Integrated rate-dependent and dual pathway AV nodal functions: principles and assessment framework

Jacques Billette and Rafik Tadros
Département de physiologie, Faculté de médecine, Université de Montréal, Montreal, Quebec, Canada
Submitted 2 July 2013; accepted in final form 6 November 2013

Billette J, Tadros R. Integrated rate-dependent and dual pathway AV nodal functions: principles and assessment framework. Am J Physiol Heart Circ Physiol 306: H173–H183, 2014. First published November 8, 2013; doi:10.1152/ajpheart.00516.2013.—The atrioventricular (AV) node generates a delay between atrial and His bundle activation that helps optimize ventricular filling and blood pumping. The AV node also has rate-dependent conduction and refractory properties accounting for the filtering of atrial impulses during supraventricular tachyarrhythmias. The optimization of this filtering to control the ventricular rate constitutes a cornerstone of atrial fibrillation therapy (3). Another consistent feature of the normal AV node is its built-in fast pathway (FP) and slow pathway (SP) (29, 36, 45, 50, 60, 73). In some human hearts, SP and FP interplay to result in a clinical arrhythmia known as AV nodal reentrant tachycardia, the most common form of paroxysmal supraventricular tachycardia that can now be successfully cured by ablation therapy (24, 34, 59, 61). These properties are obviously sensitive to autonomic tone (54–57), itself modulated by conditions such as rest, exercise, pregnancy, stress, diseases, drugs, etc. However, the basic AV nodal physiology and its assessment tools remain debated. Their understanding is the primary goal of this review.

The understanding of AV nodal function remains indeed challenging. Zipes borrowed a famous Churchill statement to aphoristically refer to the AV node as “a riddle wrapped in a mystery inside an enigma” (76). Data characteristics and interpretation from functional studies remain particularly confounding despite progress made with mapping, immunohistochemistry, and imaging techniques (18, 23, 38, 42, 69). One problem concerns discrepant changes in classical indexes of AV nodal refractoriness, effective refractory period (ERPN) and functional refractory period (FRPN), which are defined further below. Another puzzling issue concerns the absence of a definite relationship between AV nodal conduction and refractory properties (65), in contrast to their presumed common involvement in atrial impulse filtering. Moreover, while the preceding recovery time is the primary determinant of AV nodal conduction time, its assessment with the preceding atrial cycle length or His-atrial interval yields different data when assessing rate-induced changes in AV nodal function. The same AV nodal responses to a given protocol, i.e., in the absence of a differing functional state, yield different data that support different conclusions depending upon the chosen re-

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determined and thus are all included in its functional definition. Conduction times from which its properties are extension, compact node, and lower nodal bundle) that together contribute to the AV nodal function. The His bundle and coronary sinus ostium provide its atrial and lower (ventricular) sides of the triangle correspond to the atrioventricular (AV) nodal function.

**AV Nodal Preparation Landmarks and Sensing**

The data supporting the proposed framework of AV nodal function were obtained from the classical rabbit heart preparation (27). This preparation exhibits AV nodal properties analogous to those documented in human hearts (5, 62), allows for a direct access to AV nodal inputs and output, and undergoes no extrinsic autonomic and humoral modulations (22). It results from the opening of the right atrium and ventricle and removal of most of the left atrium, left ventricle, and right ventricle i.e., is composed of the right atrium and AV junction (Fig. 1A). The preserved right atrium maintains an atrial activation pattern similar to in situ physiology. The AV node occupies Koch’s triangle (Fig. 1B). The upper (atrial) and lower (ventricular) sides of the triangle correspond to the tendon of Todaro and tricuspid valve insertion, respectively. The His bundle and coronary sinus ostium provide its anterosuperior apex and posteroinferior base, respectively. The AV node contains substructures (transitional zone, posterior extension, compact node, and lower nodal bundle) that together contribute to AV nodal function.

