

# In Vivo Measurements of Atrial Repolarization Alternans Based on Standard Pacemaker Technology

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## Abstract

*It has been shown that repolarization alternans, a beat-to-beat alternation in action potential duration, enhances dispersion of repolarization above a critical heart rate and promotes susceptibility to ventricular arrhythmias. It is unknown whether repolarization alternans is measurable in the atria using standard pacemakers and whether it plays a role in promoting atrial fibrillation. In this work, atrial repolarization alternans amplitude and periodicity are studied in a sheep model of pacing-induced atrial fibrillation. Two pacemakers, each with one right atrial and ventricular lead, were implanted in 4 male sheep after ablation of the atrioventricular junction. The first one was used to deliver rapid pacing for measurements of right atrial repolarization alternans and the second one to record a unipolar electrogram. Atrial repolarization alternans appeared rate-dependent and its amplitude increased as a function of pacing rate. Repolarization alternans was intermittent but no periodicity was detected. An increase of repolarization alternans preceding episodes of non-sustained atrial fibrillation suggests that repolarization alternans is a promising parameter for assessment of atrial fibrillation susceptibility.*

## 1. Introduction

Atrial fibrillation (AF) is the most frequent sustained arrhythmia, and is commonly responsible for morbid and fatal complications. The present project intends to investigate the ability of original electrophysiological parameters to predict AF susceptibility in a pacing-induced model of AF.

Decreased action potential duration, increased dispersion of refractory periods and inhomogeneous atrial conduction [1] are the hallmark of patients suffering from AF. However, in patients suffering from AF: 1) up to 30% of episodes occur without cardiopulmonary disease and 2) the critical amount of dispersion of repolarization required for reentry does not appear to be always present at rest. Re-

polarization alternans (Re-ALT), a beat-to-beat alternation in action potential amplitude and duration [2], enhances dynamically dispersion of repolarization when conduction velocity is engaged at long coupling intervals (i.e. slowing of propagation at long diastolic intervals) [3]. It is unknown, however, whether Re-ALT plays a role in promoting AF, and whether the engagement of conduction velocity at slower pacing rate as well as pacing-induced atrial electro-anatomical remodeling decrease alternans threshold. We report on the feasibility of studying atrial Re-ALT amplitude and periodicity in a sheep model of pacing induced AF. We first describe the experimental procedure and the parameters extraction approach used. Then, we present preliminary results on the kinetics of Re-ALT amplitude.

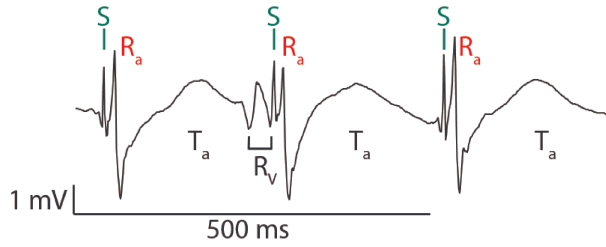
## 2. Methods

Two pacemakers (Vitatron<sup>TM</sup>), each with 2 leads, were implanted in four sheep. Two leads were screwed in the right atrium (RA) and two in the right ventricle to insure atrioventricular (AV) synchrony. The first pacemaker was used to record a broadband (sampling frequency 800 Hz, 0.4 Hz high pass filter) intracardiac unipolar atrial electrogram (EGM), as shown in figure 1, and to perform ventricular pacing during burst pacing. The second pacemaker was used to deliver long term intermittent burst pacing and electrophysiological protocols (S1S1), and to insure AV synchrony during sinus rhythm. Atrial EGM and subcutaneous ECG were recorded with a Holter device.

At short pacing cycle length (CL), 2:1 AV conduction artificially produced atrial Re-ALT because the far-field ventricular depolarization impinged on the preceding atrial repolarization on an every-other-beat basis. To overcome this issue, the AV junction was ablated and ventricular leads were implanted to pace the ventricles [4].

