Paradoxical Dynamic Interaction of Heart Period and Vagal Activity on Atrioventricular Conduction in the Dog

Paul Martin

SUMMARY The dynamic interaction of simultaneously changing heart period and single vagal stimuli on atrioventricular conduction (AV interval) was quantified by subtracting the vagally induced responses of the paced heart preparation from those of the unpaced heart preparation. This difference was significantly greater (P < 0.05) than the AV responses to changes in heart period (ΔAA) alone without vagal stimulation (using the identical ΔAA recorded from the unpaced heart in the same preparation, but with a crushed sinoatrial node). That is, for a given increase in AA interval, the AV conduction time was considerably less when the change in AA was associated with increased vagal activity than in the absence of any vagal activity. Data from some dogs in which a complete AV block was produced for both paced and unpaced hearts suggested that one mechanism of the paradoxical response was located in AV nodal tissue. Data from other dogs, in which two surface atrial recording sites were used, indicated that shifts of pacemaker site and atrial activation patterns also are an important mechanism of the paradoxical response. The relative contribution of these two mechanisms is not fixed, but can vary considerably from animal to animal.

IT HAS BEEN SHOWN by us previously that a single stimulus applied to the vago sympathetic trunk of an un paced dog heart preparation can lead to changes of atrioventricular (AV) conduction time that are extremely complex, with several different mechanisms contributing to the resultant response. Thus, a generalized increase in vagal activity at the sinoatrial (SA) and AV nodes results in two oppositely directed effects on AV conduction time (the AV interval): (1) the acetylcholine (ACh) released will prolong the AV interval via a direct effect on the AV node, and (2) it will indirectly decrease the AV interval by increasing heart period (AA interval), primarily an AV nodal effect. I wished here to define quantitatively the interaction between these two responses. The specific question asked was: Do the two independent effects on AV conduction combine as a simple sum when applied simultaneously, or is there a more complex, nonlinear interaction that produces the resultant response? The second alternative was found to prevail in almost all animals.

The basic protocol used an open-chest, anesthetized dog and consisted of noting the AV conduction responses to the following sequence of experiments: (1) single vagal stimulus bursts delivered at different times throughout the cardiac cycle in the spontaneously beating heart preparation; (2) the identical experiment as above, but with the heart paced at a constant rate just above its spontaneous rate; and (3) with the heart driven at the identical sequence of changing cardiac cycle lengths obtained in part 1 above, but with no vagal stimulation. Thus, the sum of the independent effects of vagal activity and increasing cycle length (parts 2 and 3) can be compared with the response to these combined perturbations (part 1). If the sum of the responses to parts 2 and 3 is significantly different from the responses of part 1, it can be concluded that there is an interaction between these two mechanisms.

Methods

Fifty-five mongrel dogs (10–15 kg) were used, of which 51 yielded satisfactory results. All dogs were anesthetized with morphine sulfate, 2 mg/kg, intramuscularly (im) followed 30 minutes later by chloralose, 75 mg/kg, intravenously (iv), dissolved in polyethylene glycol. In one group of 44 dogs the chest was opened and bipolar recording catheters were inserted through a small incision in the right atrial appendage into the right atrium, and through the right external jugular vein into the right ventricle. The catheter was lodged against the ventricular wall. The atrial catheter was secured to the atrial appendage just above the proximal electrode (electrode separation was 6 mm), thus eliminating timing errors due to electrode position changes. The electrodes were connected to a Brush Mark 200 oscillograph to record the atrial (A) and ventricular (V) activations. The onset of the atrial potential was the reference event for all other measured, computed, and generated time intervals.