**Fig. 1. Assessment approaches of rabbit atrioventricular (AV) nodal function. A: AV node preparation with right atrium and upper portion of right ventricle (box). B: open preparation with anatomic landmarks, pacing site, and recording sites (●). C: AV node as a black box with an atrial input (A) and a His bundle exit (H). D: atrial and His bundle recording obtained during an S1S2 protocol designed to control the basic (BCL, A1A1) and test (TCL, A1A2) cycle length. E: atrial and His bundle recording obtained during an S1S2S3 protocol designed to independently control the basic (BCL, A1A1), pretest (PTCL, A1A2) and test (TCL, A1A3) cycle length. SN, sinus node; AVN, AV node; RA, right atrium; LA, left atrium; RV, right ventricle; LV, left ventricle; SVC, superior vena cava; IVC, inferior vena cava; CS, coronary sinus; UA, upper atrium; CT, crista terminalis; IAS, interatrial septum; TT, tendon of Todaro; CN, compact node; PNE, posterior nodal extension; LNB, lower nodal bundle; TV, tricuspid valve; HIS, His bundle.**
assessment. However, atrial input characteristics may vary during arrhythmias such as atrial fibrillation and thereby affect resulting measurements (21). The AV nodal conduction times illustrated in this review arose from upper atrial pacing and were measured from crista terminalis to His bundle unipolar signals (Fig. 1B).

**AV Nodal Function as Assessed with S1S2 Protocols**

The S1S2 protocol (also called the premature or extrastimulus protocol) is widely used to assess AV nodal function in humans but also in experimental studies. This protocol involves a fixed number of constant basic S1S1 cycles followed by a test S1S2 premature cycle. The 1 and 2 subscripts mark basic and test events, respectively. An example of the resulting basic (BCL, A1A1) and test (TCL, A1A2) cycle length events is illustrated in Fig. 1D. This pacing sequence is repeated while maintaining S1S1 constant and progressively reducing S1S2 (Fig. 2A) until an S2 beat initiates an atrial response but no His bundle activation i.e., results in an AV nodal block. The constant S1S1 allows for each test beat to be assessed in a virtually constant steady state, a postulate that can be assessed from the pretest conduction time (A1H1) i.e., the conduction time at the beat that precedes the test beat (Fig. 2B). A recovery curve representing the recovery property can be constructed by plotting each test AV nodal conduction time (A2H2) against the corresponding A1A2 (Fig. 2B). The curve typically shows an exponential-like A2H2 increase with a flat and a steep portion in long and short A1A2 ranges, respectively. Notably, the recovery time that is here assessed from A1A2 constitutes the primary determinant of A2H2; it increased A2H2 by up to 100 ms in the data in Fig. 2B. The longest A1A2 that does not induce a His bundle response yields ERPN. The shortest H1H2 yields FRPN. While ERPN increases with basic rates (14, 16, 70), FRPN shortens (13, 14, 16, 20, 25, 51), so that the significance of these changes remains confounding.

The dependence of A2H2 on the preceding cycle length is similarly expressed at all BCL (41, 54, 66). However, a short BCL (Fig. 2C) shifted the recovery curve upward and rightward compared with the control BCL (Fig. 2, D vs. B). Two factors contribute to these shifts. One factor is the fatigue property that increases nodal conduction time with the magnitude and duration of the fast rate (11, 40, 41, 52). Fatigue develops rapidly during the first minute of a fast rate and has usually reached a steady state after 5 min (11, 54). Mean maximum fatigue measured in the flat portion of the curve increases A2H2 by up to 12 ms in rabbit and dog hearts (11, 20, 41, 54). Although fatigue remains to be selectively characterized in humans, it is expected to be analogous to that of other species (62). The second factor is the prolongation of A1H1 that results in a delay in the distal nodal cell activation and thereby recovery. An atrial activation with the same A1A2 will thus be more premature when A1H1 is increased and thus results in a prolonged A3H2. In the illustrated example (Fig. 2D), A1H1 increased by 29 ms compared with control. Importantly, a single short cycle can result in a similar A1H1 prolongation that in turns prolongs A3H2 at all A1A2. Hence, fatigue and A1H1 effects ought to be sorted out. The short BCL increased ERPN by 25 ms but decreased FRPN by 10 ms (Fig. 2D), a typical conflicting result leaving unanswered the question of whether refractoriness is then prolonged or curtailed.

Lewis and Master (41) promptly recognized the necessity to sort out fatigue and A1H1 effects. They proposed using the
electrocardiographic RP interval rather than the PP interval to assess the AV nodal recovery time. This approach as well as the His atrial interval assesses the AV nodal recovery time independently from A1H1. However, this approach underestimates the recovery time in the proximal portion of the AV node proportionally to the A1H1 increase (19, 39, 47, 53). Another means to limit the impact of A1H1 increases on A2H2 has been the insertion of a control cycle length between the last BCL and TCL (9, 11). The long cycle allows for the return of A1H1 to a value that differs from control only by fatigue effect, i.e., by a 12-ms average. The resulting recovery curve is then more uniformly shifted upward (11, 66), i.e., primarily reflects fatigue effects.

