Selective Functional Characteristics of Rate-Induced Fatigue in Rabbit Atrioventricular Node

Jacques Billette, Robert Métayer, and Marie St-Vincent

The slowly developing rate-induced prolongation in atrioventricular nodal conduction time, termed "fatigue," was selectively studied using specifically designed stimulation protocols in isolated rabbit heart preparations. A nodal recovery curve (A,H2 versus H,A1 intervals; nodal conduction time of each premature beat plotted against corresponding recovery time) was obtained before and after a stable and nearly maximum fatigue had been reached by driving the atrium for 5 minutes at a fast rate close to the upper limit of 1:1 nodal conduction. The fatigue uniformly prolonged all A,H2 intervals (12.3 ± 1.3 msec) and systematically increased the minimum H,A1 interval at which complete nodal block occurred (24.8 ± 4.0 msec) (p < 0.01, n = 6). To study the rate and time dependence of fatigue, nodal conduction times were obtained during three rapid 5-minute pacings corresponding to 50%, 75%, and 100% shortening of the pacing interval in the 1:1 nodal conduction range. The respective maximum fatigue-induced increases in conduction time were 5.4 ± 1.8, 9.0 ± 2.7, and 12.5 ± 2.1 msec (p < 0.01, n = 6). However, the pacing interval had no significant effect on the time required to reach either 50% (17.1 ± 3.5 seconds) or 90% (92.6 ± 15.4 seconds) of the fatigue observed after 5 minutes of fast rate. At the termination of any rapid stimulation, the fatigue effect dissipated with a time course that was inverse but symmetrical to that of its induction. These findings support the existence of an independent, slow, nodal memory process by which the conduction time changes according to past events with a long time constant. (Circulation Research 1988;62:790-799)

Three intrinsic properties contribute to rate-induced changes in the transit time of the cardiac impulse through the atrioventricular node. The main contribution comes from the slow recovery of nodal cell excitability, which causes nodal conduction time to increase exponentially with prematurity of the incoming impulse. The second property, termed "fatigue," contributes the prolongation of the nodal conduction time, which develops slowly during a fast rate and dissipates slowly after its termination. The third property, facilitation, acts with a short time constant to curtail the nodal conduction time of premature beats introduced with brief recovery times, thereby opposing the effects of the other two properties. However, the definition of the selective characteristics and respective contributions of these properties in the various rate-induced nodal responses is complicated by intricate interactions and remains debated.

For instance, intricate interactions between these properties occur during a pacing-induced constant fast atrial rate. At the beginning of the fast rate, the node enters a positive feedback loop in which the increase in conduction time due to the shortened recovery time (RP or His-atrial interval) curtails proportionally the recovery time for the next beat, the conduction time of which is then further prolonged, and so on, until a steady-state conduction or a second-degree nodal block occurs. Although this phenomenon accounts for the largest fraction of the rate-induced increase in nodal conduction time, the fatigue that develops with the duration of the fast rate adds a direct contribution to the prolongation of the conduction time and an indirect contribution by way of the consequently shortened recovery time. Despite these prolongations, the conduction times observed during a constant fast rate are shorter than expected from recovery time and fatigue, thus showing a net facilitatory effect.

Similar complications are encountered in the determination of the rate-induced changes in the nodal conduction time of atrial premature beats. When the nodal conduction times of premature beats tested at different basic rates are compared for identical RP or His-atrial intervals, fatigue-induced prolongations of the conduction times are small and are visible only in the long RP or His-atrial interval range. Fatigue is, therefore, obviously underestimated in the short RP or His-atrial interval range. When the same conduction times are compared for identical atrial coupling intervals, a fatigue effect similar to that seen on the RP or His-atrial interval plotting is observed in the long atrial interval range, while a marked prolongation of conduction times is found in the short atrial interval range. However, to avoid overestimating the contribution of fatigue in this range, this contribution must be dissociated from that of the shortened recovery time caused by the increased conduction time of the basic beats.

In the present study, the rate-induced nodal fatigue was dissociated from concomitant changes in other

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intrinsic factors and was characterized functionally. This was achieved with specifically designed stimulation sequences during which changes in recovery time and facilitation were controlled. The dependence of fatigue on rate, time, and prematurity was studied during both its induction and dissipation. The resulting functional characteristics of fatigue were found to differ in several respects from those previously reported and to apply directly to the interpretation of numerous nodal responses obtained during fast rates.