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Both cervical vagosympathetic trunks were crushed and ligated. One of these trunks (in all but a few experiments the right) was connected to a bipolar shielded electrode (Grass) peripheral to the ligature. β-Adrenergic blockade was achieved with propranolol (1.0 mg/kg, iv) given approximately 10 minutes before onset of data collection, and at approximately 1½-hour intervals thereafter or as the effect wore off, as tested by supramaximal right stellate ganglion stimulation. This agent was used to avert any effects of simultaneous stimulation of cardiac adrenergic fibers in the vagosympathetic trunk. Two types of electrical signals were applied to the dog; hereafter the term “stimulus” will refer only to the signal applied to the vagosympathetic trunk; the electrical signal used to drive the atrium will be referred to as the “pacing” signal. For the constant heart rate sequences, the right atrium was paced by an isolated Grass S4 stimulator. The pacing electrodes were attached near the SA node to minimize the effects of abnormal AV nodal entry and excitation. The amplified A and V signals from the oscillograph were coupled capacitively to an EAI-580 analog/parallel logic computer which was used, as previously described, to (1) generate the timing and gating signals by which the vagal stimulus burst was positioned in a cardiac cycle (with a resolution of 1 msec); (2) condition the A and V signals for input to the real-time clock of a PDP 12 digital computer (Digital Equipment); and (3) derive the analog signals proportional to the cardiac cycle duration (AA), the interval between A-onset and V-onset (AV), and the time from A-onset to the onset of the vagal stimulus burst (AD). The systemic blood pressure, A, V, and stimulus signals were recorded on analog tape (Honeywell 7600). The digital computer was used to collect the AA, AV, and AD intervals for on-line data reduction and subsequent listing. The stimulus parameters generated by the analog computer were: 1 msec pulse width, 3 msec pulse interval, 10 V pulse height, and less than 10, but usually 1–4, stimuli per burst, with at least 60 seconds between bursts. Hereinafter these bursts simply will be referred to as the stimulus.

An additional set of experiments was conducted using these same vagal stimuli patterns, but here the focus was on the changes in atrial excitation and conduction patterns. These experiments were performed to elucidate the mechanism of the unpaced heart responses observed in the earlier experiments, and used two pairs of atrial clip electrodes rather than the catheter in the atrium. These electrodes were located (1) just superior and medial to the location of the SA node (lateral junction of superior vena cava and right atrium), and (2) at the low medial margin of the right atrial appendage near the ostium of the coronary sinus, and on the epicardium as close to the septum and AV nodal area as possible. Although it would have been advantageous, the activity of additional electrode sites could not be measured simultaneously because of lack of further recording channels.

Results

The primary data analysis tool used is a modification of the so-called “vagal effect curve,” as originally used by Brown and Eccles4 for the SA node, and previously extended to the AV node6 but in modified form. Such curves show the time course of the AV response to vagal stimulation by combining the responses from many individual stimuli. The ordinates of these curves represent the change in AV interval (∆AV). The time intervals from the stimulus to the beginnings of the next several V waves are plotted on the abscissa. The mathematically detailed algorithm used to compute the points of these curves for AV and AA is given elsewhere.8

Figure 1 illustrates the results of part 1 of the protocol, i.e., applying a sequence of single vagal stimuli to a spontaneously beating (unpaced heart) preparation. The top panel of Figure 1 shows a typical vagal effect curve in which a single burst of three stimulus pulses (each 1 msec wide, 5 msec in total burst width) was used. Each of the three bottom panels (A–C) is a ladder diagram, illustrating how the data points following one stimulus contribute to the curve. The record of panel A was taken with AD = 56 msec; each datum point appears as x on the curve. This stimulus had no effect on the AV interval (AAV), so that the t and ∆AV coordinates of the first datum point were t = A0V0 = 113 = 56 = 57 msec and ∆AV = 0. This vagal stimulus did, however, affect the length of the cardiac cycle in which it was given; A0A1 increased by 680 = 525 = 155 msec. This increase in A0A1, combined with the residual vagal effect on the AV node at the time of A1V1, caused a change of A1V1 by 93 – 113 = –20 msec. The abscissa of this point on the curve is simply the elapsed time from the stimulus to the V1; i.e., (A0A1 – AD) + A1V1 = 680 – 56 + 93 = 717 msec. Subsequent points fall on the negative portions of the oscillating curve at approximately one AA interval apart. The prestimulus control AA interval was identical in all of panels A–C, i.e., AA – control = 525 msec. Panel B shows what happens when the first cardiac cycle (AA0A1) is not much increased, i.e., when AD is relatively long (443 msec). The first AV after the stimulus (A1V1) is prolonged by 5 msec (the first open circle on the curve), but the second and third AV intervals are more affected by the forces associated with the lengthened AA and fall on the negative portion of the curve. In panel C it is clear that the direct depressant effect of ACh on the AV node predominates throughout the record (open triangles), since an increased AV obtains for each cardiac cycle except the last. At intermediate values of AD, such that the increase in AA falls in an intermediate range, vagal stimuli produce relatively little change in AV intervals (not illustrated); i.e., here the oppositely directed forces appear to balance one another.

