Role of Positive Feedback in the Atrioventricular Nodal Wenckebach Phenomenon

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ABSTRACT

In the atrioventricular (AV) nodal Wenckebach phenomenon, there is a progressive increase in the P-R interval and a concomitant reduction in the R-P interval. Two series of experiments were conducted on anesthetized dogs to ascertain whether the changes in the P-R interval depended on the associated changes in the R-P interval. In one series of experiments, the atrium was paced at various basic cycle lengths, and a single test cycle was interposed about every 100 beats. When the test cycle was very short, the increase in the P-R interval sometimes exceeded the associated reduction in the R-P interval. During the subsequent basic cycle, although the P-P interval was much greater than it was during the test cycle, there was a further reduction in the R-P interval. When this change in the R-P interval was appreciable, AV conduction failed despite the increase in cycle length. In the second series of experiments, the AV nodal Wenckebach phenomenon was induced by rapid atrial pacing. When the stimulation mode was suddenly altered to maintain a constant R-P interval, the Wenckebach rhythm immediately ceased, although the mean heart rate had not changed significantly. Therefore, it appears that above a critical heart rate a positive feedback loop is established in which an increase in the P-R interval evokes a corresponding decrease in the R-P interval. In turn, the curtailed R-P interval that reflects a less complete recovery of AV nodal excitability elicits a still greater increase in the P-R interval. This cycle continues until an impulse is ultimately blocked. Clamping the R-P interval opens the feedback loop and terminates the arrhythmia.

KEY WORDS anesthetized dogs arrhythmia computer atrioventricular conduction atrioventricular node biological control system cardiac electrophysiology electrocardiogram second-degree heart block

In the atrioventricular (AV) nodal Wenckebach phenomenon, there is a cyclic, progressive increase in the conduction time of the cardiac impulse from the atria to the ventricles with each successive beat. Typically, such changes in conduction time represent alterations in the passage through the AV node, since the intra-atrial and His-ventricular conduction times usually remain constant (1, 2). Periodically, an impulse is blocked in the AV node, and the conduction time of the next conducted beat is minimal. Thereafter, the conduction time again increases progressively, and the cycle is repeated. The electrocardiographic counterparts of these changes in cardiac conduction involve cyclic alterations in the P-R interval, which is an index of AV conduction time. In the Wenckebach phenomenon, the P-R interval increases progressively from beat to beat until an atrial impulse is blocked. The variations in the P-P interval are usually minimal. Therefore, the increments in the P-R interval are associated with decrements in the R-P interval, because P-R + R-P = P-P.

Certain electrocardiographers (3, 4) have interpreted the R-P interval as an index of the recovery of excitability of the AV conduction system. Therefore, a causal relationship has been imputed to the concomitant changes in the P-R and the R-P intervals during the Wenckebach phenomenon. The diminished R-P interval that is associated with the prolonged P-R interval is thought to represent a greater degree of prematurity; hence, it is believed to evoke a still greater P-R interval on the next passage of the cardiac impulse through the AV conduction system. This process continues until an impulse is blocked, and then the cycle is repeated. Such behavior resembles that of a positive feedback system, since a primary change in a variable (e.g., the P-R interval) produces a sequence of events (reflected by a reduction in the R-P interval) which ultimately results in a secondary change in the same direction in the originally perturbed variable (a still greater P-R interval).

There is abundant experimental evidence that certain interventions, notably an increase in heart rate, exert cumulative effects on AV conduction (5–7). Such cumulative influences might...
also account for the progressive changes in the P-R interval in the Wenckebach phenomenon. In 1926, Lewis and Master (5) proposed that the progressive prolongation of the P-R interval during a Wenckebach rhythm reflected “exhaustion of the tissue responsible for the variations in conduction.” Scher and his collaborators (6) postulated that the apparent cumulative effects might be ascribed to progressive ionic shifts, probably an efflux of potassium, within the AV conduction system. Since the P-P interval does not usually change appreciably in the Wenckebach phenomenon, the increasing P-R interval is associated with a commensurate reduction in the R-P interval. However, in this instance the change in the R-P interval is purely coincidental; it is simply a mathematical consequence of the fact that the P-P interval is arbitrarily subdivided into P-R and R-P intervals.

The present experiments were designed to determine whether the AV nodal Wenckebach phenomenon induced by rapid atrial pacing represents a cumulative response of the AV conduction system to such rapid pacing or whether it is a manifestation of a positive feedback system. If the former hypothesis is true, the progressive reduction in the R-P interval during a Wenckebach cycle would merely be an irrelevant observation. If the latter hypothesis is true, each successive reduction in the R-P interval would be responsible for the prolongation of the immediately following P-R interval. The following specific hypotheses were tested: (1) that the R-P interval is an index of the phase of excitability of critical cells in the AV conduction system and, consequently, a determinant of AV conduction time, (2) that the P-P interval also is a determinant of AV conduction time, regardless of the prevailing R-P interval, and (3) that, at a mean P-P interval which would ordinarily evoke the Wenckebach phenomenon, experimental clamping of the R-P interval opens the positive feedback loop and terminates the Wenckebach cycle.

