

# Role of the Dual AV Nodal Pathway Physiology in the Ventricular Response during Atrial Fibrillation

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## Abstract

*Dual AV nodal pathway physiology is described as two different wavefronts that propagate from the atria to the His bundle. By using His electrogram alternance on 5 rabbit preparations, we have developed a mathematical model of atrioventricular conduction that incorporates dual AV nodal physiology. The ability to predict AV conduction time and the interaction between FP and SP wavefronts has been analyzed during regular and irregular atrial rhythms. In addition, the role of dual AV nodal pathway wavefronts in the generation of multimodal ventricular response patterns during AF has been evaluated. The presented model can help in understanding some of the intriguing AV node mechanisms and should be considered as a step forward in the studies of AV nodal conduction.*

## 1. Introduction

The Atrio-ventricular (AV) node is a small region of the heart that governs the relation between atrial and ventricular activations. During normal sinus rhythm a relatively slow conduction along the AV node causes a delay between atrial and ventricular activations and allows an efficient pumping of blood. This reduced conduction velocity is adjusted according to the atrial rate. This behavior is usually expressed by the so-called conduction curve. However, the behavior of the AV node under certain pathological conditions is complex and not well understood. During atrial tachyarrhythmias such as atrial flutter (AFL) or atrial fibrillation (AF) the time between two atrial activations is shorter than the refractory period of AV nodal cells. Consequently, the AV node works as a filter, blocking some atrial activations and limiting the number of ventricular beats. The way in which this natural filter works, and how it could be used to perform efficient ventricular rate control therapies, remains beyond the scope of the simple conduction curve.

One of the more intriguing properties of the AV conduction is the so-called dual pathway AV node

electrophysiology. This term is used in reference to two different wavefronts that propagate in tandem from the atria to the His bundle [1], one with a shorter effective refractory period (ERP) and another with a longer ERP (i.e. slow and fast pathways respectively, from now SP and FP). Nowadays, the role that FP and SP play in the conduction from the atria to the His bundle under AFL and AF still remains debatable.

By analyzing novel recording techniques, we have developed and tested a functional mathematical model of the atrioventricular node that includes dual pathway physiology. In this study the model has been detailed, validated and used to explain some of unclear phenomena related to AV nodal conduction. Specifically, the model has been used to elucidate the role of dual AV nodal pathway and their interaction in the generation of multimodal ventricular response patterns during AF. The existence of multimodal ventricular response patterns has been used in the literature as an indirect identification of dual AV nodal physiology [2]. However, as we previously demonstrated [3], the presence of short and long His to His (HH) intervals may be due mainly to different AV nodal conduction patterns (2:1, 3:1, 4:1, etc.) rather than FP or SP conductions.

## 2. Methods

**In-vitro Experiments.** Experiments were performed on 5 New Zealand White rabbits. Atrial-AVN preparations were instrumented as described previously [1].  $A_1A_2A_3$  protocol was used to calculate the relation of an AV nodal conduction time with preceding AA intervals and AV conduction times (Fig. 1A). Briefly, all preparations were first paced at a basic cycle length ( $A_1A_1$  interval) of 300 ms, followed by an extrastimulus  $A_2$  introduced with at least three different coupling intervals ( $A_1A_2$ ) (i.e. 300, 200, 150 and 130). In addition to the identification of the conduction curve, regular and irregular AA interval series were applied to each node. These segments were used to evaluate the response of both pathways after blocked stimuli.

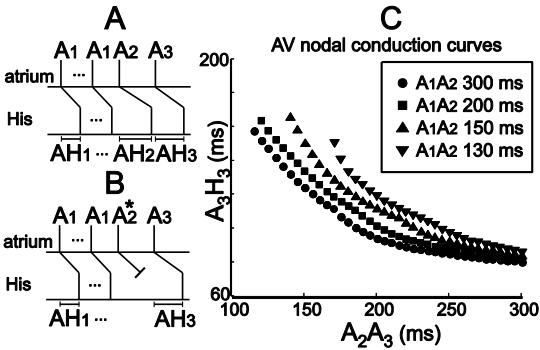


Figure 1. Schematic presentation of atrial and ventricular activation periods and atrioventricular conduction times. Panel A:  $A_1A_2A_3$  stimulation protocol without blocked beats. Panel B: conduction with a blocked atrial activation ( $A_2^*$ ). Panel C: AV nodal conduction curves.

We have used the His-electrogram alternance to assign each conducted beat observed in the rabbit heart experiments to the corresponding AV nodal pathway during programmed pacing, fast atrial rates, or AF. The phenomenon of His-electrogram alternance has been previously described and validated as a reliable index of dual pathway electrophysiology [1]. Specifically, when bipolar recordings are obtained from the inferior His bundle domain, the FP is associated with low-His amplitudes, and pronounced amplitude increase heralds the transition to SP conduction.

