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Validation of A Novel Atrial Fibrillation Model Through Simulated Atrial Pacing Protocols

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Abstract — **We have previously reported a novel model to elucidate the effects of ventricular pacing (VP) on RR intervals during atrial fibrillation (AF). This model treats the AV junction (AVJ) as a lumped structure with defined conductivity, refractoriness and automaticity. We have shown that this model could account for various patterns of RR intervals that are consistent with experimental observations. In this study, we further validate this model by comparing its behavior with that of a real AVJ obtained in isolated rat heart preparation, through application of programmed atrial pacing protocols. We demonstrate that the AV conduction time and ventricular response of the present model are consistent with experimental findings, thus providing additional evidence to support the validity of our model.**

Keywords — **atrial fibrillation, AV conduction, RR interval**

I. Introduction

Atrial fibrillation (AF), which is characterized by rapid and irregular ventricular response, represents the most common sustained cardiac arrhythmia in clinical practice, and is associated with increased morbidity and mortality [1].

Although there have been tremendous efforts in the past decades to investigate the ventricular response in AF, the underlying mechanisms are not sufficiently understood and controversies remain [2-9]. In a previous study, we have reported a novel AF-VP model to elucidate the effects of ventricular pacing (VP) on RR intervals during AF [10]. Through computer simulations, we have shown that: (1) the model could account for most principal statistical properties of the RR intervals during AF; (2) the AV conduction and the ventricular rate in AF depended on both AF rate and the degree of electronic modulation in the AV node; and (3) the multi-level interactions between AF and VP could generate various patterns of ventricular rhythm that are consistent with previous experimental observations [10].

In this study, instead of dealing with more complex situations when both AF and VP are present, we proceed to further validate our model through simulated atrial pacing protocols – a simpler-case scenario with well-controlled settings. Specifically, we attempt to validate the model by reproducing some major results reported in a previous experimental study during application of standard atrial pacing protocols in isolated rat hearts [11,12]. Our hypothesis is that, for a valid AF model, it should be able to quantitatively explain, as we demonstrate later, the following well-studied phenomena (see [11,12] for details):

(a) A step change of the atrial cycle length is accompanied by a transient adaptation of the AV conduction time toward a new steady state.
(b) The AV conduction time of a premature atrial stimulus is related to steady-state AV conduction time of the preceding cycles.
(c) A blocked impulse within the AV node affects its refractoriness and conduction properties.
(d) An atrial extrasystole following a sequence of steady atrial intervals can result in longer or shorter RR interval.
(e) Alternately short and long atrial cycle lengths may be associated with relatively stable RR intervals.
(f) Sufficiently high atrial rate can result in progressively lengthening of AV conduction time and periodic AV block (Wenckebach phenomena).

II. Methods

Our AF-VP model can be viewed as an extension and enhancement of Cohen's AF model [8], by taking into account ventricular pacing, physiological conduction delays, and electrotonic modulation in the AV junction (AVJ) [10].

For the purpose of this study, we focus on the AV conduction properties and null the effects of VP. We further replace the random AF generator with programmed atrial stimulation, which is simulated based on the protocols developed by Heethaar et al. [11,12].

The AVJ is modeled as a lumped structure with defined electrical properties, including automaticity, conductivity, and refractoriness [10]. The automaticity is neglected in this study because each atrial pacing pulse has supra-threshold strength to activate the AVJ. The activation of the AVJ generates an activation wave which starts an AV conduction delay (*AVD*). The firing of AVJ also starts a refractory period (τ) during which time the AVJ is non-responsive to any pacing impulses. The AVJ recovery time, *RT*, is defined as the interval between the end of the last AVJ refractory period and the current AVJ activation time.

We assume that the AV conduction delay is related to the AVJ recovery time by the following equation [9,10]:

$$AVD = AVD_{min} + \alpha \exp(-RT / \tau_c) \quad (1)$$

where AVD_{min} is the minimum AV delay when $RT \to \infty$, α is the maximum extension of the AV delay when $RT = 0$, and τ_c is the conduction-curve time constant.