### 2.1. Experimental procedure

Two different pacing protocols were used in the experimental procedure. The first one (S1S1) was used to de-



**Figure 1:** Representative right atrial EGM with pacemaker impulses ( $S$ ), atrial depolarization ( $R_a$ ) and atrial repolarization waves ( $T_a$ ) and far-field ventricular depolarizations ( $R_V$ ) as acquired by the recording pacemaker.

termine the atrial Re-ALT threshold and its evolution as a function of pacing CL. It included atrial pacing for 400 beats starting at a CL of 400 ms with 10 ms decrement until stimuli failed to depolarize the RA (i.e. effective refractory period (ERP)).

The second protocol was designed to remodel the atria and consisted of bursts of programmable CL and duration in intermittence with sinus rhythm in order to mimic salvos of pulmonary vein tachycardia. The burst pacing CL was usually programmed at 20 ms above the ERP.

## 2.2. Signal preprocessing

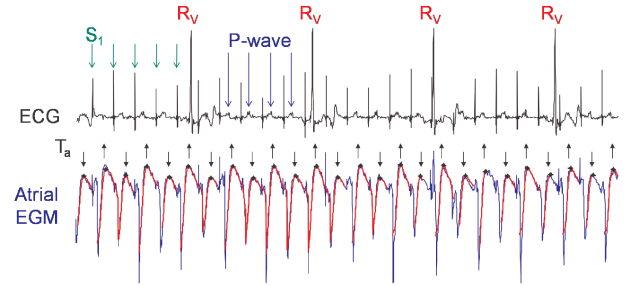
The ECG baseline wandering was suppressed with a Butterworth high-pass filter with a cutoff frequency at 1.5 Hz. The signal was first filtered in the forward time direction and then the filter output was filtered again in the backward time direction. The result had precisely zero-phase distortion.

A wavelet denoising method was applied on both the EGM and ECG signals. The wavelet decompositions (Daubechies 4 level 3 decomposition) were soft-thresholded. The threshold was rescaled based on a level-dependent estimation of the level noise. As explained in [5], the denoising procedure proceeds in three steps:

1. *Decomposition.* Compute the wavelet decomposition of the signal at level 3.
2. *Detail coefficients thresholding.* For each level from 1 to 3, select a threshold and apply soft thresholding to the detail coefficients.
3. *Reconstruction.* Compute wavelet reconstruction based on the original approximation coefficients of level 3 and the modified detail coefficients of levels from 1 to 3.

## 2.3. Signal analysis

To analyze the atrial repolarization, identification of the timing of each event must first be extracted from EGM signals. These different events are the pacemaker impulses, the atrial depolarization and repolarization waves and the



**Figure 2:** Representative example of atrial Re-ALT. The upper panel shows a subcutaneous ECG at an atrial pacing CL ( $S_1S_1$ ) of 260 ms. Note the complete AV block with atrial waves (P-wave) dissociated from ventricular ones ( $R_V$ ). The lower panel shows the simultaneous atrial EGM recording. Note the indisputable alternans in atrial repolarization ( $T_a$ ) as depicted by the alternating black arrows.

far-field ventricular depolarization waves (Figure 1). The atrial depolarization was detected by applying a nonlinear energy operator (NEO) to the EGM and thresholding its output. The NEO is defined by [6] as:

$$\psi \{x[n]\} = x^2[n] - x[n + \delta]x[n - \delta], \quad 1 \leq \delta \leq 4 \quad (1)$$

This first stage emphasized the spikes and the threshold determined its position. The parameter of the NEO was typically set to  $\delta = 4$  and the threshold to 30% of the maximal value of the processed signal.

Once the atrial depolarizations have been detected, the successive repolarization waves were smoothed by a Savitzky-Golay filter of order 3 [7]. This filtering minimizes the least-squares error by fitting a polynomial to each frame of noisy data. Then, the zeros of the second derivative set the onset and end of the repolarization wave. For each fitted T wave segment, the local maximum was extracted and defined the amplitude apex  $T_a$ .

The time series of  $T_a$  was used to detect Re-ALT. Re-ALT was considered present when the two following conditions were fulfilled:

1. The  $T_a$  were alternating for more than four beats
2. The odd and even  $T_a$  distributions were statistically different ( $p < 0.01$ ).

## 3. Results

### 3.1. Kinetics of atrial repolarization alternans

Atrial Re-ALT was detected in all sheep with AV block. Figure 2 shows a representative example of Re-ALT after ablation of the AV junction. Atrial  $T_a$  were alternating on an every-other-beat basis independently of ventricular depolarization.