Another property called facilitation contributes to BCL-induced changes in the recovery curve. The AV node conducts more rapidly than at control an impulse introduced with a short cycle length when the cycle length preceding the TCL is also short (41). This phenomenon develops after a single short cycle and dissipates after a single long cycle (6). Although obvious as a leftward curve shift when the recovery time is assessed from the preceding H1A2, facilitation is more difficult to identify when recovery is assessed from A1A2. On this basis, the very existence of AV nodal facilitation has been questioned (19, 47). The true nature of facilitation is further obscured by the fact that it shortens FRPN and prolongs ERPN (10).

In brief, the S1S2 protocol is widely used and supports the identification of the recovery and fatigue properties but nevertheless suffers from limitations that confound the interpretation of conduction and refractory data. These limitations particularly arise from the effects of changing pretest conduction time on test beat events.

**Rate-Dependent AV Nodal Function as Assessed with S1S2S3 Protocols**

S1S2S3 protocols. The effects of increased pretest conduction time can be sorted out from recovery, facilitation, and fatigue properties with the use of S1S2S3 protocols (64–67). S1, S2, and S3 mark the basic, pretest, and test stimulus, respectively. The same subscripts apply to resulting atrial (A) and His bundle (H) responses (Fig. 1). A 2 subscript here identifies a pretest event, while a 3 subscript identifies a test event. This protocol allows for the independent variation of the basic (BCL, A1A1), pretest (PTCL, A1A2), and test (TCL, A2A3) cycle lengths. In our laboratory, we tested with a different S1S2S3 protocol each of 30 paired combinations from 5 BCL and 6 PTCL (64–67). In five protocols, BCL and PTCL were identical, thereby reproducing conditions similar to those prevailing during standard S1S2 protocols performed at different basic rates where BCL and PTCL do not differ and are not distinguished. Thus our S1S2S3 protocols allow for the sorting out of BCL and PTCL effects including some analogous to those resulting from S1S2 protocols.

Four examples of S1S2S3 protocols are displayed as S1S1, S1S2, and S2S3 data points in Fig. 3. They include the control protocol and protocols that induced maximal facilitation, fatigue, and combined facilitation and fatigue effects. The control protocol involves equal constant 360-ms S1S1 and S1S2 and progressively shorter S2S3 (Fig. 3A). The selective maximal facilitation effect was obtained while S1S1 was maintained at its control value and S1S2 was shortened to 135 ms before each S2S3 (Fig. 3B). The steady-state fatigue effect was determined after a 5-min 180-ms S1S1 constant rhythm. The testing se-

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**Fig. 3.** S1S1, S1S2, and S2S3 data points from the 4 S1S2S3 protocols used to characterize rate-dependent AV nodal function in 1 preparation. A: control S1S2S3 protocol in which S1S1 and S1S2 are equal and constant at 360 ms during S2S3 testing of the recovery property. B: selective facilitation S1S2S3 protocol. S1S1 remains at 360 ms, while S1S2 is shortened to a constant 135-ms value. C: selective fatigue S1S2S3 protocol. S1S1 is shortened to a constant 180-ms value while S1S2 is returned to its control 360-ms value before each S2S3 to dissipate facilitatory effects associated with the short S1S1. D: combined facilitation and fatigue S1S2S3 protocol. S1S1 is shortened to a constant 180-ms value and S1S2 to 135 ms.
sequence (Fig. 3C) included one 360-ms S1S2 that returned A2H2 close to its control value and dissipated facilitation before the S2S3 test. The combined maximal facilitation and fatigue effect was determined with a stimulation sequence made up of a 180-ms S1S1, a 135-ms S1S2, and a variable S2S3 (Fig. 3D).