Methods

Experiments were conducted on 23 mongrel dogs anesthetized with morphine sulfate (2 mg/kg, im) followed in 30 minutes by chloralose (75 mg/kg, iv). A tracheal cannula was inserted, and both vagi were transected at the midcervical level. In most experiments, propranolol (1 mg/kg, iv) was administered at least 10 minutes before any experimental observations were made. The purpose of the vagotomy and the administration of propranolol was to avert neurally induced changes in AV conduction during the experiments.

Intermittent positive-pressure respiration was instituted, and the chest was opened at the fourth right intercostal space. Bipolar electrode recording catheters were inserted into the right ventricular cavity and the right atrial appendage. Bipolar stimulating electrodes were applied to the wall of the right atrium in the region of the sinoatrial node. Stimuli were generated by a parallel-logic analog computer (EAI 580).

Arterial blood pressure and atrial and ventricular electrograms were recorded on an eight-channel ink-writing oscillograph (Brush, Mark 200) and on analog magnetic tape (Honeywell model 7600). The atrial and ventricular electrograms also served as inputs to the analog computer and to a digital computer (PDP 12). The analog computer provided a beat-by-beat recording of the P-P, the P-R, and the R-P intervals on the oscillograph throughout the experiment. These same intervals were printed out to the nearest millisecond by the digital computer for selected portions of each experiment. These same digitized data were also stored on magnetic tape.

Essentially two types of experiments were conducted: those related to the effects of premature atrial activations on AV conduction and those in which the postulated positive feedback loop was opened by clamping the R-P interval.

PREMATURE ATRIAL ACTIVATIONS

The first type of experiment was performed on all 23 dogs. Basically, the relationship of the P-R interval to the P-P and the R-P intervals was determined at various pacing frequencies. A given atrial pacing frequency was established. After 2 or 3 minutes, when a steady state had been attained, the P-P interval was changed for 1 beat at a preselected frequency, usually about once every 100 beats. The test P-P intervals were varied over a range from the unpaced interval to an interval that was too brief to be conducted to the ventricles. At each basic frequency, a continuous plot of the P-R interval vs. the preceding R-P interval (to be designated P-R = f₁[P-P, R-P]) was displayed on the oscilloscope screen of the digital computer for the test P-P interval. On the same axes the locus of all points for which R-P = P-P – R-P was plotted, where the P-P interval was the prevailing basic pacing interval. This locus is a straight line with a slope of -1 and with x- and y-intercepts that both equal the pacing interval. The locus of these points is designated R-P = f₂(P-P, P-R) for reasons to be explained below. The two curves, i.e., P-R = f₁(P-P, R-P) and R-P = f₂(P-P, P-R), always intersect at one point; the x- and y-coordinates of this point represent the P-P and the P-R intervals, respectively, at the basic pacing frequency. Near the lower limit of the test P-P intervals which yielded conducted impulses at any given pacing frequency, the test P-P interval was varied by very small increments to achieve a second intersection of the two curves at a point to the left of and above the first point of intersection. This region of the graph was especially important because successful acquisi-
tion of a point on the curve of \( P - R = f(P - P, R - P) \) above the second point of intersection permitted separation of the influences of the P-P and R-P intervals on AV conduction time.

**CLAMPED P-P OR R-P INTERVALS**

After the premature atrial activation experiments had been completed, the atrial pacing frequency in nine dogs was increased in steps until the AV nodal Wenckebach phenomenon supervened. Observations were then made at a constant pacing interval, which represents the clamped P-P mode. By setting a specific push button on the analog computer, the atrial stimulation pattern could then be switched instantly to the clamped R-P mode. In this mode, atrial pacing stimuli were generated by the computer at a fixed interval of \( n \) milliseconds after each R wave. The value of \( n \) was equal to the last R-P interval measured in the clamped P-P mode minus a constant value equal to the interval from the time of atrial stimulation to the beginning of a P wave. Hence, the heart was no longer paced at a constant frequency. Instead, the P-P intervals varied from beat to beat by an amount equal to the concomitant changes in the P-R interval. When the same push button was reset manually, the clamped P-P mode could be reinstated, i.e., stimuli were again delivered to the atrium at the original, fixed P-P interval.

**Results**

**PREMATURE ATRIAL ACTIVATIONS**

The results of a representative experiment in which basic atrial pacing intervals of 300, 400, and 500 msec were used are plotted in Figure 1. The atrial and ventricular electrograms for this experiment during atrial pacing at a P-P interval of 300 msec are shown in Figure 2. Small pacing artifacts appeared before each P wave; they were also evident in the ventricular electrogram. In this experiment, test stimuli of different interstimulus intervals were delivered about every 100 beats, e.g., the test interval was 200 msec in the record shown in Figure 2. Various test intervals were applied while the heart was paced at the basic interval of 300 msec (Fig. 1). The P-R interval increased as the R-P interval decreased. The curve became progressively
steeper from right to left, indicating that, as the R-P interval diminished, a given decrement in the R-P interval evoked a greater increment in the P-R interval.