Materials and Methods

Preparation and Apparatus

The experiments were performed in two groups of six isolated superfused rabbit heart preparations.\(^9\) Group 1 preparations were used to study the effects of fatigue on the nodal conduction time of premature beats. Group 2 preparations were used to study the dynamics of the induction and dissipation of the fatigue effects. Each preparation, which included the right atrium, atrioventricular node area, and part of the interventricular septum,\(^10\) was fixed on a grid mounted in a tissue bath and superfused with oxygenated (95% O\(_2\),5% CO\(_2\)) Tyrode’s solution maintained at 37°C and pH 7.4. A 6-1 volume of the solution was continuously oxygenated and recirculated at 200 ml/min. The millimolar composition of the solution was NaCl 128.2, KCl 4.7, CaCl\(_2\) 2, MgCl\(_2\) 1, NaHCO\(_3\) 25, NaH\(_2\)PO\(_4\) 0.7, and dextrose 11.1. The atrium was driven electrically through a bipolar platinum-iridium stimulating electrode placed on the crista terminalis close to the sinus node. Unipolar silver electrodes were positioned on the sinus node region, on the crista terminalis near the ostium of the coronary sinus, on the nodal margin of the interatrial septum, and on the His-bundle. Electrograms were amplified (model 7P511 amplifiers, Grass Instruments, Quincy, Massachusetts) and simultaneously sent to a monitor, an EMG1600 ink jet-writing polygraph (Siemens-Elema, Solna, Sweden), and a PR-2200 tape recorder (1 ½ ips) (Amplex, Glendale, California). An analog signal of the stimulation pulses, a time code, and a tachogram were also recorded.

The stimulation sequences were generated with a new program implemented on a PDP114A computer (Digital Equipment Corporation, Marlborough, Massachusetts). This program provided greater flexibility than an earlier one\(^11\) in controlling pulse sequence evolution. It also allowed beat-to-beat synchronization of the stimulation pulse with the previous His-bundle complex with a 1-msec precision. Stimulation voltage pulses were twice threshold and had a 2-msec duration.

Stimulation Protocols

To avoid uncontrolled changes in nodal recovery time that may occur in the presence of a constant atrial cycle length,\(^8\) all stimulations were imposed with predefined His-stimulus intervals. Each His-bundle complex was detected, and the next stimulus was given according to the defined His-stimulus interval. Four basic rates, corresponding to 0%, 50%, 75%, and 100% shortening of the His-stimulus interval in the 1:1 nodal conduction range, were used. This range was established at the beginning of each experiment with an incremental pacing during which the His-stimulus interval was decreased at every 20th beat until a second-degree nodal block occurred. The His-stimulus interval was initially reduced by 20 msec and then by 10 msec when the nodal conduction time started to increase rapidly. The 0% basic rate corresponded to the His-stimulus interval that shortens spontaneous atrial cycle length by 30 msec. This rate gave a nearly "basal" nodal conduction time\(^11\) and was used as the control basic rate. Slower rates were not used as this would have required extensive destruction or removal of atrial tissues, which would have perturbed normal inputs to the node. The 100% basic rate corresponded to a His-stimulus interval 30 msec longer than the one that resulted in second-degree nodal block during the incremental pacing. This 30-msec margin was required to maintain 1:1 nodal conduction during the entire duration of fast rates, which lasted 5 minutes or more. The His-stimulus intervals corresponding to one half and three fourths of the 1:1 conduction range defined the remaining two intermediate basic rates.

The sequential patterns of atrial pacing used in the present study are illustrated with vertical bars representing the stimuli (Figure 1). Sequences A–D represent the four periodic premature stimulation protocols used in each Group 1 preparation. The nodal conduction times required to construct the control recovery curve were first obtained with a periodic premature stimulation performed at the 0% basic rate (Figure 1A). To obtain the selective effects of the steady-state fatigue produced by the 100% fast basic rate on the recovery curve, the periodic premature stimulation was repeated (Figure 1B), starting the testing of premature beats only after 5 minutes of fast rate. Moreover, to eliminate the facilitatory effects on premature conduction times,\(^8\) a long His-stimulus interval (L) equal to that used at the control basic rate was introduced (Figure 1B) between the last short basic cycle (S) and the premature cycle (P). During stimulation sequences A and B, 20 basic cycles separated each premature cycle, and premature His-stimulus intervals were varied by 20, 10, and 1 msec in their long, intermediate, and short ranges, respectively.