**Independent effects of BCL and PTCL on AV nodal recovery curve.** The recovery curves (A3H3 vs. A2A3) resulting from the above four S1S2S3 protocols are displayed in Fig. 4A. Importantly, the shape of the recovery curve only slightly varies with BCL and/or PTCL. However, both BCL and PTCL shortenings induce rightward and upward shifts of the recovery curve compared with the control. Maximal shifts occurred under combined BCL and PTCL shortenings (open squares in Fig. 4A). Notably, even the facilitation protocol that involves a single short cycle, i.e., could not induce any fatigue, shifted the recovery curve rightward and upward in the short A2A3 range as if affected by fatigue (open circles in Fig. 4A). Our studies established that the degree of rightward shift of any recovery curve on the x-axis as assessed at constant 130-ms A3H3 (dashed line in Fig. 4A) linearly depends on the A2H2 increase regardless of its BCL and/or PTCL origin (66). Interestingly, Climent et al. (15) characterized AV nodal function with S1S2S3 protocols equivalent to our PTCL-induced facilitation protocols and found that A2H2 is a critical for a successful prediction of A3H3 values. However, the A2H2-induced rightward shift was not self-evident at longest A2A3 in Fig. 4A. This difficulty arose from the fact that the first tested S2S3 (Fig. 3) and thereby A2A3 (Fig. 4A) were identical in different protocols.

![Graphs of recovery curves](image_url)

**Fig. 4. Effects of A2H2 increases on recovery curves.** A: A3H3 vs. A2A3 recovery curves observed under control, facilitation, fatigue, and combined facilitation and fatigue protocols of Fig. 3. B: calculated recovery curves obtained by adding a constant A2H2-related increase to all control A2A3 values and a constant fatigue-related increase to all control A3H3 values. Note similarity between curves in A and B. C: corrected recovery curves obtained by subtracting the increase in A2H2 (ΔA2H2) from A2A3 of curves displayed in A. D: observed recovery curves when the A1H1 displayed in A were plotted against corresponding observed H2A3. Note reduction of rightward shift and correspondence of curve shape in D despite distinct x-axes. The horizontal dashed line overlapping the recovery curves in A marks a constant 130-ms A1H1 and thereby the rightward shift undergone by the recovery curves. Reproduced from *Journal of Cardiovascular Electrophysiology* (65) with permission.
circles and squares in Fig. 4C). The second way to free fatigue and facilitation data from A2H2 increases consists in plotting A3H3 against H2A3 (Fig. 4D). Despite their distinct x-axes, the observed H2A3-based curve (Fig. 4D) and corrected recovery curve (Fig. 4C) yield virtually identical fatigue and facilitation effects. Because it is constructed from direct measurements rather than calculations, the H2A3-based curve may perhaps offer a net advantage. Yet, because A2A3 is an easily accessible variable in clinical settings, it may be practical to use it with the appropriate A2H2-based correction. In the absence of His bundle recordings, the ventricular signal may be used as a surrogate. Thus different recovery indexes yield identical AV nodal recovery, facilitation, and fatigue properties provided that A2H2 changes are taken into account in their assessment (66). In our understanding, these two formats of A2H2-free changes in recovery curves equally and adequately reflect genuine changes in rate-dependent AV nodal conduction.

Effects of pretest conduction time on refractory periods. Increases in A2H2 also affected ERPN measurements. Because ERPN is the longest A2A3 that does not induce a His bundle response and corresponds to an A2H2 + H2A3 sum (Fig. 1E), it undergoes the same A2H2-induced rightward shift as the whole recovery curve and thus is accordingly prolonged (65). This occurs regardless of whether the A2H2 prolongation is caused by BCL and/or PTCL shortenings. FRPN (shortest H2A3 or sum of H2A3 + A3H3) is by definition insensitive to A2H2-induced rightward shift of the recovery curve. The consideration of A2H2 effects on ERPN allowed us to establish a new relationship between ERPN and FRPN. As expected from classical discordant effects of basic rate on refractory indexes, our raw ERPN and FRPN data did not correlate whatsoever (Fig. 5A). Conversely, FRPN values closely correlated with ERPN values corrected for A2H2 increases as studied with 30 protocols in each of 6 preparations (Fig. 5B). ERPN and FRPN similarly increased with BCL and decreased with PTCL effects (64). This also applied to identical BCL and PTCL shortenings as occurring during increased basic rates of the standard S1S2 protocol. Although FRPN and corrected ERPN occur at different H2A3 values, these values varied in parallel under BCL and PTCL effects (unpublished observations). In brief, BCL- and PTCL-induced changes in ERPN and FRPN are closely related when associated changes in pretest conduction time are taken into account in their assessment. Specifically, BCL shortening prolongs refractoriness, while PTCL shortening curtails it.