The left diagonal line in Figure 1 represents the locus of all points for which R-P = 300 - P-R; 300 msec was the pacing interval for the data represented by the solid squares. The curve, P-R = f₁(P-P, R-P), defined by the solid squares and the left diagonal line, R-P = f₂(P-P, P-R), intersect at two points. The lower of these points of intersection represents the steady-state values of the R-P and the P-R intervals during constant pacing at a P-P interval of 300 msec. As indicated by the two paced beats preceding the test interval in Figure 2, the steady-state R-P and P-R intervals were 155 and 145 msec, respectively; these values are the coordinates of the lower point of intersection in Figure 1. All solid squares (Fig. 1) to the right of this point of intersection were obtained from test intervals greater than the pacing interval; all solid squares to the left of the lower point of intersection were obtained from test intervals less than the pacing interval. In this experiment, only one point (encircled solid square, Fig. 1) was obtained above the upper of the two points of intersection; it was produced by a test P-P interval of 200 msec.

Curves representing P-R = f₁(P-P, R-P) at pacing intervals of 400 and 500 msec were obtained in a similar fashion (Fig. 1). The points for all three pacing frequencies fell along approximately the same curve when the R-P interval exceeded 150 msec. Below this value, however, they diverged; as the pacing interval was diminished, the curves shifted to the left. Also, the shorter the basic pacing interval, the greater the maximum P-R interval at the left extremity of the curve. Since the diagonal lines representing R-P = f₂(P-P, P-R) shifted upward and to the right as the pacing interval was increased (Fig. 1), there was a diminished likelihood of obtaining points above the relevant diagonal line at higher pacing intervals.

The curves of P-R = f₁(P-P, R-P) obtained in the 23 dogs were similar qualitatively to those shown in Figure 1. At pacing intervals above 350-400 msec, the curves representing different pacing intervals tended to be superimposable in any given experiment. For pacing intervals less than 350 msec, the curves tended to diverge, particularly over the lower range of R-P intervals, as in Figure 1. In many of these experiments, atrial echoes (8-11) were observed, particularly at the lower test P-P intervals and at the faster pacing frequencies. Such atrial echoes were not included in any of the data analyzed in the present study.

The curves of P-R = f₂(P-P, R-P) which are defined by the data points in Figure 1 represent the changes in the P-R interval for the very first conducted impulse following the test P-P interval. At a considerably shortened test P-P interval, the P-R interval did not immediately return to the steady-state value when the basic pacing interval was reinstated. This phenomenon became more apparent as the basic pacing interval was shortened (Fig. 3). The basic pacing interval for this experiment was 370 msec, and the steady-state P-R and R-P intervals were 81 and 289 msec, respectively. A single test P-P interval of 200 msec was interposed, and the resultant R-P interval was reduced to 119 msec. There was a concomitant increase in the P-R interval to 236 msec. On the next beat, the basic interval of 370 msec was restored, but because of the prolonged P-R interval the next R-P interval was 134 msec, i.e., 370 - 236. The second impulse following the test cycle was conducted with a P-R interval of 125 msec, which was still well above the steady-state level. The P-R interval was still slightly

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**FIGURE 3**

Atrial (P) and ventricular (R) electrograms and corresponding P-R and R-P intervals observed when a single test P-P interval of 200 msec was interposed while the atrium was paced at a basic P-P interval of 370 msec in a representative experiment. The time marker at the top of the figure denotes seconds.
WENCKEBACH PHENOMENON

elevated on the next beat, but it was not detectably different from the steady-state level on the beat after that.

When curves of the P-R intervals were plotted against the immediately preceding R-P intervals, the curve for the beat after the test interval had a configuration resembling that for the test beat, but it was significantly lower. The curves obtained with various test intervals for the experiment shown in Figure 3 are presented in Figure 4. The solid circles represent the test intervals; for each test interval there was a different value for the P-P interval. The open circles represent the cardiac cycle which followed the test cycle; the P-P interval for each of the open circles was equal to the basic cycle length (370 msec). The extent of the deviation between the open- and the solid-circle data varied from one experiment to another, but the curve representing the second beat invariably fell below that for the test beat.

As noted before, most of the curves, $P-R = f_1(P-P, R-P)$, intersect the diagonal lines, $R-P = f_2(P-P, P-R)$, at only one point; the coordinates of this point are the steady-state R-P and P-R intervals, respectively. At rapid pacing frequencies, it is often possible to obtain a second intersection

where the steeply rising curve at low R-P intervals intersects the diagonal line above and to the left of the other point of intersection. In the experiments in which there was only one point of intersection, the changes in the P-R interval during the test beat and the subsequent beats were directionally similar to those shown in Figure 3. The same applies to those data falling below the upper point of intersection in the experiments in which two points of intersection were obtained. In all such instances, when a short test P-P interval was interposed, the P-R interval of the first conducted impulse was increased. However, the increment in the P-R interval was not as great as was the decrement in the preceding R-P interval. In Figure 3, for example, the R-P interval was reduced from 289 msec to 119 msec, a decrement of 170 msec, but the P-R interval increased from 81 msec to 236 msec, an increment of 155 msec. On the second beat after the test interval, the R-P interval increased and the P-R interval decreased toward their respective steady-state levels. The R-P interval of 119 msec for the first beat was associated with the abridged test P-P interval of 200 msec, and the R-P interval of 134 msec for the next beat was associated with the basic P-P interval of 370 msec. To account for the change in the P-R interval from 236 msec to 125 msec from the first to the second beat, it would be difficult to dissociate the influence of the P-P interval from that of the R-P interval, since both intervals change in the same direction from the first to the second beat.