Figure 2 illustrates the results of part 2 of the protocol by showing the response of the same heart to the identical sequence of vagal stimuli, but now where the heart has been paced at a constant interval of AA = 520 msec. This curve thus represents the pure vagal effect on AV conduction uncomplicated by a changing AA interval. It is seen that the effect is purely a lengthening of AV interval, i.e., there is no negative excursion of the curve. Also, there is a second and third peak in the curve, at about an AA interval displaced from the first peak, such second peaks occurring in about half the dogs but a third peak rarely occurring, as previously reported.5
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An AP (x) = 56 B (x) = 443 C (A) = 356

FIGURE 1 Top panel: unpaced heart preparation, vagal effect curve of changes in AV conduction time (ΔAV) as a function of time after a vagal stimulus. The continuous curve is drawn through the responses of 25 stimulations. Panels A–C: ladder diagrams of three individual sequences of ΔAV in response to a single vagal stimulus given at the arrow of each panel. The lengths of the cycles preceding that of the stimulus are identical in all panels, i.e., AA – control = 525 msec. The three sets of discrete data points on the vagal effect curve show how these sequences of responses contribute to the vagal effect curve (note dashed vertical lines for the first ΔAV after the stimulus for each of panels A–C). See text for further explanation.

The bottom curve of Figure 3 shows a typical result of part 3 of the protocol from the same dog used for Figures 1 and 2. Here the SA node has been crushed, and the identical sequence of changing AA intervals recorded in part 1 and stored in the computer memory have been played back into atrial pacing electrodes located on undamaged tissue as near to the original SA nodal pacemaking site as possible. This ΔAV playback response is seen, as expected, to be entirely negative, i.e., the lengthening AA intervals, plotted as the upper vagal effect curve on the figure, act purely to facilitate or decrease AV conduction time. Note also that the negative peaks of this ΔAV playback curve correspond to but are displaced in time to the right of the AAA peaks by approximately the V to A intervals plus the succeeding AV intervals. This simply reflects the fact that the decreased ΔAV occurs, in time, on the beat just after the lengthened AAA beat.

Other variants of the ΔAA response are shown in Figures 4–6. In Figure 4, the positive peak of the unpaced hearts (ΔAA-U) is brief and very low (about a third of that of the paced (ΔAA-P) peak) and in some preparations there was virtually no positive excursion at all. Figure 4 also shows that there may be no negative to positive oscillation at all. Note in Figures 4–6 that the curves of paced and unpaced hearts are coincident for about the first 350–400 msec. In this AD region the stimulus had little or no effect on the cardiac cycle length during the cycle in which it was applied. In four out of 46 dogs there was little deviation of ΔAA-U from ΔAA-P, as illustrated in Figure 5. There was no negative excursion of ΔAA-U at all in two dogs (not illustrated).

The only instances in which curves from paced heart preparations, ΔAA-P, would go negative was in the cardiac cycles just after complete AV blockade, as shown in Figure 6. Here the portions of the curves in the expected region of the positive peaks are missing (i.e., corresponding to the AV block). Thus, the negative ΔAA-P points occur

FIGURE 2 Vagal effect curve taken from the same dog used for Figure 1, but now the heart has been paced at a rate just below the spontaneous (unpaced) cardiac rate. An identical set of vagal stimulus bursts as those producing Figure 1 were used. As in Figure 1, the entire AD interval range of one cardiac cycle was used. This curve thus represents the pure effect of vagal stimulation on AV conduction, uncomplicated by the effect of suddenly changing AA intervals.

FIGURE 3 The top curve shows the vagal effect on the cardiac interval (AA) in the unpaced heart, from the same dog and using the same stimuli as used to produce Figures 1 and 2. The bottom curve shows, after sinoatrial nodal crush, the results on the AV interval of "playing back" into the atrial pacing electrode the identical changing AA intervals used to produce the top (ΔAA) curve of this figure. This lower ΔAV curve thus represents the pure effects on the AV interval of a suddenly changing AA interval, uncomplicated by vagal activity.
on the beat subsequent to the block, and seem to form a discontinuity in this curve. Results from experiments with complete block will be discussed in detail below. The half-filled symbols of Figures 4 and 5 represent the simultaneous changes in cardiac cycle length (ΔAA) associated with the ΔAV-U curve.