The stimulation protocols illustrated in Figures 1C and 1D were designed to study the dependence of the fatigue effects as determined with recovery curves on prematurity, pacing time, and beat number in the presence and absence of facilitatory effects, respectively. The induction of fatigue effects was studied by testing a constant premature cycle (CP) introduced with a selected His-stimulus (H\(_S\),S\(_2\)) interval after every 20th beat during the first 5 minutes of a 100% fast basic rate. To study the fatigue effects in the absence and presence of facilitatory effects, a long His-stimulus interval (L) was added (Figure 1C) or omitted (Figure 1D) before the test premature cycle. A long, an intermediate, and a short H\(_S\),S\(_2\) interval corresponding respectively to one cycle of the 0%, 50%, and 100% basic rates were tested.
Data Processing

Interval measurements were carried out off-line with the PDP1134-A computer. Analog signals corresponding to the stimuli and the various electrograms triggered independent waveform generators, the pulses of which were detected by the computer at a sampling rate of 10 kHz/channel. Each trigger was synchronized with the fastest phase of the complex by means of threshold, polarity, and slope detectors. During the analyses, S, SN, CT, IAS, and HIS identified the stimulus, sinus node, crista terminalis, interatrial septum, and His-bundle complexes, respectively. However, for the sake of simplicity, the AH interval refers to the time separating the interatrial septum and the His-bundle complex. The HS interval is the time from the His bundle to the septum complex. Measurements that refer to the crista terminals input are specified in the test. Subscripts 1 and 2 (Figure 1) identify the basic and premature stimuli regardless of their His-stimulus intervals.

FiguRe 1. Pacing protocols. Pulse sequences A–D represent the various periodic premature stimulation (PPS) protocols used in group 1 preparations. Sequence A shows the last of a series of 20 long (L) cycles (0% basic rate) and one premature cycle (P) that were used to establish the control nodal recovery curve. Sequence B, which was used to determine the selective effects of fatigue on the recovery curve, shows the last of a series of 20 short cycles (S) at the 100% fast rate followed by a facilitation-dissipating long cycle and by one premature cycle. Note, as indicated at the right, that the first premature cycle was tested after 5 minutes of short cycles. Sequences C and D were used to study the induction of fatigue effects on premature beats in the presence and absence of facilitatory effects, respectively. Sequence C is identical to sequence B, but the selected constant premature cycle (CP) was tested after every 20 short cycles from the beginning to the end of a 5-minute 100% fast rate. Sequence D differs from sequence C only in the absence of the facilitation-dissipating long cycle. Sequences E and F represent the two types of frequency steps to which Group 2 preparations were subjected to study the time and rate dependence of the induction and dissipation of fatigue. In sequence E, 5 minutes of the 0% basic rate, represented by a long cycle, alternated with 5 minutes of a fast rate, represented by a short cycle. Sequence F was identical to sequence E except for the addition of a facilitation-dissipating long cycle after every 20th short cycle. n. Number of cycles; the 1 and 2 subscripts identify basic and premature stimuli regardless of their His-stimulus interval.
stimulations with predefined His-stimulus intervals. 

Recovery curve. Relation between the premature nodal conduction times (A₂H₂ intervals) obtained during a periodic premature stimulation and the corresponding recovery times (H₁A₂ intervals). The recovery curve obtained at the 0% basic rate reflected exclusively changes in conduction time due to changes in recovery time and was used as the control recovery curve. 

Fatigue. A time-dependent prolongation in nodal conduction time that cumulates during a fast rate and dissipates slowly after its termination.¹⁻³ This slow dissipation accounts for the frequently reported anamnestic retention of a fraction of the prolonged delay beyond the termination of the fast rate.¹⁻⁴,¹⁶⁻¹⁹

Facilitation. A shorter nodal conduction time than expected from the recovery time and the prevailing level of fatigue.² The facilitation is present on the nth beat occurring with a short recovery time when the recovery time of the (n — 1)th beat is also short. Facilitation effect dissipates entirely within one normal cycle.²

Time-dependent effect. One in which time is a necessary variable. Because fatigue invariably requires time to develop during a fast rate and to dissipate afterward, it is time-dependent. However, the prolongations in nodal conduction time, which occur during a fast rate due to the successive shortenings of the nodal recovery time per se, will be found for any number of short cycles achieving the same recovery time and are, therefore, considered to be time-independent or only circumstantially related to time.