However, such a dissociation is possible for points that fall above and to the left of the upper point of intersection in those experiments in which two points of intersection are obtained. For all points above this upper point of intersection, the increment in the P-R interval for the first conducted impulse was actually greater than was the decrement in the R-P interval during the shortened test interval. As a consequence, during the next beat at the basic pacing interval, although the basic P-P interval was substantially greater than the test P-P interval, there was a further reduction in the R-P interval.

In Figure 2, the basic pacing interval was 300 msec, and a single test interval of 200 msec was interposed. The steady-state P-R and R-P intervals were 145 and 155 msec, respectively. During the short test interval, the R-P interval diminished to 55 msec, a decrement of 100 msec.
Concomitantly, the P-R interval increased from 145 msec to 265 msec (impulse P4), an increment of 120 msec, which exceeded the decrement in the R-P interval. As a consequence, although the P-P interval was increased again to 300 msec on the next beat, there was a further reduction in the R-P interval to 35 msec. The next impulse (P5) was blocked in the AV conduction system (Fig. 2).

Examples of curves that intersected the corresponding diagonal line at two points were obtained in 12 different dogs. In 10 of these dogs, the responses were similar to those in Figure 2; the impulse terminating a short test cycle was conducted with a long P-R interval, and the impulse terminating the next, longer cycle at the basic pacing frequency was blocked in the AV conduction system. In all 10 of these dogs, the prolongation of the P-R interval exceeded the reduction of the preceding R-P interval. Hence, the points which represented these observations were located above the upper of the two points of intersection. In 1 of the 12 dogs, there were also a few instances in which the response resembled that in Figure 2, but the corresponding points fell just below rather than above the upper point of intersection.

In 8 of the 12 dogs in which curves that intersected the diagonal lines at two points were obtained, some points fell above the upper point of intersection, but neither the premature impulse nor the next impulse was blocked. Such responses occurred in 6 of the dogs in which responses similar to those shown in Figure 2 were also obtained, and they were also noted in 2 other dogs. In the 6 dogs in which both types of responses were seen, the type of response depended on the distance from the upper point of intersection. Conducted impulses were observed for both the premature and the next basic cycle when the points were located above but relatively close to the upper point of intersection; however, when the point was more widely displaced above the upper point of intersection, the impulse following the premature impulse was blocked (Fig. 2).

The difference between the R-P interval of the test cycle (R-Pt) and that of the next basic cycle (R-Pb) is an index of the distance above the upper point of intersection. At the upper point of intersection, R-Pt − R-Pb = 0. In the example in Figure 2, R-Pt − R-Pb = 55 − 35 = 20 msec. The values of R-Pt − R-Pb were compared for the six dogs in which both conducted and blocked impulses were obtained for the cycle following the premature cycle for points that fell above the upper point of intersection. The mean ± SE of R-Pt − R-Pb was 13.0 ± 3.0 msec when the impulse terminating the test cycle was conducted and 35.0 ± 10.4 msec when the corresponding impulse was

![Graph](http://circres.ahajournals.org/content/i/200.png)

**FIGURE 5**

Relationship of the P-R interval to the preceding R-P interval in a representative experiment in which the AV nodal Wenckebach phenomenon was produced by pacing at a P-P interval of 260 msec (left), 250 msec (center), and 240 msec (right). The corresponding conduction ratios were 55:54, 7:6, and 4:3, respectively. The diagonal lines in each section represent the loci of points for which P-R + R-P = 260, 250, and 240 msec, respectively.
WENCKEBACH PHENOMENON

blocked. This difference was significant ($P = 0.05$), as determined by the t-test for paired samples.

CLAMPED P-P OR R-P INTERVALS

In every dog in this series of experiments, when the pacing frequency was increased to a sufficiently high level, the AV nodal Wenckebach phenomenon appeared. At the lowest pacing frequency at which it first occurred, the impulse was blocked infrequently in its passage through the AV conduction tissue. If the conduction ratio is defined as the ratio of $n$ atrial depolarizations to $n - 1$ ventricular depolarizations, then $n$ is relatively large at the lowest frequency at which the Wenckebach phenomenon first appears. As the pacing frequency is progressively increased, $n$ diminishes.

