Insights Into Atrioventricular Nodal Function From Patients Displaying Dual Conduction Properties Interactive and Orthogonal Pathways

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Background—There is a significant variability observed in the conduction properties of the atrioventricular node. In a subset of hearts, impulse transmission tends to fall into two distinct conduction regions, termed the slow and fast pathway, and a further subset are capable of dual conduction of a single input stimulus, termed double firing.

Methods and Results—In this article, we closely characterize two distinct responses in patients with double firing properties of the atrioventricular node, separating these into discrete types: those with slow and fast pathway interaction and interdependence (interactive), and those with independent pathway properties (orthogonal). We use novel mathematical techniques to evaluate the relative decrement and unique properties of conduction during the overlapping slow and fast pathway conduction zones.

Conclusions—Our analysis demonstrates two distinct patterns of pathway conduction in double firing patients, termed interactive and orthogonal. We show parallel overlapping segments of slow and fast pathway decremental conduction curves in interactive pathways, with no such findings with orthogonal conduction. These findings suggest anatomic correlates of pathway conduction, with interactive pathways likely having a common distal segment and orthogonal pathways able to independently activate downstream structures. (Circ Arrhythm Electrophysiol. 2013;6:364-370.)

Key Words: arrhythmia ■ atrioventricular node ■ dual pathways ■ electrophysiology ■ modeling

The normal atrioventricular (AV) node is able to conduct electric impulses over a wide range of input periods. The inverse relationship between input period and conduction time is known as decremental conduction. Quite often, these parameters fall into readily distinguishable ranges with various plateaus between regions, empirically determined for ranges of normal patients. Subsequent characterization of conduction using narrow-spaced recording and mapping catheters has shown that the distinct regions of conduction properties are likely related to the physical location or macroscopic pattern of electric conduction within the AV nodal structure itself.1

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In many patients, distinct regions of the AV conduction curve are exaggerated into distinct patterns denoted as the slow and fast regions of conduction. Anatomic correlation suggests that slow conduction involves impulse transmission to the compact AV node from regions inferior to the coronary sinus or through transitional cells (posterior input), whereas fast regions involve direct input to the AV node from septal and left-sided inputs. These are supported by animal models,2 theoretical modeling,3 and anatomic1,4 testing in humans. There seems to be wide variability to this general rule, and there is likely substantial overlap of conduction input ranges in the normal heart leading to a continuous conduction curve in most hearts. In other patients, when sudden refractory periods of a nodal input is reached, there is a distinct jump, or relative discontinuity, in conduction parameters.5 In fewer hearts still under certain conditions, there is capability for conduction of two ventricular impulses from each atrial depolarization, termed double firing, presumably from simultaneous conduction down a fast and slow AV nodal system. These theories are confirmed by response to ablation.6,7

Patients with double firing offer a unique opportunity to study properties of the AV node and the interaction between various inputs into the node. In this article, novel techniques of characterization of nodal input pathways, and interactions between these, are performed in two patients presenting to a single hospital.

Methods

Two patients with suspected and subsequently confirmed diagnosis of double firing were studied in the electrophysiology laboratory at University of Pittsburgh Medical Center Shadyside Hospital. All exhibited spontaneous episodic 1:2 tachycardia under baseline conditions, with minimal difference between all conducted QRS complexes on surface electrocardiogram recording.

During electrophysiological study, standard quadripolar recording catheters were placed in the right ventricular apex, His bundle, and high right atrial positions. A decapolar catheter was placed into the coronary sinus. Spontaneous recording of A1A1 intervals and A1H1, A1H2 (for double firing), and A1H (single conduction) were...
performed for 120 s. All measurements were obtained at high paper speed (400 mm/s) giving a recording pixel resolution of 1 ms. Measurements of the H2A2 interval were calculated by difference.