The filled squares of Figure 6 represent the AV changes that were obtained after the SA node had been crushed. In this dog, and in all other dogs, the spontaneous cardiac interval stabilized to a value somewhere in the range of 675-900 msec, usually closer to 750-825 msec, after crushing the SA node. As in Figure 3, ΔAV values shown in Figure 6 were the responses to the identical sequences of AA changes that had been stored from the unpaced heart preparation with vagal stimulation after these sequences had been played back and converted to a pacing signal to the right atrium. There is a great difference between this playback curve, ΔAV-PB, and ΔAV-U curve over the time range from about 600-1400 msec. Note especially that AV conduction is faster in the presence than in the absence of vagal activity in the face of identical heart period changes. This not the expected response. Rather, it was expected a priori that ΔAV-P would lie intermediate to ΔAV-P and ΔAV-PB. Thus, this phenomenon will hereafter be referred to as the "paradoxical response."

The best comparison, however, is not between playback curves and unpaced heart curves. Rather a new curve, ΔAV-D, obtained by subtracting the paced heart and unpaced heart curves, i.e., ΔAV-D = (ΔAV-U) - (ΔAV-P), should be compared with the playback curve ΔAV-PB. Subtracting these curves at each point in time represents the linear elimination of the direct vagal effect, since ΔAV-U represents the combined effect of vagal activity, and ΔAV-P represents the effect of vagal activity alone. Figure 7, taken from yet another dog, illustrates that there can be a considerable difference between ΔAV-D and ΔAV-PB, indicating a considerable interaction between the direct vagal effect and ΔAA (otherwise the curves would be coincident).

Not all preparations exhibited such great disparities between the difference and playback curves as those shown in Figure 7, although in all dogs some degree of paradoxical response obtained. The statistical significance of the disparities between ΔAV-D and ΔAV-PB for all dogs studied therefore was sought. For each curve the computer was programmed to derive the difference curve, ΔAV-D of Figure 7. The time axis of all curves was divided into bins 100 msec wide, so that each bin would contain enough (5-20) points to permit a proper statistical inference, and so that the curves could still be compared at different regions of the time axis. For general analysis,
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P - Δ AV paced
U - Δ AV unpaced
PB - Δ AV playback
D - DIFFERENCE

(• U - P)

TIME, sec.

+1.2

500 - 999 msec, and t = 1,000 - 1,499 msec.

The null hypothesis that the paced heart, ΔAV-PB, and the difference, ΔAV-D, curves were equal for each bin was tested with Student's t-statistic. If this hypothesis could be rejected at the 0.05 level for three or more bins out of each group of five in each time range, it was concluded that there was a significant difference between the curves in that range. This analysis shows that of the 20 dogs studied, ΔAV-D was more negative than ΔAV-PB for 34 out of 40 of the curve sets in the 500- to 999-msec range, but for only 22 out of 40 of the curve sets in the 1,000- to 1,499-msec range. Thus in the 500- to 999-msec time range, it is likely that the decrease in AV interval resulting from a combination of vagal stimuli and lengthened cardiac cycle was greater than that due purely to the lengthened cycle per se. In the range of 1,000-1,499 msec the evidence for such a paradoxical response was less convincing, and beyond the upper limit of this range it was highly variable from dog to dog (and not statistically analyzed).

The remainder of this work was concentrated on uncovering the mechanism of the paradoxical response. This mechanism could be located in either or both of two broadly defined components of the cardiac conduction system, viz., in the SA node and atrial conduction system, or in the AV node. Data were collected that suggest that both possibilities exist.

COMPLETE AV BLOCK DATA

In a few experiments it was possible to block ventricular activation by vagal stimulation in both the paced and unpaced heart preparations, as illustrated by the curves of Figure 6. The results of these experiments suggest an AV nodal mechanism for the paradoxical response. Such a set of data is shown in Figure 8, a diagrammatic representation of A and V occurrences in time similar to panels A-C in Figure 1. Comments on panel F, and the intervals marked N1N2, N2N3, etc., are given under Discussion. Each of panels A-E of Figure 8 represents the average responses of five records taken from one dog. The vagal stimulus bursts were identical and at the same AD for all of the responses summarized in panels A, B, D, and E. Panels A and B were obtained during atrial pacing. The atrial impulse (A1) after the vagal stimulus (vertical arrow) was conducted to the ventricle in panel A, but was blocked in panel B. The numbers to the right of each panel are the mean absolute changes in AV from control (ΔAV, msec)

FIGURE 7 Top panel: paced heart (P) and unpaced heart (U) vagal effect curves from a fifth dog. Bottom panel: ΔAA and playback (PB) vagal effect curves from the same dog, and difference (D) curve (broken line) derived by subtracting the curves of the paced heart from those of the unpaced heart preparations.