Results

Effects of Fatigue on Nodal Recovery Curve

The selective effects of a steady-state fatigue induced by a very fast rate on the nodal conduction time of premature beats were determined in each Group 1 preparation by comparing a control with a fatigue-affected recovery curve (A₂H₂ versus H₁A₂ intervals) on the same graph (Figure 2A). The control curve was obtained with a periodic premature stimulation performed at the 0% basic rate (H₁A₂ interval, 320 ms). The fatigue curve was obtained when the periodic premature stimulation was repeated at steady-state fatigue obtained with 100% fast basic rate imposed with H₁A₂ interval of 90 ms. Note systematic fatigue-induced upward shift of recovery curve and prolongation of the value of H₁A₂ interval at which block occurred from 69 to 102 ms. Panel B depicts three vertical stacks of symbols corresponding to the A₂H₂ interval values obtained in the same preparation when constant H₃S₂ intervals of 320 (right), 180 (center), and 90 msec (left) were tested independently during the first 5 minutes of three identical 100% fast rate episodes. These stacks are superimposed on recovery curves obtained at control and fast basic rates (same as in Panel A). For the three H₃S₂ intervals, the fatigue-induced prolongation of the A₂H₂ intervals, with respect to those of the control recovery curve, started after the first 20 beats of the fast rate (lowest stack value) and stopped increasing at values corresponding to the recovery curve obtained at the 100% basic rate.
of facilitation by the introduction of a facilitation-
dissipating long cycle before each premature cycle (Figure 1B). In these conditions, the rate-induced fatigue prolonged the nodal conduction time of all premature beats, resulting in a systematic upward shift of the recovery curve (Figure 2A). This shift was quite uniform for all A2H2 intervals, increasing only slightly in the very short H, As interval range. The average upward shift was close to 12 msec (see "Induction of Fatigue Effects"). Qualitatively similar observations were made in all six preparations. The rate-induced fatigue also increased systematically the shortest H, A2 interval, which resulted in a conducted A, beat from 60.3 ± 3.7 to 85.2 ± 4.5 msec, p < 0.01. This corresponded to an increase in the minimum A, A2 interval from 109 ± 5.3 to 147 ± 6.8 msec, p < 0.01. Thus, when measured under steady-state conditions, in the absence of facilitation, and for comparable recovery times, a nearly maximum rate-induced fatigue prolonged the nodal conduction time of all premature beats uniformly and caused nodal block to occur at longer coupling intervals.

Induction of Fatigue Effects

The effects of prematurity, pacing time, and beat number on the magnitude of the fatigue-induced prolongation in nodal conduction time of premature beats were studied in each Group 1 preparation with the stimulation sequences illustrated in Figures 1C and 1D. To determine the fatigue-induced changes in conduction time for a given prematurity, a premature beat was introduced with a constant H, S, interval after every 20th basic cycle during the first 5 minutes of a 100% fast rate. Three constant H, S, intervals (long, intermediate, and short) were tested separately in each preparation with (Figure 1C) and without (Figure 1D) a facilitation-dissipating long cycle. The symbols corresponding to the values of the A, H, intervals (Figure 2B) resulting from the premature beats tested with the long (right), intermediate (center), and short (left) H, S, intervals in absence of facilitatory effects formed three independent stacks joining the control and fatigue-shifted recovery curve obtained in the same preparation (Figure 2A). The form and magnitude of these stacks were largely independent of prematurity. The maximum increases in A, H, intervals over values corresponding to the control recovery curve were 10.5 ± 1.9, 12 ± 2.2, and 14.3 ± 2.8 msec (p < 0.001) for the long, intermediate, and short H, S, intervals, respectively; overall mean was 12.3 ± 1.3 msec. In the data obtained without a facilitation-dissipating long cycle (not shown), the respective maximum fatigue-induced prolongations in A, H, intervals were 10.7 ± 1.4, 13 ± 1.7, and 14 ± 1.4 msec (p < 0.001) and did not differ significantly from those obtained with a long cycle. Although small, the greater increase in A, H, intervals seen at shorter H, S, intervals with both stimulation protocols was statistically significant (p < 0.01). However, this small cycle-length–dependent difference may have been produced by an uncontrolled recovery-dependent factor (see "Discussion") rather than by a fatigue effect. Thus, fatigue-induced prolongations of nodal conduction time are largely independent of the prematurity of the considered beat but vary greatly with the duration of the fast rate.

Time and Rate Dependence of Fatigue

The time and rate dependence of fatigue induction and dissipation for the three selected fast rates that corresponded to 50%, 75%, and 100% shortening of the His-stimulus interval in the 1:1 nodal conduction range was studied with two distinct protocols in each Group 2 preparation. In the first protocol (Figure 1E), 5 minutes of the 0% basic rate was alternated with 5 minutes of fast rate until the three fast rates had been tested independently. As the facilitation remains constant for any given fast rate, the induction of fatigue effects was thus obtained in the presence of presumably constant facilitatory effects. The pattern of accommodation of nodal conduction times obtained in one preparation at the onset of the 100% fast rate imposed with a constant His-stimulus interval of 40 msec is shown in Figure 3. At the first beat of the fast rate, the conduction time reached a maximum value. At the second beat, it decreased by 8 msec because of the facilitatory effect induced by the first short cycle. This decrease of the conduction time between the first and second beat was also present but was smaller at the 50% and 75% fast rates. During subsequent beats of the fast rate (Figure 3), there was a slowly developing upward drift of the conduction time caused by the induction of fatigue. These time-dependent prolongations in nodal conduction time occurring between the second and the last beat of each 5-minute fast rate were used to characterize the induction of the fatigue effects in the