After characterization of the double firing, slow pathway (SP) ablation was performed in a standard anatomically based fashion in both patients. Both patients had unremarkable coronary sinus anatomy, and application of 50 W of energy between the area of the coronary sinus ostium and tricuspid valve, at the base of the triangle of Koch, with a 4-mm nonirrigated catheter resulted in junctional ectopy followed by quiescence. Subsequent testing showed elimination of all observed double firing observations and SP conduction, removing any ambiguity to diagnosis.8

**Figure 1.** Direct recording and putative interaction mechanisms of interactive and orthogonal pathways, with definition of intervals as measured for study. The correlated intervals for Figures 3 and 4 are displayed along with a schematic of conduction in the interactive pathway, with fast pathway block. FP indicates fast pathway; HRA, high right atrium; and SP, slow pathway.
Results

Intracardiac and surface tracing for patients 1 and 2 are shown in Figure 1. Patient 1 exhibited continuous baseline interactions of the fast pathway (FPs) and SPs, which prevented obtaining isolated refractory periods for the individual pathways. Any attempts at regularization of nodal input via delivery of S1 impulses to the atria are met by progressive retrograde interaction of FP by SP, or vice versa, that gives constant varying ventricular response behavior at slow cycle lengths. The interaction between the SPs and FPs is shown schematically in Figure 1 below the interactive pathway electrograms.

At faster atrial drive cycle length, apparent effective refractory period (ERP) of the FP is reached. However, again because of progressive interaction of the now concealed FP via the SP, immediate Wenckebach behavior of the SP is reached with occasional transmission of impulses via the FP during stimulation that occurred when the SP was refractory and FP was able to conduct.

Straightforward analysis of the atrium to His timing (AH) values observed is shown in Figure 2, which demonstrates the interaction described. The paired dual conduction points are widely spaced apart, whereas single conduction points are generally in an intermediate AH region. However, single conduction via a relatively pure slow or fast conduction pathway is also visualized.

For patient 2, there was minimal interaction between FP and SP at spontaneous cycle lengths. As seen in Figure 2B, the AH values do not display any intermediate values with a large separation between fast and slow conduction. ERP values may be determined by standard methods.

Because of the inability to normalize the nodal input for decrement characterization caused by constant interaction of the nodal pathways, an alternate method of characterizing decrement is formulated. To characterize the relationship between any commonality of nodal decrement between the two pathways in the double firing patient, A1H1 versus A1H2 for the dual firing
beats were plotted for all dual firing beats. These occur at differing relative refractory states of the pathways because of the demonstrated pathway interaction, but the normalization state (A1A1) of any common input to the node should be relatively preserved because of the absence of true atrial echoes to reset the sinus pacemaker. This result is shown in Figure 3 (black circles), along with a linear regression trendline. This slope was 1.06 with high correlation value of $R^2=0.94$. For the orthogonal pathway also graphed in Figure 3 (red squares), correlation is markedly reduced during double fire, with slope 2.6 and $R^2=0.65$. An alternative derivation of this graph result and interpretation of these findings is found in the Discussion section.

To investigate and characterize any relationship between the retrograde input into a specific AV nodal pathway and subsequent single conduction (non dual conduction), a surrogate of AV nodal input ($A1H_{x-1}$) was plotted against A1H1. In this plot, $A1H_{x-1}$ is the H-A time from the previously doubly conducted His to the next sinus atrial beat. This is related to the proximity of the previous SP activation to the next singly conducted impulse, presumably conducted over a heavily decrementing FP. This plot is shown in Figure 4. In the case of an interactive dual pathway (Figure 4A), there is correlation between the additive inverse of the A-H2 interval of the previous beat (-A1H2) and the A-H1 interval (A2H1) of subsequent beat, with $R^2=0.65$. For the orthogonal pathway as shown in Figure 4B, there is no significant correlation $R^2=0.02$.