**Mathematical Model of an AV Nodal Pathway.** The mathematical model used in this study was presented elsewhere [4]. Briefly, the model described below is used for description of either the FP or the SP with constants specific for each of them. The following expression represents the test conduction time  $A_3H_3$  as a function of the test atrial coupling interval  $A_2A_3$  and the preceding conduction time  $A_2H_2$  (see Fig. 1):

$$A_3H_3 = AH_{\min} + \beta \exp(- (A_2A_3 - A_2H_2) / \tau_{\text{rec}}) \quad (1)$$

where  $AH_{\min}$  is the minimum observed time for an atrial activation to reach the His bundle;  $\tau_{\text{rec}}$  is AV nodal recovery period, which is related to the effective refractory period and  $\beta$  is a modulating factor. The  $\tau_{\text{rec}}$  and  $\beta$  factors were modeled by the following expressions:

$$\tau_{\text{rec}} = \gamma_1 + (A_2H_2 / \gamma_2)^{\gamma_3} \quad (2)$$

$$\beta = \lambda_1 \cdot A_2H_2^2 + \lambda_2 \cdot A_2H_2 + \lambda_3 \quad (3)$$

where  $\gamma_x$  and  $\lambda_x$  are pathway dependent constants.

**Incorporation in the Model of “Concealed” Conduction.** Eq. 1-3 are used as a first estimate of the conduction time for an atrial stimulus through a single AV nodal pathway. However, if the estimated conduction time is longer than a physiological maximum conduction time ( $AH_{\max}$ ), then the pathway is considered blocked. When an atrial stimulus fails to be conducted it is marked  $A_2^*$  (Fig. 1B). Its effect on the test beat  $A_3$  depends on the degree of penetration (concealment) of the  $A_2^*$  beat into

the pathway. Specifically, if the propagation wavefront initiated by  $A_2^*$  is blocked near the atrial (proximal) side of the pathway, its effect on the subsequent conduction time  $A_3H_3$  is lesser than if  $A_2^*$  has been blocked distally. In the model, the degree of  $A_2^*$  penetration is computed by using eq. 1-3, where the activation time  $A_2H_2$  is replaced by a “virtual” conduction time  $A_2^*H_2$ :

$$A_2H_2 \rightarrow A_2^*H_2 = c_1 - c_2 \cdot \exp(- A_1A_2^* / c_3) \quad (4)$$

where  $c_x$  are constants and  $A_1A_2^*$  is the coupling interval for the blocked beat  $A_2^*$  (Fig. 1.B). The term “virtual” indicates that, in fact, there is no  $H_2$  electrogram since  $A_2^*$  is a blocked beat.

**Description of the Dual Pathway Structure.** For each rabbit, both FP and SP AV nodal conduction were modeled using eq. 1-4 with constants fitted for each pathway. In this manner, two different  $A_3H_3$  conduction time functions were computed:  $A_3H_3^{\text{FP}}$  and  $A_3H_3^{\text{SP}}$ . As illustrated in Fig. 2, for modeling purposes we used a simple Y-shaped structure to represent the SP and FP starting at the atrium and converging into a “final common pathway” that reaches the bundle of His. The dominant pathway is the pathway with a shorter conduction time for each atrial beat. Depending on the atrial coupling intervals sequence  $A_1A_2A_3$ , the leading wavefront can be the FP (Fig. 2A,D), or the SP (Fig. 2B,C).

After a complete block of the AV node, the conduction pattern in the subsequent beat would depend on the degree of penetration of each wavefront in the corresponding pathway, as modeled by eq. 4. Accordingly, any of the scenarios shown in Fig. 2 A-E may be possible after a blocked beat.

Accuracy of the computed AV conduction times and the dominant pathway for each conducted beat was established by comparison with the animal experiments performed, since His electrograms with high-amplitudes indicate SP conduction, whereas low-His amplitudes are associated with FP conduction.

**Role of the Dual AV Nodal Physiology in the Ventricular Response Pattern during AF.** In order to clarify the role of dual AV nodal pathway physiology in the ventricular response pattern, different experiments were developed by using the presented AV node model and a database of realistic AA interval series generated synthetically.