A representative example of this phenomenon is presented graphically in Figure 5. At a pacing interval of 260 msec, the conduction ratio was 55:54. A plot of the P-R interval as a function of the R-P interval (P-R = $f_1$(R-P)) has a configuration similar to the graphs of P-R = $f_1$(P-P, R-P) in Figures 1 and 4, in that the curves become progressively steeper as the R-P interval is diminished. At the pacing interval of 260 msec, the curve, P-R = $f_1$(R-P), was tangent to the diagonal line, R-P = $f_2$(P-P, P-R). As the pacing interval was decreased to 250 msec and then to 240 msec, the conduction ratios became 7:6 and 4:3, respectively. The diagonal lines shifted toward the left as the pacing interval was diminished, and the distance between the curves and the diagonal lines progressively increased. When the data for all three pacing frequencies were superimposed on common coordinate axes, the curves of P-R = $f_1$(R-P) did not deviate detectably from one another.

To obtain the data in Figure 5, the analog computer was operated in the clamped P-P mode, i.e., the right atrium was paced at a constant P-P interval. When the computer was switched to the clamped R-P mode, the Wenckebach cycle was terminated immediately (Figs. 6 and 7). In Figure 6 (top), the computer was operated in the clamped P-P mode and delivered pacing stimuli at a constant interval of 331 msec. The electrograms revealed that the AV nodal Wenckebach phenomenon was present with a conduction ratio of 5:4.

At the time represented by the end of the electrograms in Figure 6 (top), the computer was switched to the clamped R-P mode. The electrograms in Figure 6 (bottom) are a direct continuation of those in Figure 6 (top). The Wenckebach phenomenon disappeared instantly and 1:1 AV conduction supervened. The analog computer outputs of the P-R and the R-P intervals for this same experiment are shown in Figure 7. Between the two arrows, the computer was operated in the clamped R-P mode; on either side of the interval bounded by the arrows, it was operated in the clamped P-P mode. In the clamped P-P mode, there were cyclic changes in the R-P and the P-R intervals characteristic of the Wenckebach phenomenon. Initiation of the clamped R-P mode (left arrow) caused these cyclic changes to cease, but reinstitution of the clamped P-P mode (right arrow) elicited an immediate resumption of the Wenckebach cycles.

The digital computer printouts of these data revealed that the P-P interval was constant at 331 msec during the clamped P-P phase of the experiment. When the computer was switched to the clamped R-P mode, the R-P interval remained between 171 msec and 173 msec, and the

![Figure 6](http://circres.ahajournals.org/)

**Figure 6**

Atrial (P) and ventricular (R) electrograms in the clamped P-P (top) and clamped R-P (bottom) modes in a representative experiment. The electrograms in the bottom section are a direct continuation of those in the top section. The time marks at the top of the figure denote seconds.
concomitant P-P interval varied from 334 msec to 339 msec with an average of 336 msec, i.e., 5 msec greater than that in the clamped P-P mode.

Immediately after the experimental observations shown in Figures 6 and 7 were made, the computer was set in the clamped P-P mode at a pacing interval of 341 msec, which exceeded by 5 msec the average value for that obtained previously in the clamped R-P mode. This interval again generated a Wenckebach rhythm but with a conduction ratio of 8:7. Hence, clamping the R-P interval was compatible with 1:1 AV conduction at an average P-P interval which is within the range of P-P intervals which would otherwise evoke a Wenckebach rhythm when the P-P interval is held constant and the R-P interval is permitted to vary spontaneously.

Similar results were obtained in all nine dogs in which experiments were conducted in the clamped P-P and R-P modes. In all experiments, the pacing frequency was increased until the Wenckebach phenomenon appeared. Maintenance of this frequency constituted the clamped P-P mode. Switching to the clamped R-P mode resulted in an immediate cessation of the Wenckebach cycles in all experiments. Reinstatement of the clamped P-P mode resulted in an abrupt resumption of a Wenckebach rhythm (Fig. 7). These procedures were repeated several times in each experiment with identical results. However, in one of these experiments although Wenckebach cycling usually ceased when the mode was switched from the clamped P-P mode to the clamped R-P mode, occasionally second-degree block did persist. However, the cycle period was much longer and the blood pressure was much lower in the clamped R-P mode than it was in the clamped P-P mode.

**Discussion**

Various factors affect AV conduction, including the activity of the cardiac sympathetic and parasympathetic nerves, the adequacy of coronary perfusion, the concentration of certain electrolytes, notably potassium, and the blood levels of various drugs, hormones, and other substances. The time of arrival of a given cardiac impulse is also a critical factor that has been studied extensively (5, 7, 8, 12–16). In assessing the role of this factor in the AV conduction system as a whole, the P-R interval is usually taken as a reliable index of AV junctional conductivity, since the other components of this interval such as intra-atrial conduction time are of smaller magnitude and remain relatively...
WENCKEBACH PHENOMENON

The P-R interval is expressed graphically as a constant. Most commonly, in evaluating the role of the impulse arrival time on AV conductivity, the P-R interval is expressed graphically as a function of the time between successive entries into the AV node, i.e., as a function of the P-P interval (7, 8, 12, 15, 16).