![Figure 3. Fatigue-induced accommodation. Changes in nodal conduction time (AH interval) obtained at the onset (first 10 seconds) of a fast rate imposed with a constant His-stimulus interval of 40 msec in a Group 2 preparation are plotted against time. The four control values of AH intervals (41 msec) seen at the left were obtained at the 0% basic rate (HS, interval, 220 msec). At the first beat of the fast rate, the AH interval increased instantaneously to 75 msec. At the second beat, the AH interval decreased to 67 msec and thereafter showed small alternans followed by a slow fatigue-related upward drift. Note the absence of marked beat-to-beat increases in AH interval, such as those usually seen when a similar fast rate is achieved with a constant stimulus interval.](http://circres.ahajournals.org/)

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presence of constant facilitatory effects. Decreases in nodal conduction time that occurred during the ensuing 5-minute slow rates were used to characterize the dynamics of the corresponding dissipation of the fatigue.

These changes were plotted together against time for the three fast rates tested in each preparation (Figure 4). The curves corresponding to the fatigue induction (FI) and dissipation (FD) appear above and below the zero change line, respectively. It may be worth noting that the upper curve (FI-HS 40) comes from the same 5-minute fast rate episode as the curve whose onset is illustrated in Figure 3. The three fatigue-induction curves (Figure 4) show a slow and progressive prolongation of nodal conduction time toward a new plateau value, which is greatest at the fastest rate (FI-HS 40). At the termination of the fast rates (curves below the zero change line), the cumulated prolongations in nodal conduction time dissipate slowly along time courses inverse but largely symmetrical with those of their respective inductions. This dissipation appeared as a progressive shortening in the AH interval toward a plateau value that corresponded to the return to the control value. Qualitatively similar results were obtained in the six preparations. The maximum fatigue reached was 5.4±1.8, 9.0±2.7, and 12.5±2.1 ms for the 50%, 75%, and 100% fast rates, respectively (Table 1). These values differed significantly (p<0.01) from control and among themselves. As expected, the magnitude of the induced and dissipated fatigue did not differ significantly nor was it affected by the input (interatrial septum versus crista terminalis) from which the conduction time was measured (Table 1).

To verify the assumption that the presence of constant facilitatory effects did not affect the above-described fatigue-induced changes in nodal conduction time, the same fast rates were tested with a second frequency-step protocol (Figure 1F), during which a facilitation-dissipating long His-stimulus interval (L) was introduced after every 20th beat during the fast rates. The long His-stimulus interval (identical to that of the control rate) allowed the fatigue effects to be assessed in the absence of facilitatory effects and for an identical recovery time at all rates. The magnitude of the induced and dissipated fatigue (Table 1), as seen on the beat ending the long His-stimulus interval, tended to be slightly smaller than that obtained during fast rates without long cycles. Only the smaller magnitude of the dissipated fatigue was statistically significant (p<0.05). This small difference can be explained by the fact that in the protocol without long cycles, the fatigue was obtained from the changes in the conduction time occurring during short cycles. The slight prematurity dependence of fatigue (Figure 2) caused the fatigue measured on the beat coming after a shorter HA interval to be slightly greater than that seen after the long cycle. Nevertheless, the lack of sizable differences in the fatigue obtained in the presence and absence of facilitatory effects was confirmation that these facilitatory effects neither varied markedly during the fast rates nor affected the absolute magnitude or time course of the fatigue.

Despite the consistent symmetry of the fatigue induction and dissipation curves for the three rates and for both protocols, there were frequent small individual differences among these curves. For instance, the fatigue induction seen (Figure 4) during the first minute at the 100% fast rate (FI-HS 40) progressed less rapidly than the corresponding fatigue dissipation (FD-HS 40), while the reverse was observed at the 50% rate (FI-HS 130 and FD–HS 130). Another observation made on the curves obtained at the 100% fast rate was the presence of alternans, which were seen in one form or another in all six preparations. In the example illustrated in Figure 4, the nodal conduction time alternated increasingly from the second minute to the end of the 100% fast rate (FI-HS 40). Despite the consistent presence of the alternans, their beginning, end, time course, and magnitude were unpredictable in the different experiments. Their functional characteristics could not, therefore, be quantified.