**Discussion**

Double firing requires two impulses exiting the AV nodal structure with a period longer than the effective refractory period of activations of the His bundle and all distal structures. There remains some debate regarding the precise method that the SPs and FPs input or merge to form the compact AV node, and the extent of existence of common structures, after the merge, that display decremental properties. This study shows two distinct patterns of relation between FP and SP conduction, viz, interactive, where the pathways display a correlation of decrement, or orthogonal, where activation of one pathway does not interact with another pathway. The term orthogonal is borrowed from similar meanings in the fields of mathematics, statistics, engineering, and computer science for independent or perpendicular entities that, when combined, may span the realm of output for a system. Orthogonal pathways are separate (ie, do not interact or project onto each other via retrograde activation or suppression).

Figure 3 demonstrates a property of dual nodal conduction pathways that is neither immediately obvious nor exists by necessity. Standard nodal conduction characterization is performed by conditioning the AV node with regular input at a fixed atrial cycle length followed by a premature atrial stimulus, with subsequent measurement of the A2H2 (output from premature stimulus) against A1A2 (additive inverse of prematurity of A2 stimulus). These graphs typically show a sloped relation of the output and input, often with a relatively sharp discontinuity of regions, assigned as a slow and fast conduction pathway. When a critical coupling interval (A1A2) is reached, the effective refractory period of the faster pathway is reached, and conduction continues over the SP, which has a longer ERP. Conduction may also occur via an anatomically longer pathway or via more distal structures that are protected by proximal decrement, giving an effectively longer ERP. This phenomenon is responsible for various gap phenomenon conduction patterns under conditions of proximal decrement.

In patient 1, with spontaneous activation or pacing of the atria at any cycle length, the interplay of FP and SP activation prevents standard determination of A1A2/A2H2 graphs. This is shown in Figure 2A, where the presence of the second firing (via SP) leads to Wenckebach behavior in the FP, resulting in an intermediate appearing AH singly conducted beat after every double firing. This may be because of the effective rapid stimulation (twice the atrial input frequency) of the ventricle on common distal decremental structures, or another interplay between the retrograde penetration or effects of the SP on the FP and vice versa, or sudden ability to conduct via a third/intermediate pathway. To obtain the AHx relation as a function of atrial stimulation (AA), another approach may be used.

For typical A2H2 versus A1A2 graphs, the continuous function derivative (slope of tangent line) would be given by:

$$\text{slope(slow)} = \frac{\partial(A2H2\text{slow})}{\partial(A1A2)} \quad (1)$$

and similarly,

$$\text{slope(fast)} = \frac{\partial(A2H2\text{fast})}{\partial(A1A2)} \quad (2)$$

The ratio between these is given by:

$$\frac{\text{slope(slow)}}{\text{slope(fast)}} = \frac{\partial(A2H2\text{slow})}{\partial(A2H2\text{fast})} \quad (3)$$

and a plot of $A2H_{\text{slow}}$ versus $A2H_{\text{fast}}$ is what is shown in Figure 3. Thus, this graph shows us the relative ratio of the slopes of...
a typical decremental plot, for an overlapping portion of the extended conduction curves, shown in Figure 5. Please note that the notation of A1H2 or A2H2 is arbitrary given the canceling out of the A1A2 terms, as above. There was no specific driving train and prematurity (A1A2) required to reach this result, plotted over all observed results, and thus all encountered values of A1A2.

For standard measurement of nodal properties, a conditioning stimulus is essential to obtaining valid results, with standard A1A1 premature train given over several seconds. However, in the above equations, the A1A2 (premature stimulus) is continually variable, but we are comparing the overall response of the nodal output at any given A1A2 (each has paired measurement of SP and FP output), with all measurements are taken simultaneously, when both pathways are firing. What does the slope of the graph in Figure 3 say about the AV node? The slope is near unity, meaning that the slope of the A1Hx versus A1A2 for both SPs and FPs are identical (ie, they respond identically to increasing degree