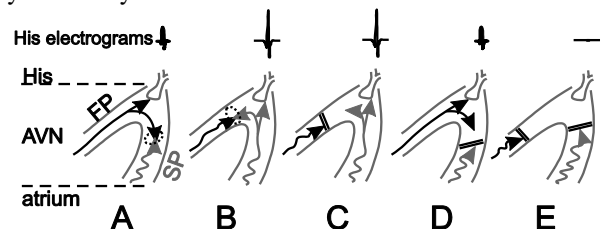


Figure 2. Illustration of different conduction interaction scenarios between fast and slow pathway propagations. Black arrows indicate fast pathway (FP) whereas gray arrows indicate slow pathway (SP) wavefront.

Specifically, realistic AA intervals series were generated by means the methodology presented elsewhere [5]. Briefly, realistic AA interval series were synthesized by first generating a random series with a desired Probability Density Function and then filtering it to force a given autocorrelation function. We have used a Type IV Pearson distribution which allows for varying mean, standard deviation, skewness and kurtosis independently.

AA interval series with different statistical moments were applied to the mathematical model of each rabbit: 1) by using both FP and SP, 2) by using only the FP and 3) by using only the FP.

### 3. Results

**Validation of the Model in Predicting Wenckebach Periodicity.** In Fig. 3A an example of regular atrial pacing is illustrated. In this case, a 5:4 Wenckebach behavior is present (i.e. four out of five atrial activations are conducted and one is blocked). Importantly, as indicated by the amplitudes of the recorded His electrograms, the 1st atrial stimulus after AV block was conducted via the FP (low-His) whereas the 2nd, 3rd and 4th atrial stimulus were conducted via the SP wavefront (high-His). By applying the same atrial pacing series to the model, both the utilized pathway and the AV nodal times were faithfully reproduced.

An average of  $17 \pm 3$  Wenckebach recordings were obtained in each rabbit experiment with a constant-rate atrial pacing with atrial coupling intervals between  $158 \pm 22$  and  $134 \pm 19$ ms. When the same AA interval series were applied to each corresponding AV node model, the correct AV node pathway used in a particular beat was predicted 100% of times, and the root mean square errors of the calculated conduction times via the FP and SP were  $9 \pm 5$ ms and  $14 \pm 9$ ms, respectively.

**Validation of the Model in Atrial Fibrillation.** In Fig. 3B, the participation of AV nodal dual pathways during an episode of AF-like atrial stimulation is illustrated. The His-electrogram alternance indicate that during irregular AA intervals some beats propagated via the FP (low-His) while others utilized the SP (high-His).

Similar percentage of FP and SP conduction during AF was found in 4 of the 5 cases, and only in one case we observed almost-exclusive SP conduction. Table 1 summarizes mean values of sensitivity and specificity of the mathematical model in the prediction of the AV node response for a series of 200 random AA interval series.

Table 1. Accuracy of model predictability for presence of FP and SP conduction during atrial fibrillation.

	N	Specificity	Sensitivity
FP conduction	$57 \pm 21$	$96 \pm 2\%$	$89 \pm 6\%$
SP conduction	$89 \pm 15$	$93 \pm 3\%$	$88 \pm 5\%$
Block conduction	$54 \pm 9$	$93 \pm 3\%$	$91 \pm 9\%$

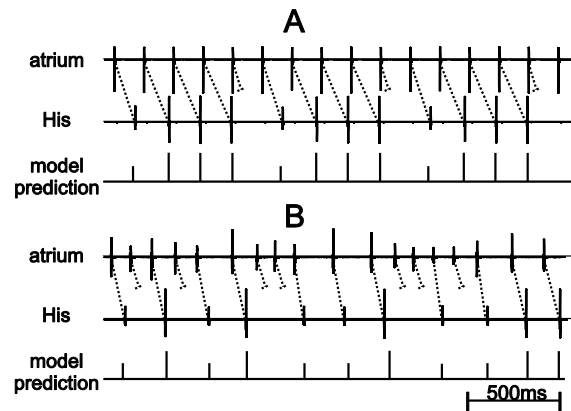


Figure 3. Panel A, schematic depiction of atrial and His electrograms recorded during regular atrial pacing intervals in an intact AV node. Panel B, atrial and His electrograms during AF-like stimulation rates.

**Multimodal HH interval Histograms: Role of the Dual AV Nodal Physiology.** In Fig. 4, the four possible scenarios resulting from the stimulation of AV node mathematical models with different AA interval series are illustrated.

In the first scenario (panels 1A to 1D) an example for rabbit 4 is illustrated. The intact AV node presented a unimodal histogram although both FP and SP conduction were present. The mean AA interval in this case was 110ms and the most probable HH interval was around 220ms which may represent a predominant 2:1 conduction pattern. When a simulated ablation of the SP (panel 1C) or the FP (panel 1D) was produced, no significant differences were observed in the ventricular response pattern since unimodal histograms were present.