Physiology and Assessment of Transient AV Nodal Responses

The above data from S1S2S3 protocols were obtained in steady-state conditions as assessed from A1H1 (66) and/or A2H2 (65) low variability. The question then arises of whether rules established from steady-state responses apply to transient responses. Do recovery, fatigue, and facilitation properties established in steady-state conditions also account for transient rate-dependent AV nodal function? There is evidence that this is effectively the case, although the contribution from the three AV nodal properties then varies over time. For instance, these properties account for transient responses to linear ramp increase and decrease in cycle length inducing hysteresis in AV nodal conduction time (12, 75). These properties also quantitatively account for a variety of other rate-induced AV nodal responses including Wenckebach cycles (54, 62, 68, 74). A recent study also provides analytical and modeling data supporting their involvement in human supraventricular tachyarrhythmias (46). Factors contributing to the wide variety of transient AV nodal responses can be appreciated from the following three examples.

S1S2S3 protocols. An example of the effects of transient changes in functional state during S1S2S3 protocols on recovery curves is illustrated in Fig. 6. The control S1S2S3 protocol was performed at steady-state constant 400-ms BCL and PTCL (filled circles in Fig. 6). A second S1S2S3 protocol was performed at constantly shortened 175-ms BCL (8 basic beats) and an identical 175-ms PTCL while testing the first S3 at the beginning of the protocol and rapidly decrementing the TCL...
Conversely to that seen during steady-state conditions (Fig. 4), fatigue and A2H2 effects then concurrently developed during the protocol and accordingly prolonged A3H3 of beats tested with increasingly shorter A2A3 (Fig. 6). A third S1S2S3 protocol also was performed at the constant 175-ms BCL and PTCL combination, but the BCL number was increased to 20 and TCL was decremented more slowly (filled squares in Fig. 6). These two changes increased the time at which any A2A3 occurred after the beginning of the protocol so that A3H3 were longer over the entire A2A3 range compared with the protocol with eight basic beats (Fig. 6). Associated ERPN and FRPN values (not shown) also varied with functional state. Thus transient changes in the functional state during S1S2S3 protocols markedly affect the resulting recovery curve and thereby the assessment of rate-dependent AV nodal conduction and refractory properties.

**Incremental pacing protocol.** This widely used protocol involves stepwise decreases in atrial cycle length and aims at establishing WCL, i.e., the cycle length at which AV nodal blocks of the Wenckebach type develop. Some insight into factors controlling these AV nodal responses is provided by comparing them with those from S1S2S3 protocols in the same preparation. The AH obtained at the end of each constant pacing sequence of an incremental protocol (20-ms shortening every 40th beat) are plotted against atrial cycle length (Fig. 7A). The resulting curve is displayed together with two S1S2S3-based steady-state curves, one obtained at control and one at identical short BCL and PTCL in one preparation. The AH obtained at the end of each constant pacing sequence of an incremental protocol (20-ms shortening every 40th beat) are plotted against atrial cycle length (Fig. 7A). The resulting curve is displayed together with two S1S2S3-based steady-state curves, one obtained at control and one at identical short BCL and PTCL in one preparation. The AH from the incremental protocol first overlaps the control curve and then increases to reach values close to those from the incremental pacing curve arising from S1S2S3 protocol.

**Constant fast rate.** Another particularly intriguing example of transient AV nodal responses was obtained at a constant pacing interval and fatigue level (Fig. 8). In this experiment (67), the preparation was subjected to a constant short 170-ms SS for 5 min during which a long 350-ms SS (slightly shorter than spontaneous atrial cycle length) was intercalated after every 30th short SS. The AH from the long cycle length rapidly increased during the first minute of pacing and reached a steady state after ~2 min, then reflecting a constant fatigue level. However, the constant SS and constant fatigue did not prevent a beat-to-beat increase in AH from occurring in a repetitive consistent manner after each long SS. This likely occurred because each AH increase curtailed the AV nodal recovery
time at the next beat that further increased the AH and so on until the long cycle occurred and reset the system. Anyhow, these transient responses were highly organized and reproducible, suggesting that they obey very specific rules.

The above three examples of transient AV nodal responses suggest that, despite their diversity, they share a common origin in the recovery, fatigue, and facilitation properties as for other rate-induced responses. However, further studies with specifically designed protocols will be necessary for the quantification of the role of each of these properties in these responses.