Figure 4. Correlation between prior slow pathway conduction time (-A1H2 interval) and subsequent single conduction (AH) for spontaneous episodes of single conduction in patient 1 (interactive pathways; 4A) and 2 (orthogonal pathways; 4B). In both graphs -A1H2 (slow pathway conduction time of prior beat) is on x axis, and A2H1 (subsequent beat fastest transmitted impulse) is graphed (could be fast or intermediate in nature. Correlation coefficient is displayed on graph.
of prematurity over the observed range). The overlapping segments, if able to be plotted on a single plot of A2H2 versus A1A2, would thus be parallel (identical slope) with a fixed separation, over a relatively wide range. Note that the slope of the individual graphs would not have to be zero, as outlined in Figure 5, with overlapping segment shown with the arrow.

Further characterization of the FP and SP interdependence is presented in Figure 4, where the node is tested for decremental properties of the subsequent beat conduction by correlation with the stimulation from the previous opposite pathway (ie, if the FP conduction for single impulse conduction time is correlated with the additive inverse of previous SP conduction time). Thus, if the SP has an influence on the FP decrement through any sort of interaction, there will be a tighter correlation for truly independent pathways. Here, we see evidence of this with a much higher correlation coefficient for interactive pathways in Figure 4A than orthogonal pathways of Figure 4B, with no correlation observed.

Taken together, these findings are novel supportive evidence for either identical subsequent decremental properties after the pathway separation or common use of a lower pathway of decremental fibers in patients with interactive pathways. Interestingly, this observation is perfectly compatible with both longitudinal dissociation theories of AV nodal function, in addition to separate inputs into a lower common pathway. In our observations, interactive pathways have a lower common pathway giving identical decremental properties, consistent with the slope of unity in Figure 3.

It is unlikely that there would be two separate decremental pathways that could have identical and fixed decrement over a wide input range. In orthogonal pathways, there is no observation of evidence of a lower common pathway, with each pathway able to independently activate the ventricle, as schematized in Figure 6.

There are several assumptions that are included with this model. The first is that there is no significant common nodal conditioning that occurs over the time frame observed (ie, autonomic state remains the same), which is likely over a period of 2 minutes, and any changes in this would likely affect both pathways. However, it should be clearly noted that our analysis in Equations 1 to 3 does not require that the A1A2 input cycle remain constant; indeed, there was marked ventriculophasic variability of the A1A2 intervals during dual fire phenomena as there were 0, 1, or 2 QRS complexes for each atrial depolarization. This variability also enhanced the range of comparison of the FP and SP slope comparison, as shown in Equation 3. The presence of a third pathway cannot be excluded in the case of interactive pathways that is active only when pathways 1 and 2 are not active (Figure 1A). This third pathway may have been damaged or eliminated because of the physical proximity to the SP. Finally, we only have 2 patients here to prototype two distinct response patterns possible. The fraction of patients displaying each type of response has yet to be determined.
Conclusion

In patients exhibiting dual nodal conduction properties with double firing, some patients have the presence of electrophysiological interaction between the pathways, termed interactive pathways, whereas others display largely independent activation of the ventricle, termed orthogonal pathways. The interacting pathways are likely because of retrograde penetration, and these display evidence of parallel electrophysiological properties strongly supporting the presence of common pathway segments, most likely after the individual pathways join before activation of the His bundle and downstream structures. There seems to be variability in the length of common segments, and those with orthogonal pathways do not seem to have significant commonality. It is straightforward to postulate anatomic correlates consistent with this model, with presence of the lower common pathway of decremental conduction tissue, as conjectured in some forms of AV nodal reentry, in the interactive double firing patients, and absence in those displaying orthogonal properties.

Disclosures

None.

CLINICAL PERSPECTIVE

Several variants of atrial nodal conduction parameters are observed in patients, from a continuous decremental pattern to patterns of discrete regions of conduction, named slow and fast pathways, and a subset of patients is capable of simultaneous conduction down these pathways. Here, we characterize distinct subtypes of dual nodal conduction based on mathematical analysis of conduction properties and tie these to anatomic correlates.

References