FIGURE 8 Ladder diagrams of A and V occurrences in time similar to panels A-C in Figure 1. The vertical arrows in the A, cardiac cycle indicate the time at which the vagal stimulus was given. The numbers at the center of each cycle are the values of A for that cycle. Each panel is the average of five stimulations. The AV response (dotted line) to the far right of each panel is the superimposed control AV response for comparison. The numbers at the far right of each panel are the actual mean changes in AV from the control value. Panels A and B were obtained from the paced heart without and with, respectively, complete AV nodal block. Panel C was obtained from playback data for the similar ΔAA prolongations of panels D and E. The unpaced heart responses without and with, respectively, complete block are shown in panels D and E, and panel F illustrates an idealized pure (i.e., paced heart) vagal effect curve with the same time origin as the vagal stimulus in the above panels.
during the second beat after the vagal stimulus. The dotted AV line shows the position that a control AV interval would have been expected to occupy in the absence of vagal stimulation. The elapsed times from the vagal stimulus to these second V waves (V2) after the stimulus were very similar for panels A and B (879 and 876 msec). Thus, a comparison of appreciably different time points on the vagal effect curve was averted. The average increase above control in the second AV in the absence of block (panel A) was 73.6 msec. When beat A1 was blocked (panel B), the next atrial impulse (A2) was conducted to the ventricle much more rapidly, i.e., with a mean change in AV of -7.1 msec from control. The difference between the responses in panels A and B is ascribable purely to the effect of the block of the preceding beat in panel B, since the same amount of ACh was probably liberated and the time course of its disappearance was probably similar during the observations in panels A and B.

Panel C shows the response to a suddenly lengthened AA with no vagal stimulation. The pacing was timed from the playback data derived from the unpaced heart experiment from which the data of panels D and E were obtained. When AA was lengthened to a mean interval of 860.5 msec, similar to two paced intervals (AApAep interval = 890 msec in panel B), the mean decrease in AV was only 11.3 msec. If there was no interaction between the direct vagal effect and ΔAA, the ΔAV response of panel B should only thus be about 11.3 msec less than that of panel A, since this would represent the additional effect of the lengthened AA per se. That the difference (80.7 msec) between the responses of panels A and B is considerably greater than 11.3 msec (ΔAV response of panel C) again confirms the existence of an interaction, and it also suggests one site for this interaction. This site must be at or distal to the block, since all other factors up to this site of block were presumably the same for the experiments shown in panels A and B of Figure 8.

The same qualitative results were obtained with the unpaced heart. Panel D of Figure 8 from the same preparation shows that when there was no block with vagal stimulation, AV decreased by an average of 2.4 msec when AA increased from 448 to 815.5 msec. When a block occurred (panel E), the average decrement in AV was 30.0 msec for about the same increase in AA. Because of nodal escape, it was not possible to increase heart period suddenly to the extent of 448 + 820 = 1268 msec, as in panel E, without vagal stimulation in this dog. However, experience with other dogs in this series indicates that the decrement of panel C is near maximal, and that a ΔAA 2–3 times greater than that of panel C will lead to only an additional 2- to 3-msec decrement in AV over that observed in panel C. This, again, would be considerably less than the difference between the decrements of panels D and E (30.0 − 2.4 = 27.6 msec). If there were no interaction between direct vagal effects and ΔAA this difference of 27.6 msec should only be about 2–3 msec more than the 11.3-msec decrement of panel C (i.e., 13–15 msec). Hence, a decrement of perhaps 13–15 msec represents the effect of the increased interval only between excitations to the whole AV node. However, with vagal activity, and with the similar increased interval between excitations of AV nodal tissue distal to the site of block, a much greater decrement in the AV interval on the beat subsequent to the blocked beat results. Thus, again, an interaction obtains, but of a reduced magnitude (only 27.6 msec of panels D and E instead of the expected 13–15 msec, as opposed to the 80.7-msec difference between panels A and B instead of the expected 11.3 msec). Nonetheless, note that the effect leading to the difference in panels A and B occurred about 450 msec closer to the vagal stimulus than that of panels D and E. This indicates that the interaction is time-dependent, being of greater magnitude the closer in time it occurs to the peak of local ACh concentration after a vagal stimulus.

