. This steep slowing paralleled the susceptibility to AF as shown by bouts of non sustained AF at pacing rates near atrial refractory periods after 15 and 30 days of burst pacing. Because atrial repolarization alternans was measured in a single point, and because its threshold could not be determined reliably, the role of repolarization alternans and propagation velocity in enhancing dispersion of refractory periods and susceptibility to AF could not be established. Future studies are warranted in which ventricular rate will be controlled by producing atrioventricular block. In conclusion, these preliminary results show the feasibility of measuring both atrial repolarization alternans and propagation velocity kinetics and their potential in predicting susceptibility to AF.

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