In considering the AV nodal Wenckebach phenomenon, it is not feasible to relate the P-R interval to the P-P interval, because the P-P interval usually does not vary appreciably from beat to beat during this arrhythmia. During a Wenckebach cycle, the P-R interval increases with each successive beat, and there is a concomitant reduction in the R-P interval. The P-R intervals have been plotted against the preceding R-P intervals in this arrhythmia (4, 5, 17). For any given beat, the P-R interval has been interpreted as an index of the relative prematurity of the arrival of the cardiac impulse at the site of retarded conduction in the AV node (3, 4).

However, Moe and his collaborators (18) have challenged the "sacrosanctity of the RP-PR relationship." They have described certain pitfalls in the use of the R-P interval as an index of the prematurity of impulse arrival; they have proclaimed that "it is the interval between successive entries of the node rather than the interval between the last emergence and the succeeding entry which determines how facile will be the transit." Hence, they argue that the P-R interval should be related to the preceding P-P interval and not to the R-P interval.

In interpreting the electrocardiographic changes in the Wenckebach phenomenon, therefore, the critical question is whether there is a causal relationship between the progressively increasing P-R interval and the progressively decreasing R-P interval during a Wenckebach cycle. Conversely, are the changes in the R-P interval purely coincidental, and do the progressive changes in the P-R interval represent a cumulative response to the constant P-P interval?

The present series of experiments support the contention that both the P-P and the R-P intervals are independent determinants of AV conduction time. The principal lines of evidence are as follows: (1) the relationship of the P-R interval to the R-P interval for premature atrial activations and for subsequent basic beats, (2) the occurrence of AV conduction blocks during the cardiac cycle following premature atrial activation in which the increment in the P-R interval exceeds the decrement in the preceding R-P interval, and (3) the relationships between the P-R and the R-P intervals during pacing at high frequencies in the clamped P-P and the clamped R-P modes.

The first line of evidence is illustrated by the data in Figure 4. The solid circles depict the changes in the P-R interval that occur during a series of premature atrial depolarizations. For each solid circle, the values of both the P-P and the R-P intervals differ from those for any other solid circle. However, from such data it is impossible to assess the relative importance of the P-P and the R-P intervals as determinants of the P-R interval. The open circles represent the changes in the R-P interval during the beat following the premature atrial activation or test beat. The P-P interval during the beat after the test beat is the basic pacing interval (370 msec), and therefore it is constant for all data represented by the open circles.

However, the variations in the P-R interval illustrated by the open-circle data represent those alterations ascribable to the changes in the R-P interval alone, i.e., P-R = f(R-P). The solid-circle data, on the other hand, depend on the changes in both the P-P and the R-P intervals, i.e., P-R = f(P-P, R-P).

Therefore, the difference in ordinate values at any given R-P interval may be ascribed to the corresponding P-P interval. Such evidence by itself is presumptive, however, since the changes on the beat following the test interval may represent a residual influence from the short test interval.

Figures 1 and 2 show the second line of evidence that both the P-P and the R-P intervals are determinants of the P-R interval. The solid squares in Figure 1 represent the changes in the P-R interval produced by alterations in the P-P interval and the R-P interval, i.e., P-R = f(P-P, R-P) for a basic pacing interval of 300 msec. The left diagonal line represents the locus of points for which R-P = P-P - P-R, i.e., R-P = f(P-P, P-R), where the P-P interval is 300 msec. As stated previously, all points lying above the upper point of intersection for P-R = f(P-P, R-P) and R-P = f(P-P, P-R) represent changes in AV conduction in which the evoked increment in the P-R interval exceeds the provoking decrement in the R-P interval. As shown in Figure 2, one such point was obtained by interposing a premature atrial activation with a P-P interval of 200 msec. Because the increment in the P-R interval (120 msec) for impulse P, exceeded the

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The decrement in the R-P interval (100 msec), the R-P interval for the next beat (35 msec) was even less than that for the premature beat (55 msec), although the P-P interval was 100 msec greater than that for the premature beat. The next atrial impulse (P5) was blocked in the AV conduction system.

In comparing the propagation of impulses P4 and P5 (Fig. 2) through the AV conduction system, the relative effects of the P-P and the R-P intervals may be contrasted. Interval P4-P5 was 100 msec longer than interval P3-P4. If the P-P interval alone were the critical determinant of AV conductivity, the conduction of P5 should have been more facile than that of P4, but P4 was conducted and P5 was blocked. The R-P interval preceding P5 was 20 msec less than that preceding P4, suggesting that P5 may have arrived at an earlier phase than did P4 in the recovery of excitability of certain critical cells in the AV conduction system, despite the longer P-P interval. Blocking of the impulse during the longer cycle following the premature depolarization was observed in ten dogs. With only one exception, this phenomenon was observed only when the R-P interval for the first basic beat following the premature beat was less than that for the premature beat itself.