**PACEMAKER SHIFT AND ATRIAL ACTIVATION PATTERN EXPERIMENTS**

An additional set of experiments was conducted to determine whether the paradoxical response could be explained in part by a shift in pacemaker location or atrial activation patterns. Seven dogs were prepared in which the two sets of bipolar clip electrodes were used instead of the catheter in the atrium. The electrograms recorded from these two sites, designated A1 and A2, respectively, then gave a relative indication of the conduction velocity between these sites (time difference in onset of A1 and A2) and change in activation pattern (a shift in initial deflection of the electrogram from positive to negative or vice versa). Only two dogs of the seven exhibited spontaneous (nonvagally induced) changes in A1 and A2 over an extended period of time.

When maximal vagal stimulus bursts not producing complete AV blockade were delivered to the dog, there was a significant decrease in conduction velocity and shift of activation pattern in 42 out of 62 records from those seven dogs on the first beat after the stimulus, and in 27 out of 62 on the second beat after the stimulus. These changes were not caused by the altered heart period; a change in heart period per se altered conduction velocity slightly, but had no effect on activation pattern. Figure 9 illustrates the extreme response, seen in only one of the seven dogs. The cardiac cycles are numbered consecu-
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First beat

216.8 (18.5)  
-6.4 (0.8)  
-13.6 (2.0)  

r = 0.112  
= 0.200  

Second beat

-251.2 (26.9)  
-10.8 (3.3)  
-16.3 (5.1)  

r = 0.140  
= 0.101  

Composite means (ss) from 62 stimulations in seven dogs.

Dramatic as when induced by vagal stimulation. Thus, the cardiac interval in the absence of vagal stimulation was often followed by small shifts of atrial activation coefficient, r, of Table 1 shows that there is a relatively low correlation of AA,AA, AA,AA 2 AA,AV amplitude with AAA interval per se. It is thus in the 500- to 1,500-msec time range of the vagal effect curves that this report concentrates.

Since it is well known that vagal activity slows AV nodal conduction, but an increased AA interval speeds this conduction, it was assumed a priori that the simultaneous combination of these two interventions would have an intermediate effect. This was not found; rather, a paradoxical response obtained over the time range of 500-1,500 msec of the curves. The combined response was a decrease in conduction time of significantly greater magnitude than that due to the lengthened AA alone. In other words, for a given increase in AA interval, the AV interval actually was considerably less when the change in AA was associated with increased vagal activity than in the absence of any vagal activity. Two extreme cases of this difference are shown in Figures 6 and 7, where it is seen that the maximum negative excursion of the unpaced heart curve represents about a 6-fold greater decrease in AV conduction time with vagal activity than without (the playback curve). For a linear summation, the only difference between the vagal effect curves for the paced and unpaced heart should be the effect of AAA alone. Symbolically, the null hypothesis was $\Delta A V-D = (\Delta A V-U) - (\Delta A V-P) = \Delta A V-P B$. This hypothesis was rejected for the vast majority of the dogs studied. It was thus shown that some sort of interaction exists between the direct vagal effect and the effect of AAA to produce a paradoxical dromotropic response. It was found that both AV nodal and atrial mecha-