Moreover, we model the AVJ recovery time as a function of the AVJ recovery time [8,10]:

$$\tau = \tau_{min} + \beta(1 - \exp(-RT / \tau_r)) \qquad (2)$$

where τ_{min} is the shortest AVJ refractory period when $RT = 0$, β is the maximum extension of the refractory period when $RT \to \infty$, and τ_r is the refractory-curve time constant. For simplicity, we limit only one activation wave in the AVJ. This is achieved by the additional constraint $\tau \geq AVD$.

Finally, we model the electrotonic modulation of the AVJ refractory period by a concealed impulse [5,9,10]:

$$\tau' = \tau + \tau_{\min}(t / \tau)^{\theta}\left[\max(1, \Delta V /(V_T - V_R))\right]^{\delta} \qquad (3)$$

where τ and τ' are respectively the original and prolonged refractory periods, and t is the time when blockage occurs ($0<t<\tau$). The extension of the AVJ refractory period depends on both timing and strength of the blocked impulse, which are modulated by two positive parameters θ and δ, respectively.

In the following simulations, we set the following default model parameters unless otherwise specified: AVD_{min}=0.07s, τ_{min}=0.03s, α=0.13s, β =0.13s, τ_c=0.10s, τ_r=0.50s, θ =10, δ=10.

III. Results

A. Step Change of Atrial Cycle Length

We first investigate the dynamic changes of *AVD* in response to a step change of the atrial cycle length, that is, a regular atrial rhythm is changed at a given instant to another regular rhythm. The initial steady state is established after a train of 20 atrial paces (S1) with fixed cycle length.

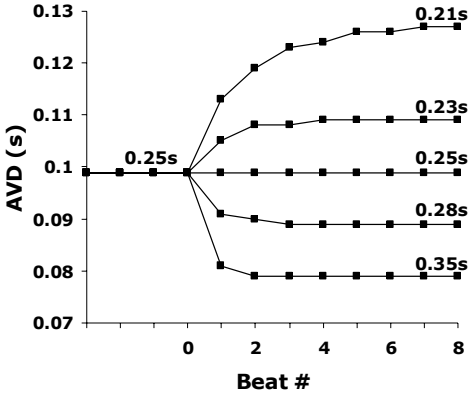

Fig. 1 Dynamic changes of AVD after step change of atrial pacing interval.

As shown in Figure 1, the steady state *AVD* is 0.099s when atrial pacing interval is fixed at 0.25s. A step increase of atrial pacing interval (0.28s, 0.35s) results in transient decrease of *AVD*, while a step decrease of atrial pacing interval (0.21s, 0.23s) results in transient increase of *AVD*. In this example, the new steady state is reached within 2 to 8 beats after the change of the atrial pacing interval, and the adaptation to long intervals takes fewer beats than the adaptation to short intervals. These model-predicted results, which can be analytically derived from equation (1), are in good agreement with experimental observations (compared to Fig. 2 in [11]).

B. AV Conduction After A Premature Atrial Stimulus

Next, we study the relationship between the stead-state *AVD* (after a train of S1 with fixed cycle length) and that of a premature atrial pace (S2) with various coupling intervals.

Figure 2 shows the *AVD* curves obtained at steady state and during application of standard S1S2 pacing protocol. Curve 1 (diamonds) shows that the steady state *AVD* and atrial cycle length (PP interval) have a typical inverse relationship. Curve 2 (rectangles) and curve 3 (triangles) respectively show the *AVD* of test impulse initiated at varying S1S2 intervals after a train of S1 stimulus at a cycle length of 0.294s and 0.2s. When the basic cycle length is long (resp. short), the difference of *AVD* between test impulse and the corresponding steady state increases (resp. decreases) as the S1S2 coupling interval decreases. Again, the model's behaviors can be quantitatively predicted from equation (1), and are consistent with experimental results (compared to Fig. 12 in [11]).