The intermittent burst pacing protocol was successfully activated in 2/4 sheep. During the time course of atrial

remodeling, no change in Re-ALT threshold was observed. However, pacing-induced atrial remodeling progressively increased the range of pacing CL during which Re-ALT occurred until sustained AF developed (from 45 ms to 95 ms), which closely followed the gradual reduction in atrial ERP (from 215 ms to 135 ms).

Importantly, Re-ALT amplitude increased as the pacing CL decreased. Figure 3, panel A shows representative examples of unipolar atrial recordings at different pacing CL. Although some Re-ALT was detected, it was hardly visible at 400 ms pacing CL. The decrease of pacing CL to 300 ms and 250 ms was associated with a gradual increase in Re-ALT amplitude (from a mean peak-to-peak value of  $46 \mu\text{V}$  at 400 ms to  $141 \mu\text{V}$  at 250 ms).

Figure 3, panel B shows the amplitude (colormap) and beat locations (x-axis, from 1 to 400 beats) of Re-ALT for an entire stimulation protocol (y-axis, range 400 to 200 ms) of 400 beats per pacing CL in a representative example. Note the lack of significant alternans for long CL (400 to 300 ms, dark blue). For  $\text{CL} < 300$  ms, a progressive increase in duration and amplitude (light blue) of Re-ALT is noticed. Importantly, the amplitude of Re-ALT was much higher (red) at fast pacing CL (210 ms) and preceded an episode of non sustained AF. Note that the analysis of Re-ALT for pacing  $\text{CL} < 200$  ms was not feasible in this example as the stimuli were impinging on preceding atrial repolarization waves.

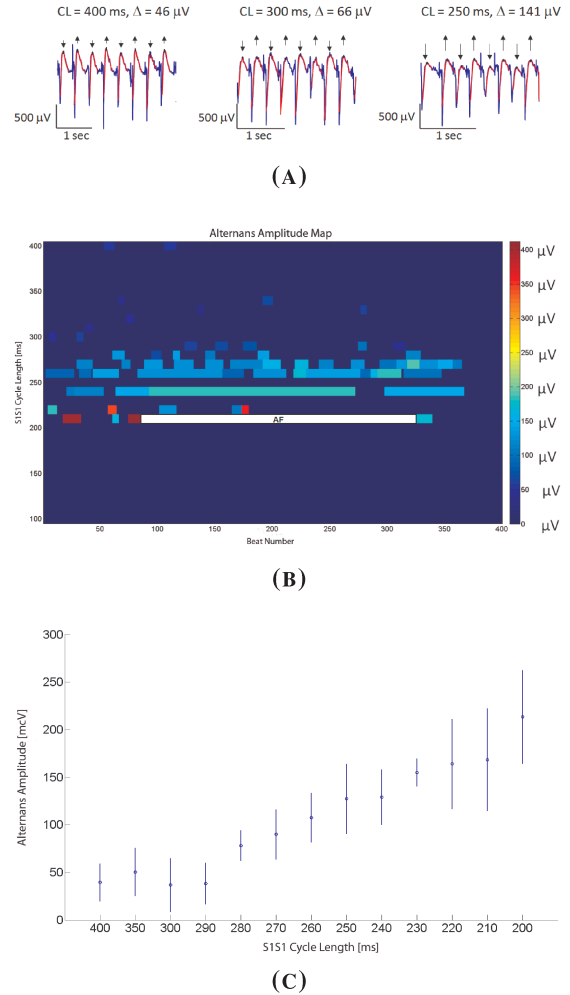
Figure 3, panel C shows summary data ( $n=4$  sheep) of the evolution of Re-ALT amplitude (mean  $\pm$  SD) at decremental pacing CL (x-axis). Only significant Re-ALT sequences were included. Note the gradual increase in Re-ALT amplitude starting at 280 ms CL (i.e. Re-ALT threshold) as the pacing CL decreased.

Importantly, episodes of AF were triggered by rapid pacing during the study protocol. Some episodes displayed atrial Re-ALT for the very last beats preceding AF onset. Figure 4 shows a representative example. Figure 3, panel B also shows that Re-ALT was of much higher amplitude before AF onset as compared to longer non-inducing pacing CL.