There were eight instances in which the R-P interval for the next basic beat was less than that for the premature test beat, but AV conduction proceeded. In these instances, the P-R interval for the premature beat was greater than that for the next basic beat. In comparing the P-P and the R-P intervals for the premature beat and the next basic beat, the P-P interval was greater and the R-P interval was less for the basic beat than it was for the premature beat. When conduction did occur, the positive dromotropic effect of the greater P-P interval probably exceeded the negative dromotropic influence of the slightly greater degree of prematurity, as reflected by the diminished R-P interval. When the increment in the P-R interval for the premature beat exceeded the decrement in the R-P interval, the average decrement in the R-P interval was significantly less for those instances in which conduction occurred during the next basic beat than it was for those instances in which conduction was blocked. The mean value of R-Pb - R-Pb was 13 msec when conduction occurred, but it was 35 msec when conduction failed, i.e., when R-Pb = R-P for the test beat and R-Pb = R-P for the next basic beat (see Results). The changes in the P-P interval were precisely the same for both instances. Thus, the degree of prematurity, as reflected by the R-P interval, probably determined whether conduction would occur on the succeeding basic beat. With only a slight decrease in the R-P interval, conduction proceeded; with greater reductions in the R-P interval, the impulse was blocked.

The third line of evidence that the R-P and the P-P intervals are both determinants of AV conduction is probably the most crucial. The experiments in which the atrium was paced alternately in the clamped P-P or clamped R-P modes also document the contention that the progressive increase in the P-R interval during a Wenckebach cycle does not represent a cumulative effect of the rapid pacing but is a manifestation of a positive feedback mechanism. There is unequivocal evidence which shows that rapid pacing does evoke cumulative effects on AV conduction (5-7). However, the present experiments indicate that such cumulative effects have probably achieved a steady state once the Wenckebach rhythm has become established. Hence, they do not account for the progressive changes in the P-R interval. When the R-P interval was clamped and the mean P-P interval was at a value which would otherwise evoke the Wenckebach phenomenon, there was neither a progressive increase in the P-R interval nor periodic block (Figs. 6 and 7). Therefore, the progressive changes in P-R interval which were observed in the clamped P-P mode indicate that there was a causal relationship between a given P-R interval and the preceding R-P interval during the Wenckebach phenomenon.

The normal feedback control of AV conduction is depicted by the block diagram in Figure 8. AV conduction depends on many factors; however, only the influence of the P-P and R-P intervals are considered. The rectangle diagrammed in Figure 8 signifies that the P-R interval is a function of both the P-P and R-P intervals. The P-R interval is also a determinant of the next R-P interval. Hence, it is shown feeding back to the summing junction (small circle), where its subtraction from the P-P interval yields the R-P interval. This subtraction is represented graphically by the diagonal lines, R-P = f2(P-P, P-R), in Figures 1, 4, and 5.

During pacing at a constant P-P interval, the diagram in Figure 8 can be simplified to that...
shown in Figure 9A. Since the P-P interval is clamped, the P-R interval is represented as a function solely of the R-P interval. Above the rectangle in Figure 9A, a sign inversion is indicated by the minus sign in parentheses, because a change in the R-P interval produces an opposite change in the P-R interval. Also, the P-R interval is subtracted from the P-P interval to produce the next R-P interval, as indicated by the minus sign.

at the summing junction. The two sign inversions in the loop are responsible for the occurrence of positive feedback. In the clamped P-P mode at sufficiently high heart rates, the Wenckebach phenomenon supervenes because of this positive feedback. As the P-R interval increases, it causes an equivalent reduction in the R-P interval. The reduction in the R-P interval evokes a subsequent increase in the P-R interval, which then produces a further reduction in the R-P interval. During the Wenckebach phenomenon, the process recurs until an impulse is blocked; after the impulse is blocked, the entire cycle is repeated. This positive feedback loop exists during normal AV conduction and second-degree heart block. Whether the Wenckebach phenomenon will supervene simply depends on the open-loop gain of this feedback system.

When the experiments were conducted in the clamped R-P mode, the computer delivered an atrial stimulus after each R wave at a time which ensured that the R-P interval would remain constant. Hence, any change in the P-R interval was associated with an equivalent change in the P-P interval in the same direction. A spon-
taneous increase in the P-R interval, for example, produced an equal increase in the P-P interval. This increase in the P-P interval then caused a reduction in the P-R interval on the next beat. In some of these experiments, operation in the clamped R-P mode was characterized by a small but consistent alternation in the P-R and the P-P intervals from beat to beat, i.e., a relatively short P-R interval resulted in a slightly curtailed P-P interval, which then evoked a relatively long P-R interval. This long P-R interval in turn resulted in a longer P-P interval, which then evoked a relatively short P-R interval. The process was repeated continuously.

PROPOSED ELECTROPHYSIOLOGICAL BASIS FOR THE WENCKEBACH PHENOMENON

The changes in the P-R interval associated with the changes in the preceding R-P interval undoubtedly reflect the electrophysiological events that occur at the cellular level in the AV conduction system. It has been amply demonstrated in various cardiac tissues (19-21), including the AV node (13), that there are electrotonically induced changes in the action potential durations of cells in the proximal portion of a zone of delayed conduction. The prolongation of the action potential is commensurate with the extent of the delay in conduction. This relationship probably serves as an integral part of the electrophysiological basis for the positive feedback system that is responsible for the Wenckebach phenomenon. Schaffer and DePasquale (22) have recently described in detail the electrophysiological events which are believed to occur in the AV node during the Wenckebach phenomenon.