To further characterize the time dependence of fatigue, the times required to reach 50% and 90% of the maximum fatigue-induced prolongations in AH intervals seen at the end of each 5-minute fast rate were determined. The times for the dissipation of 50% and 90% of the fatigue were also determined. The analyses of variance performed on the resulting values showed
that the rate did not significantly affect the mean time required to reach 50% or 90% of the maximum fatigue effect; nor did the rate affect the respective times for 50% and 90% of the dissipation. Therefore, these times were averaged for the various rates (Table 2). Resulting mean values showed that during both the induction and dissipation of the fatigue, 50% of the final change was achieved within the first 20 seconds while an extra minute was necessary to reach 90% of these changes. The time for 50% of the dissipation tended to be slightly shorter than that for 50% of the induction, but this hysteresis was statistically significant only in the data obtained with long cycles. There was no statistically significant difference between the time required for 50% fatigue induction and dissipation in either protocol.

In summary, nodal fatigue 1) develops and dissipates along symmetric slow time courses; 2) can reach different magnitudes that depend strongly on the magnitude and duration of the fast rate; 3) is independent of the input used to measure it; and 4) is not affected in its absolute magnitude by the presence or absence of facilitation.

### Atrial Fatigue

The atrial fatigue produced by the three fast rates tested in Group 2 preparations was also determined from the time-dependent changes in atrial conduction times and was analyzed statistically (Table 1). These changes were obtained for two pathways (the upper atrium to the low interatrial septum and to the low posterior crista terminalis). There was a small but statistically significant (p<0.01) rate- and time-dependent fatigue-induced increase in the atrial conduction time. As expected, the magnitudes of the induced and dissipated atrial fatigue were not significantly different; nor did the presence versus the absence of facilitation (Protocol E versus Protocol F) have any significant effect on the induced or dissipated atrial fatigue. Moreover, the atrial fatigue did not vary significantly with the pathway from which it was examined. Thus, the fast rates induced a small but significant amount of fatigue in both atrial pathways studied.

### Discussion

**Time Constants of Nodal Responses**

The present findings show that the rate-induced fatigue in atrioventricular node occurs with a long time constant. Nodal conduction time can also vary according to prematurity and facilitation, which are also rate related and act with short time constants. The prematurity depends entirely on the preceding recovery time.3,28 The facilitation depends on the preceding and penultimate recovery times.4 The node can, therefore, be influenced by, or remember, past conducted beats according to three independent memories, two fast and one slow; the fast memories are related to changes in the upper atrium; and the slow memory is related and act with short time constants.

### Table 1. Rate-Induced Fatigue Induction and Dissipation in Atrioventricular Node and Atrium in Group 2 Preparations

<table>
<thead>
<tr>
<th>Fast rate</th>
<th>Protocols</th>
<th>Phase</th>
<th>Δ IAS-His (AH interval)</th>
<th>Δ CT-His</th>
<th>Δ UA-IAS</th>
<th>Δ UA-CT</th>
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<tbody>
<tr>
<td>50%</td>
<td>E</td>
<td>FI</td>
<td>5.4 ± 1.8</td>
<td>4.5 ± 2.5</td>
<td>0.9 ± 0.2</td>
<td>1.8 ± 0.9</td>
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<td></td>
<td>F</td>
<td>FI</td>
<td>5.4 ± 1.3</td>
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<td>1.3 ± 0.7</td>
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<td></td>
<td></td>
<td>FD</td>
<td>5.2 ± 1.5</td>
<td>4.5 ± 1.0</td>
<td>0.7 ± 0.1</td>
<td>1.2 ± 0.6</td>
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<td></td>
<td></td>
<td></td>
<td>5.7 ± 1.4</td>
<td>4.8 ± 0.9</td>
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<td>1.4 ± 0.6</td>
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<tr>
<td>75%</td>
<td>E</td>
<td>FI</td>
<td>9.0 ± 2.7</td>
<td>9.2 ± 1.8</td>
<td>2.0 ± 0.7</td>
<td>2.2 ± 0.8</td>
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<tr>
<td></td>
<td>F</td>
<td>FI</td>
<td>8.9 ± 2.0</td>
<td>8.7 ± 1.3</td>
<td>1.8 ± 0.4</td>
<td>2.2 ± 0.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>FD</td>
<td>8.0 ± 2.2</td>
<td>7.9 ± 1.4</td>
<td>1.6 ± 0.5</td>
<td>1.8 ± 0.7</td>
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<td>100%</td>
<td>E</td>
<td>FI</td>
<td>12.5 ± 2.1</td>
<td>11.8 ± 1.5</td>
<td>3.8 ± 1.3</td>
<td>2.5 ± 0.8</td>
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<tr>
<td></td>
<td>F</td>
<td>FI</td>
<td>11.0 ± 1.9</td>
<td>11.0 ± 1.3</td>
<td>2.6 ± 0.7</td>
<td>2.9 ± 1.1</td>
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<tr>
<td></td>
<td></td>
<td>FD</td>
<td>9.9 ± 2.3</td>
<td>10.4 ± 1.6</td>
<td>2.4 ± 0.8</td>
<td>1.9 ± 0.6</td>
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### Table 2. Mean Time Required to Reach 50% and 90% of Final Fatigue Induction and Dissipation in Group 2 Preparations