Also, Re-ALT appeared intermittent. Figure 3, panel B shows a representative example. In spite of the progressive increase in Re-ALT amplitude as the pacing CL was reduced, no periodicity was apparent, suggesting that atrial repolarization displays complex spatiotemporal dynamics.

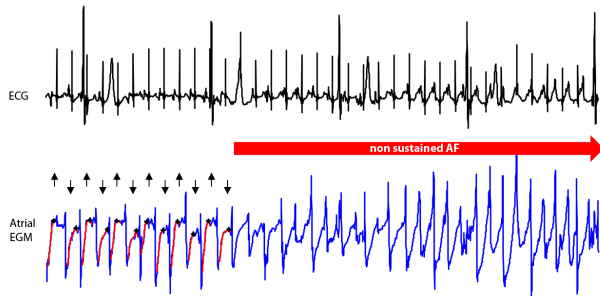
#### 4. Discussion and conclusions

The present study reports for the first time the feasibility of recording atrial repolarization and its alternans in a chronic free-behaving ovine model using standard pacemaker technology. Atrial Re-ALT and its amplitude were rate-dependent, appeared intermittent but non periodic, and preceded episodes of non-sustained AF.



**Figure 3:** Evolution of Re-ALT as a function of pacing CL. Panel (A) shows atrial EGM at different pacing CL. Panel (B) shows an example of Re-ALT amplitude over a complete S1S1 protocol. Panel (C) shows summary data (mean $\pm$ SD) of the evolution of Re-ALT amplitude as function of pacing CL ( $n=4$  sheep).

Wijffels et al. [8] reported in a similar model the lack of any increase in dispersion of ERP 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 ERP. Kim et al. [9] recently reported Re-ALT in the RA of humans using monophasic AP recordings. No increase in dispersion of ERP nor of action potential duration (APD) but an increase in APD restitution kinetics were observed in patients with persistent AF as compared to controls. Our findings show that Re-ALT is rate-dependent, i.e. appears above a critical heart rate, and may be a mean by which dispersion of repolarization is dynamically enhanced to facilitate wavebreaks and atrial reentry. Moreover, in a subset of experiments, we showed that atrial remodeling induced by intermittent



**Figure 4:** Repolarization alternans preceding an episode of non sustained AF. Subcutaneous ECG (top) and atrial EGM (bottom). The first half of the figure shows 1:1 atrial capture during rapid pacing at 180 ms CL, followed by a run of non sustained AF seen as a change in signal morphology in the second half of the figure (horizontal arrow). A detailed analysis revealed gradual and subtle Re-ALT (black arrows) over the last beats preceding arrhythmia onset.

rapid pacing mimicking pulmonary vein tachycardia did not lower Re-ALT threshold but increased the range of CL during which Re-ALT took place. This may facilitate alternation of atrial repolarization and wavebreaks over a wider range of heart rates as during the remodeling process of patients suffering from paroxysmal AF.

Intermittence of Re-ALT has been reported experimentally [3] and clinically [10]. Mironov et al. [3] showed that intermittent Re-ALT was related to unstable nodal lines and slow APD accommodation following a change in pacing rate. Selvaraj et al. [10] showed spatially out of phase (i.e. discordant) intermittent Re-ALT. Although in the present study recordings were performed at a single right atrial site, the observation that Re-ALT was intermittent suggests that intervals without alternation corresponded to nodes separating spatially out of phase regions. Hence, intermittent Re-ALT could be used as a marker of atrial and ventricular discordant alternans but requires further clinical validation.

Whether T-wave alternans is a clinical marker of arrhythmia susceptibility remains a matter of debate. Swerdlow et al. [11] recently reported an increase in Re-ALT amplitude preceding ventricular arrhythmias as provided by ICDs. Narayan et al. [12] showed that patients with atrial flutter disorganizing into AF displayed lower Re-ALT threshold and conduction block at the RA isthmus. Interestingly, as shown in Figure 3 panel B, Re-ALT surged and showed the highest amplitude in the very last beats before AF. This finding suggests that intermittent Re-ALT might promote wavebreaks and atrial reentry during atrial tachycardia, but this deserves further experimental validation.

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