In the second scenario (panels 2A to 2D) an example for rabbit 5 is shown. Again, the intact AV node presented a unimodal histogram. In this specific case the mean AA interval was 100ms and the most probable HH interval was around 200ms confirming the presence of a 2:1 dominant pattern. Notice how, after ablation of the SP, the ventricular response pattern changed to a bimodal histogram although only the FP was available. In this case both the 2:1 and the 3:1 atrioventricular conduction pattern were present. Similar behavior was achieved after the ablation of the FP. Here, although only the SP was available a bimodal histogram was found.

In the third scenario (panels 3A to 3D), an example for rabbit 2 is illustrated. A bimodal HH histogram was present with the intact node. In this specific case, the mean AA interval was 105ms and most probable HH interval were around 210ms and 315ms confirming the presence of 2:1 and 3:1 AV conduction patterns. As it can be observed in panel 3B, both FP and SP conduction were present and both contribute to the short (2:1) and long (3:1) HH distributions. After the simulated ablation of the SP or FP a bimodal HH histogram remained although only one pathway conduction was available.

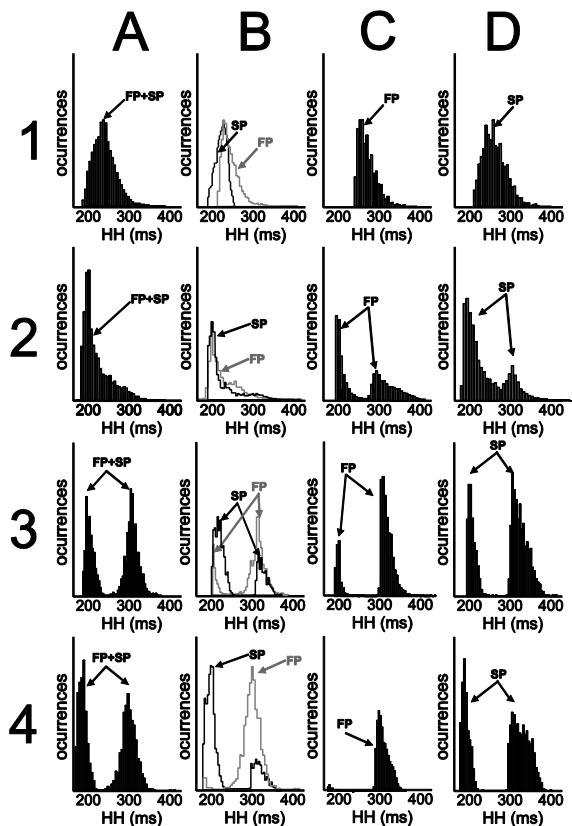


Figure 4. Four examples of HH interval histograms during basal conductions (A), during basal conductions but differentiating FP and SP conductions (B), after a simulated SP ablation (C) and after a simulated FP ablation (D). (See text for more details)

In the fourth scenario (panels 4A to 4D), a second example for rabbit 2 is depicted. The only difference with that depicted in panel 3 was the mean atrial rate (e.g. mean AA was reduced from 105ms to 100 ms). In this case, again a bimodal HH histogram was present with the intact node. However, in this experiment FP conductions were mainly responsible for the long HH distributions (3:1) whereas SP conductions were mainly responsible for the short HH distribution (2:1). The ablation of the SP produced an apparently unimodal HH histogram with only FP conductions with mainly a 3:1 conduction pattern. Notice that a little number of 2:1 conducted beats were also present. Nevertheless, ablation of the FP did not modify the bimodal HH histogram pattern and both short and long HH distributions were present.

#### 4. Discussion and conclusion

In this study we have developed and presented a novel functional model of the AV node that for the first time includes the dual pathway AV node physiology based on experimental data. The inclusion of fast pathway (FP) and slow pathway (SP) conduction properties not only

provided an excellent fit to the experimental data base, but also helped to elucidate complex and still poorly understood peculiarities of conduction through the AV node during arrhythmias.

The role of dual AV nodal physiology in the ventricular response pattern has been evaluated. It has been demonstrated that the presence of bimodal HH interval histograms should not be used as an unequivocal index for the presence of two active AV nodal pathways. We have shown that a unimodal HH histogram does not necessarily imply the presence of a single pathway since an intact node with two active pathways can produce this ventricular response pattern. In added, our results demonstrate that a multimodal ventricular response pattern can be obtained when only one AV nodal pathway is active.

Our mathematical model is derived from the rabbit heart, has several limitations, and should be applied carefully to the study of human AV conduction. Data from electrophysiological studies in humans are needed in order to improve and validate the model for clinical applications. However, the presented model can help in understanding some of the intriguing AV node mechanisms and should be considered as a step forward in the studies of AV nodal conduction.

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