<table>
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<th>Protocol</th>
<th>Phase</th>
<th>50%</th>
<th>90%</th>
</tr>
</thead>
<tbody>
<tr>
<td>E</td>
<td>FI</td>
<td>17.1 ± 3.5</td>
<td>92.6 ± 15.4</td>
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<td></td>
<td>NS</td>
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<tr>
<td>F</td>
<td>FI</td>
<td>17.7 ± 3.0</td>
<td>83.6 ± 15.0</td>
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<td></td>
<td></td>
<td>14.3 ± 3.0</td>
<td>94.6 ± 12.0</td>
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<td></td>
<td></td>
<td>p&lt;0.05</td>
<td>NS</td>
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<tr>
<td>F</td>
<td>FD</td>
<td>12.8 ± 2.2</td>
<td>84.3 ± 11.4</td>
</tr>
</tbody>
</table>

Values are mean ± SEM in seconds, n = 6. FI, fatigue induction; FD, fatigue dissipation; NS, not statistically significant.
recovery time and facilitation, and the slow memory is related to fatigue effects.

**Dynamic Interactions of Nodal Properties**

During a constant fast atrial rate, variations in the contribution of these memories to the changes in nodal conduction time occur concurrently. At the beginning of the fast rate, there is a progressive recovery-dependent prolongation of the nodal conduction time. Indeed, because the node is made up of a series of sequentially activated cells, any prolongation in nodal conduction time disperses the activation times and ensuing recovery times of the nodal cells, a more or less plate-stack sliding effect. Because such dispersion occurring at the (n – 1)th beat delays increasingly the time for the beginning of activation and recovery of progressively more distal cells, the nth beat introduced with the same atrial interval encounters less recovered nodal tissues and is accordingly delayed; the process continues until a steady-state conduction is reached or until second-degree nodal block occurs. Since a similar prolongation in conduction time can be produced by a single short recovery time (Figure 3), this process is time-independent and can be dissociated from fatigue. As fatigue develops with the duration of the fast rate, it also increases conduction time and shortens recovery time proportionally. Thus, fatigue has both a direct contribution to conduction time and an indirect one via the recovery-dependent process. Moreover, the facilitatory effects tend to counteract the recovery- and fatigue-dependent effects on beats occurring with short recovery times, thus adding to the complexity of the nodal response. Even small differences in the stimulation protocol used to impose the fast atrial rate can cause marked differences in the above dynamic interactions. Nevertheless, the same set of functional rules can be used to explain the resulting different nodal responses. In the present study, this complexity was avoided by controlling recovery time and facilitation level.

**Prematurity Independence of Fatigue**

When measured at steady state, fatigue-induced prolongations of premature nodal conduction times were largely independent of prematurity (Figure 2). Only at short H,A intervals did the prolongation increase slightly. This finding is at variance with some previous studies in which the fatigue-induced prolongation increased with prematurity in the long H,A atrial interval range and was absent in the short one. Two factors contributed to these differences. First, the absence of a preestablished steady state explains the increase of fatigue with the time required to test premature beats, and, second, the presence of facilitation masks the fatigue present at short H,A intervals. In the present study, the preestablished steady-state fatigue prevented its variation during the time required to test the premature beats, while the dissipation of facilitation before each premature beat prevented it from masking the fatigue at short H,A intervals.

The slight prematurity-dependent increase in fatigue observed in the short H,A interval range (Figure 2) may be due to a recovery-dependent effect. Because fatigue prolonged the conduction time of basic beats, the premature beat introduced in the early phase of recovery of last basic beat may have resulted in a greater delay because of a recruiting chain effect. Cells that were not contributing to the recovery-dependent delay increment in the absence of fatigue could be made to do so in presence of fatigue. In other words, a greater number of discrete cell-to-cell recovery-dependent delays could be generated by a premature beat introduced with a short H,A interval when the nodal conduction time was impaired under fatigue effects. This recovery-dependent enhancement of fatigue effects could not be dissociated from true fatigue effects in the present study.