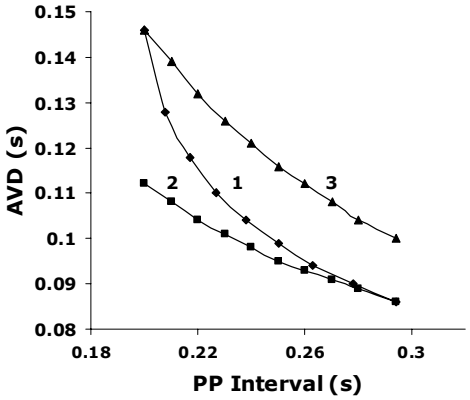

Fig. 2 The AVD curves obtained at steady state and during application of standard S1S2 pacing protocol.

C. Effects of Concealed Conduction

We then examine the effects of a blocked impulse within the AVJ on its refractoriness and conduction properties.

Figure 3 shows the *AVD* curves after a train of S1 stimuli, a test stimulus S2, and another test stimulus S3. In this example, the S1 cycle length is fixed at 0.333s, while S1S2 and S2S3 intervals are varied. Curves 1-3 are obtained when S2 with short S1S2 interval (resp. 0.05, 0.07, and 0.08s) is blocked at AVJ, while curves 4-6 are obtained when S2 with long S1S2 interval (resp. 0.10, 0.20, and 0.30s) is conducted to the ventricle. The curves are shifted to the right as S1S2 interval increases, reflecting longer

effective refractory period of the AVJ as predicted from equations (2) and (3). Therefore, we confirmed previous findings that the *AVD* of stimulus S3, and the effective refractory period after S2, strongly depend on the S1S2 interval (compared to Fig. 2 in [12]).

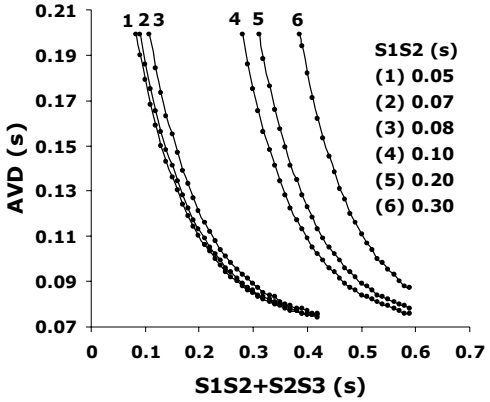

Fig. 3 The AVD curves after a train of S1 stimuli, and a pair of S2-S3 test stimuli with various coupling intervals.

D. RR Interval After A Premature Atrial Stimulus

Figure 4 shows the RR intervals after the test stimulus S2 following a train of S1 stimuli at a cycle length of 0.25s. Curves 1-5 are respectively obtained with 5 different pairs of (α, τ_c) settings: (0.13s, 0.06s), (0.13s, 0.08s), (0.13s, 0.10s), (0.15s, 0.10s), and (0.17s, 0.10s). For very premature S2 stimulus, a shorter S1S2 interval is associated with a longer RR interval because of the inverse relationship between *AVD* and *RT*. For less premature S2 stimulus, the relationship between S1S2 interval and RR interval becomes positive, because the lengthening of S1S2 interval offsets the associated shortening of the *AVD*. It is also clear that the RR interval after test stimulus S2 is affected by the *AVD* curve defined in equation (1), where the parameters α and τ_c determine the relationship between *AVD* and *RT*. We point out that these results further substantiate previous experimental observations (compared to Fig. 8 in [12]).

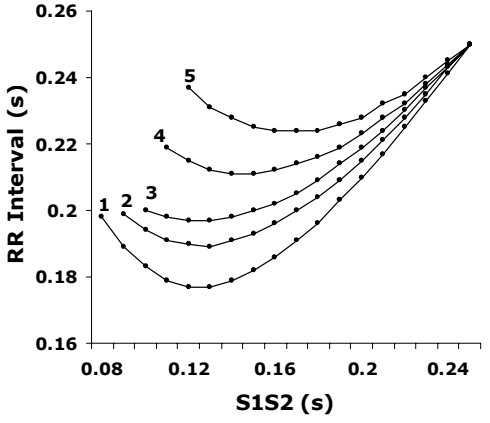

Fig. 4 RR intervals after the test S2 stimulus following a train of S1 stimuli.