The salient features of the AV conduction system are presented in Figure 10. The first block in the figure, \( r = f_1(\phi) \), represents the well-known fact that the refractoriness \( r \) of a given cell in the AV conduction system is a function of the phase \( \phi \) of the action potential in that cell (23). Specifically, with respect to the Wenckebach phenomenon, the critical cells are those just proximal to the region of slowest conduction and periodic block. The absolute refractory period of these cells begins with the onset of depolarization and extends through the ill-defined plateau of the action potential into the first portion of repolarization. The relative refractory period extends throughout the remainder of repolarization and continues well into the period of complete repolarization (7, 12). The threshold for excitation progressively diminishes throughout the relative refractory period.

For a given action potential configuration and duration, when the P-P interval remains constant, each successive cardiac action potential reaches the critical AV nodal cells at the same phase of excitability. If for any reason there is an alteration in the duration of the action potentials of these critical cells, there will be a corresponding change in the time course of recovery of excitability. Hence, even if the P-P interval between successive cardiac impulses remains constant, the phase of the recovery of excitability will be shifted by an amount that depends on the magnitude of the action potential prolongation.

The second block in Figure 10 represents the change in the impulse propagation velocity \( v \) as a function of the refractoriness of the specialized conducting fibers. Hence, the earlier in the relative refractory period an impulse reaches

\[
\begin{align*}
\text{FIGURE 10} \\
\text{Block diagram of the electrophysiological components of the AV conduction system which constitute a positive feedback loop. The first block represents the refractoriness (r) of a conducting fiber as a function of the phase (\( \phi \)) of the action potential. The second block represents propagation velocity (v) as a function of refractoriness. The third block represents propagation delay (T) as a function of conduction path length (d) and velocity. Propagation delay feeds back to the summing junction. When subtracted from the P-P interval between successive atrial impulses, it determines the phase of the action potential at which a given atrial impulse will arrive at a critical conducting fiber just proximal to a region of slow conduction.}
\end{align*}
\]
these critical cells, the more slowly will the impulse be propagated (12, 23). If \( d \) represents the distance over which delayed conduction occurs and \( v \) is the mean conduction velocity over this distance, then the conduction time \( (\tau) \) equals \( d/v \), as indicated by the third block in Figure 10.

Any change in the conduction time over the critical conduction path affects the phase of the recovery of excitability by an electrotonic interaction between the conducting fibers proximal and distal to the region of slow conduction. Consider, for example, two cells, \( A \) and \( B \), along a given conduction path in the AV node. If conduction is rapid from \( A \) to \( B \), the time delay, \( \tau \), between the respective action potentials will be relatively small. However, if conduction between these two cells is slow, the time delay between the respective action potentials will be greater. An action potential in one cardiac cell, e.g., \( B \), exerts an electrotonic depolarizing influence on another cell, e.g., \( A \), as long as the distance between the two cells is small relative to the space constant for electrotonic decay (13, 19–21). If cell \( A \) is activated before cell \( B \), the depolarization of cell \( B \) retards repolarization of cell \( A \), i.e., the action potential of cell \( A \) will be prolonged. The increase in action potential duration depends on the propagation time, \( \tau \), because it is the time over which the electrotonic interaction occurs. Since the relative refractoriness is related to the time course of the membrane potential change during repolarization, the phase of the recovery of excitability is shifted by an amount equal to the action potential prolongation, i.e., \( \phi = P-P - \tau \). Hence, in the block diagram of Figure 10, \( \tau \) is fed back at the summing junction (small circle) where the subtraction from the input (the P-P interval) yields the so-called error signal (\( \phi \)).

In the AV nodal Wenckebach phenomenon, positive feedback probably operates in the following manner. With each successive beat, there is an additional prolongation of the P-R interval, until finally an atrial impulse is completely blocked. Presumably, therefore, there is a progressive prolongation of the propagation time, \( \tau \), through some region of retarded conduction. On any given beat, as \( \tau \) exceeds that of the preceding beat, the action potentials are prolonged in the critical region proximal to the site of slow conduction. Hence, if the P-P interval between successive cardiac impulses remains constant, the next impulse will arrive at those critical cells at an earlier phase in their relative refractory periods, as reflected by the progressive reduction in the R-P interval. Consequently, the propagation velocity diminishes, and \( \tau \) increases, which produces an additional prolongation of the action potential duration in the critical cells and thus causes a greater phase shift on the next beat. This cycle recurs beat after beat until an atrial impulse finally arrives during the absolute refractory period; AV conduction is then blocked. In comparing Figures 9A and 10, it is apparent that the P-R interval reflects the overall propagation time, and the R-P interval reflects the phase of the recovery of excitability. The block in Figure 9A labeled \( P-R = f(R-P) \), therefore, incorporates the electrophysiological determinants of refractoriness, propagation velocity, and transmission time which are included in Figure 10. A more detailed control systems analysis of the AV nodal Wenckebach phenomenon is being published concurrently (24).

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