**Symmetric Time Course of Fatigue Induction and Dissipation**

The observed symmetry between the induction and dissipation of fatigue (Figure 4) is in apparent contradiction with previous reports, which showed that the rate-induced nodal delay dissipates almost instantaneously after fast rates of short durations and, in all instances, more rapidly than it develops. This difference can be explained by the fact that in the present study, there were no changes in the recovery time during the fast rates. Thus, only the increase in fatigue contributed to the increase in nodal conduction time occurring after the first beat of the fast rate (Figure 3). During the dissipation of fatigue, changes in recovery time were also prevented. However, the magnitude and time course of the dissipated fatigue were very similar to that reported when fast rates were imposed with constant stimulus intervals. This similarity is due to the fact that on its return to the slow rate, the node was operating in the flat part of the recovery curve where overestimation or underestimation of the recovery time with the preceding atrial or HA interval had little effect on the conduction time.

The origin of the slight hysteresis found between early fatigue induction and dissipation (Table 2) is uncertain. It could be related to directional differences in the mechanism responsible for fatigue. For instance, if an extracellular accumulation of K ions is responsible for fatigue, the effects of the accumulation are likely to differ from those of the dissipation insofar as distinct mechanisms are responsible for these ionic movements. Whatever the reason for the slight hysteresis, it should be remembered that the times required to achieve 90% of fatigue induction and dissipation (Table 2) neither differed significantly nor were affected by the magnitude of the rate.

**Accommodation**

The pattern of accommodation of the nodal conduction time to a sudden change in heart rate can vary substantially with the stimulation pattern used to impose the fast rate. The present study introduces the fatigue-induced accommodation pattern and explains the differences between it and the previously
Mechanisms

Although the present definition of the functional characteristics of nodal fatigue will help to sort out the origin of the changes in conduction time in various types of nodal responses, the specific molecular origin of the fatigue in the node remains to be established. There is evidence that the steady-state rate-induced changes in nodal conduction time are associated with an increased diastolic excitability threshold. The present findings support such an explanation, but the underlying physicochemical mechanism remains unknown. Possible mechanisms include 1) intracellular accumulation of Na+ and/or Ca2+ resulting in slower rate of rise of the upstroke; 2) extracellular accumulation of K+ in membranous clefts; 3) increased intercellular coupling resistance caused by increased intracellular Ca2+; 4) cumulating incomplete recovery from activation; and 5) any combination of the above. The present results cannot be used to discriminate the roles played by these various potential mechanisms.

Implications

The present findings may help to differentiate the fatigue effects on nodal conduction time from those produced by other factors. First, because fatigue develops and dissipates slowly, it can only contribute to slow changes in conduction time. For instance, fatigue cannot contribute more than 1 or 2 msec to changes occurring within 10 consecutive beats. This applies to conduction time changes occurring during sudden rate changes of short duration, Wenckebach cycles, and short episodes of supraventricular tachycardias. Second, during a lasting fast rate allowing for a steady-state fatigue to be reached, the prematurity independence and long time constant of fatigue will cause it to contribute to all conduction times equally, regardless of their length. For instance, fatigue will likely have a constant contribution to all prolonged nodal conduction times observed during lasting Wenckebach cycles and atrial fibrillation. Third, the maximum potential contribution of fatigue is limited. In the present conditions, it averaged 12 msec at the fastest rate and much less at slower rates. Fourth, to be attributed to fatigue, a prolongation in nodal conduction time must have occurred for comparable recovery times and facilitation levels or at least have been corrected for changes in the contributions of these two properties.

The application of the above attributes to the functional characterization of nodal conduction in the in situ heart will obviously require further investigation. The possibility of establishing the selective functional characteristics of nodal fatigue may also justify pharmacological studies, in which drug effects will be more specifically defined and understood. Ultimately, it may be possible to find drugs that selectively affect each of the intrinsic nodal properties.

The present study supports the following conclusions: 1) When studied in conditions of controlled recovery time and facilitation level, fatigue in the atrioventricular node produces a rate- and time-dependent but largely prematurity-independent prolongation of nodal conduction time; 2) induction and dissipation of fatigue follow a symmetric slow time course; 3) fatigue accounts for only a small fraction of the accommodation seen at the onset of a constant fast atrial rate; 4) although facilitation may mask the fatigue effects in particular circumstances, it does not affect the absolute magnitude of fatigue induced by a fast rate; 5) fatigue is unlikely involved in rapid beat-to-beat changes in nodal conduction time; and 6) fatigue is responsible for the so-called slow nodal memory.

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