Dual Pathway Origin of Rate-Dependent AV Nodal Function

Growing evidence supports the concept that the rate-dependent properties of SP and FP together account for those of the overall AV node. Although they share some common features, these dual pathways must be distinguished from those of patients suffering from AV nodal reentrant tachycardia. The typical signature of dual pathways in these patients is a broken recovery curve, i.e., a sudden >50-ms “jump” of AV nodal conduction time when conduction shifts from FP to SP under a 10-ms S1S2 decrease (61). In these patients, FP conduction prevails over long and intermediate cycle length ranges but, because of its long refractory period, fails over the short cycle length range. Because of its short refractory period, the SP can conduct over this range and initiate a retrograde activation of recovered FP, thereby causing a reentrant atrial beat. Self-perpetuated atrial reentry results in an AV nodal reentrant tachycardia. This arrhythmia can now be cured with ablation therapy of either pathway (24, 31, 32, 35). However, easiest access, greater success rate, and lower complication incidence have established the SP as a preferred target.

Normal dual pathways are observed in human, rabbit, porcine, and canine hearts (4, 26, 28, 30, 36, 43, 49, 50, 60, 71) and show FP and SP conduction ranges and refractory periods analogous to those of patients suffering from an AV nodal reentrant tachycardia. However, the normal dual pathways yield a smoother recovery curve at the transition from FP to SP than that of these patients (36, 50, 60). They can nonetheless be interrupted with ablation lesions (4, 26, 36, 43, 44, 60, 71). The typical target of a SP ablation is the crista terminalis input to the AV node, while the target of FP ablation is the interatrial septum input. The dimension of resulting successful lesions typically reaches several millimeters.

SP conduction can also be interrupted in rabbit heart preparations with microlesions applied to the posterior extension (Fig. 9, inset) as located from the timing and shape of endocardial surface unipolar electrograms (36, 43, 44, 50, 60). Such a SP ablation typically prevents conduction over the short H2A3 range and prolongs ERPN during a control S1S2S3 protocol (Fig. 9). The SP ablation similarly affects the recovery curve resulting from the facilitation protocol (open circles and squares in Fig. 9). Because of the amputated steep rising portion of the curve, no significant level of facilitation can then be detected. Conversely, the close overlap of AH values obtained before and after SP ablation in the long and intermediate H2H3 ranges indicates that baseline conduction through the FP remains virtually unchanged after SP ablation in both protocols.

Microlesions applied between transitional and compact node tissues (Fig. 10, inset) consistently interrupt FP (44, 60). FP ablation prolongs conduction time over the long and intermediate H2A3 ranges by a 16-ms average during the control

![Diagram](http://ajpheart.physiology.org/)

**Fig. 8.** Transient AV nodal responses observed during a constant cycle length and fatigue level. The preparation was driven with short 170-ms SS close to the upper 1:1 conduction limit for 5 min (ON) and then returned to control 350-ms SS for 5 min (OFF). A 350-ms SS was inserted every 30th ON response. Resulting lower AH data points reflect fatigue level. Upper data points reflect AH increases during constant short SS sequences. Note that when fatigue has reached a steady-state level after 2 min of constant short SS, each long SS still initiates a new graded AH increase. Such increases are displayed on an expanded timescale at top right. During OFF responses, AH progressively returns toward its control value (bottom right). Reproduced from *Journal of Cardiovascular Electrophysiology* (67) with permission.

**Fig. 9.** Recovery curves obtained in response to the control (BCL 352 ms, PTCL 352 ms) and facilitation (BCL 350 ms, PTCL 110 ms) protocols performed before and after a slow pathway (SP) ablation with microlesions targeted at the posterior extension (inset) in 1 preparation. Note that the SP ablation amputates the left steep rising portion of curve in both protocols while leaving virtually unchanged their flat portion, which shows a nearly perfect overlap of data points.
protocol but minimally affects conduction over the short H2A3 range (filled circles and squares in Fig. 10). ERPN is not significantly affected, either (44, 60). Conduction then occurs through SP over all H2A3 ranges including the long range. The facilitation protocol induces a typical tilting of the curve to the left both before and after the FP ablation (Fig. 10), indicating that FP ablation does not affect the facilitation property. The effects of SP and FP ablation on the fatigue property remain to be determined. However, the fact that a short BCL similarly prolongs conduction over the entire H2A3 range (Fig. 4D) suggests that SP and FP are equally sensitive to fatigue.