E. RR Intervals During AV Alternans

We further test the scenario that regular ventricular rhythm may be generated by irregular atrial rhythm.

As shown in Figure 5, following a train of S1 stimuli at a cycle length of 0.25s, the atrium is alternatively paced with S2 and S3 with respectively short (0.185s) and long (0.208s) coupling intervals. The short atrial interval results in long AV conduction time, whereas the long atrial interval results in short AV delay. Consequently, the alternans of atrial pacing interval is offset by the associated AV alternans in opposite phase, resulting in relatively stable RR intervals around 0.197s. Therefore, our simulation is able to reproduce the results obtained in real heart (see also descriptions of Fig. 9 in [12]).

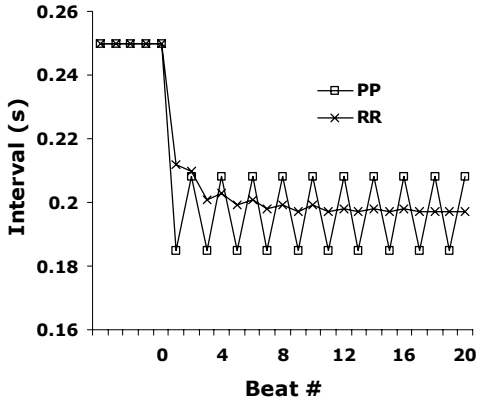

Fig. 5 An example of stable RR intervals in the presence of alternative short-long atrial pacing intervals.

F. Wenchebach Response

Finally, we show that the model can predict the Wenckebach phenomenon, which has been well documented in cardiac electrophysiological studies (see also descriptions of Fig. 10 in [12]). The classical Wenchebach response is that, when the atrium is stimulated at a slightly higher rate than the maximum rate at which 1:1 AV conduction occurs, then after each atrial stimulus there is prolongation of the *AVD* until blocking occurs.

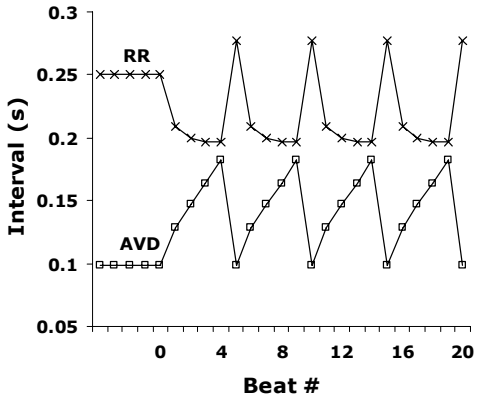

Fig. 6 An example of Wenckebach AV block.

Figure 6 shows one such example. After a train of S1 stimuli at a cycle length of 0.25s (with 1:1 conduction), the atrial pacing interval is step changed to 0.18s, when 6:5 Wenckebach periodicity occurs. The *AVD* progressively increases, and RR interval gradually decreases, until blocking of an atrial stimulus occurs.

IV. Discussion

To elucidate the mechanisms of ventricular response in AF, we have developed a novel computer model based on up-to-date knowledge on electrophysiological properties of the AVJ. Although we have previously shown that the model could explain various experimental observations [10], the model had not been validated in simpler-case scenarios where the randomness of AF impulses and the interaction with VP are factored out.

In the present study, we address this issue by conducting a validation study -- through the application of simulated atrial pacing protocols, where the sequence of atrial impulses can be precisely controlled. We have demonstrated that the model predicted AV conduction property and the ventricular response are consistent with previous findings obtained in an animal model (Figs 1-6) [11,12], thus providing important evidence to support the validity of our AF model.

As a final remark, we stress that the present study is limited by the nature of computer simulation. A more direct validation of the model in real experiments is needed to confirm its concrete behavior.

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