The His electrogram alternans also supports the dual pathway origin of the recovery property (72). Bipolar recordings taken from the inferior portion of the lower nodal bundle during a premature protocol show a small-amplitude signal during the FP conduction portion of the recovery curve and a severalfold increased signal during SP conduction. Importantly, this approach provides a tool to monitor dual pathway function during arrhythmias such as Wenckebach cycles and atrial fibrillation (71, 73). It may become a useful tool to further explore the relationship between rate-dependent and dual pathway function.

In brief, the recovery property is contributed to by the FP and SP in the long and short H2A3 ranges, respectively. A posterior extension ablation prevents SP conduction. After a FP ablation, SP conduction occurs over the entire cycle length range. The absence of facilitation after SP ablation and its persistence after FP ablation indicate that facilitation mainly depends on SP. Fatigue would equally prolong FP and SP conduction time, and thus would accordingly prolong the overall AV nodal conduction time. These results suggest that the normal recovery, facilitation, and fatigue properties of FP and SP account for those of the overall normal AV node.

Clinical Implications

The proposed functional framework provides an upgraded conceptual background for the design and interpretation of studies on rate-dependent and dual pathway function. An improved knowledge of AV nodal rate-dependent properties may help understanding of conduction phenomena observed in electrophysiological studies during atrial arrhythmia or programmed atrial pacing protocols. An integrated understanding of rate-dependent properties and dual pathway physiology may also assist in developing and interpreting pacing maneuvers performed for diagnostic purposes in patients with supraventricular tachyarrhythmias (33, 58, 63). The integrated understanding of rate-dependent and dual pathway physiology is critical to interpretation of AV nodal behavior before and after ablation in patients suffering from AV nodal reentrant tachycardia. An obvious first step toward the application of our framework in humans will be a direct demonstration that it applies to normal and perturbed human heart function.

The S1S2S3 protocols can be applied to assess specific aspects of AV nodal function, but, obviously, the 30 protocols used to establish the characteristics of the recovery, facilitation, and fatigue properties (64–67) need not be repeated in all studies. For instance, the overall profile of conduction and refractory variation limits can be established with four protocols (Figs. 3 and 4). Whatever the protocol combination used, the recovery time will remain the primary determinant of AV nodal function and its accurate assessment will require the consideration of pretest effects. This is made necessary by the fact that any increase in A2H2 regardless of its BCL or PTCL interacts with the refractory variation limits. The disparity problem between ERPN and FRPN in their capacity to reflect AV nodal refractoriness can also be solved by correcting ERPN for A2H2 increases (Fig. 5).

Another consideration that may have clinical implications is steady-state assessment from changes in AV nodal conduction time at basic beats. Transient changes in functional state can have profound effects and result in a wide variety of challenging responses even in the absence of autonomic modulations (Figs. 6, 7, and 8). Determination of stability level may help to interpret responses occurring over time. For instance, some levels of autonomic modulations may render the determination of small-dimension facilitation and fatigue irrelevant in a clinical setting. Protocols could then be limited to those targeting recovery-dependent changes in AV nodal function.

Conclusions

Our review supports a comprehensive functional framework and assessment scheme of integrated rate-dependent and dual pathway AV nodal function. It supports the concept that individual rate-dependent properties of FP and SP account for those of the overall AV node. The backbone of the rate-dependent behavior of the AV node is provided by its recovery, fatigue, and facilitation properties that can be rigorously and independently assessed with S1S2S3 protocols performed in steady-state conditions and allowing the assessment of pretest effects. These properties also provide the backbone for transient rate-induced AV
nodal responses, but the sorting out of their roles is then more complicated, yet feasible. Our assessment scheme may also apply to the characterization of autonomic and pharmacological modulation of the AV node, but this will require specifically designed studies. Although largely based on data from experimental studies, the proposed framework may well apply to the human AV node. In brief, the rate-dependent and dual pathway properties of the AV node can be integrated within a common functional framework the contribution of which to individual responses can be quantitatively determined with properly designed protocols and analytic tools.

ACKNOWLEDGMENTS

The authors thank Lise Plamondon for her contribution to figure artwork.

GRANTS

This work was supported by the Quebec Heart and Stroke Foundation.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS

Author contributions: J.B. conception and design of research; J.B. and R.T. analyzed data; J.B. and R.T. interpreted results of experiments; J.B. prepared figures; J.B. and R.T. edited and revised manuscript; J.B. and R.T. approved final version of manuscript; R.T. performed experiments.

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