Table 1 Atrial Activation Pattern Parameters

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Figure 10 Electrogams and intervals similar to Figure 7, but from a different dog and without shift of A$_2$ to precede A$_1$. This is clearly an example of a considerable shift in pace-maker sites away from the SA nodal area. The more usual response, seen in the other six dogs, is a shift in activation pattern just at one or at both sites on the same or sequential beats (Fig. 10), and/or a decrease in A$_1$A$_2$ conduction time, but with no shift of onset such that A$_2$ precedes A$_1$. Figure 10 also illustrates the relative contributions of the two measured intervals to the total paradoxical response for one dog. It is seen that while there has been a significant decrease in the conduction time through the atria $(22 - 8 = 14$ msec), the decrement from A$_2$ to V is somewhat greater $(130 - 110 = 20$ msec). This was true in six of the seven dogs, the other dog showing the opposite relative proportion. Table 1 gives the grand means of all records taken from the seven dogs, each record being taken near the maximally obtainable paradoxical response amplitude. The first beat refers to the first prolonged cardiac interval following the vagal stimulus $(\Delta A A)$ and the atrial $(A_1A_2)$ and low atrial-ventricular $(A_2V)$ intervals following this long beat in the next cardiac cycle; the second beat is the next set of such intervals, all such combinations of these two interventions would have an intermediate effect. This was not found; rather, a paradoxical response obtained over the time range of 500-1,500 msec of the curves. The combined response was a decrease in conduction time of significantly greater magnitude than that due to the lengthened AA alone. In other words, for a given increase in AA interval, the AV interval actually was considerably less when the change in AA was associated with increased vagal activity than in the absence of any vagal activity. Two extreme cases of this difference are shown in Figures 6 and 7, where it is seen that the maximum negative excursion of the unpaced heart curve represents about a 6-fold greater decrease in AV conduction time with vagal activity than without (the playback curve). For a linear summation, the only difference between the vagal effect curves for the paced and unpaced heart should be the effect of AAA alone. Symbolically, the null hypothesis was $\Delta A V-D = (\Delta A V-U) - (\Delta A V-P) = \Delta A V-P B$. This hypothesis was rejected for the vast majority of the dogs studied. It was thus shown that some sort of interaction exists between the direct vagal effect and the effect of AAA to produce a paradoxical dromotropic response. It was found that both AV nodal and atrial mecha-

Discussion

The objective of this work was to determine how the separate AV nodal effects of vagal stimulation and suddenly lengthened cardiac period $(\Delta A A)$ interact to produce a resultant effect on AV conduction. The primary analysis tool used was a derived "vagal effect curve" which purports to show the continuous effect on AV conduction of a single vagal stimulus burst as a function of time after this burst is given. For the paced heart preparation, these curves (e.g., Fig. 2) have a latency of about 200 msec, and then rapidly rise to a positive peak at 400-435 msec after the stimulus, before more slowly tailing back down, usually returning to control within 2-3 seconds. The curves from the unpaced heart preparations have a similar latency and rapid positive rise, but then usually plunge toward a negative peak in the vicinity of 700-1,000 msec after the stimulus (Figs. 1, 4, 6, and 7). The component parts of the curves spanning the time ranges from about 200 to 400-500 msec, where the paced heart curves and unpaced heart curves are similar, represent the direct vagal effect on the AV nodal conduction system, since in this time range insufficient time has elapsed to affect the cardiac cycle length plus the succeeding AV interval. However, beyond 500-700 msec, both the cardiac cycle length and the succeeding AV interval are influenced by local ACh concentration, and the AV interval is simultaneously affected in the opposite direction by the lengthened AA interval per se. It is thus in the 500- to 1,500-msec time range of the vagal effect curves that this report concentrates.
nisms play an important role in the mechanism of this paradoxical response.

**AV NODAL COMPONENT OF THE PARADOXICAL RESPONSE**

An indication of important AV nodal participation in the paradoxical response is based on both unpaced and paced heart responses from those dogs in which identical vagal stimuli induced nearly identical ΔAA values, but in which some of the ventricular activations were blocked. Only a small change in vagal stimulus intensity or timing is required to go from maximal AV prolongation to complete block. When a complete block occurred, the AV interval on the very next beat exhibited a nonlinear interaction between the vagal activity and the increased time between activations distal to the block site.

The data of Figure 8 can be interpreted to show that AV nodal tissue distal to the site of block contributes an important component to the paradoxical response. To demonstrate this, it must first be established that the data of Figure 8 represent a paradoxical response in the same sense as that defined for the previous data. In the heart without AV blockade, a paradoxical response was defined as ΔAV-D = [(ΔAV-U) - (ΔAV-P) > (ΔAV-PB)], i.e., the magnitude of the difference between paced and un paced AV changes due to vagal stimulation was greater than that due to an increased AA interval per se. Figure 8 shows that the same effect obtains if the definition of the interval between atrial activations (ΔAA) is modified to be the interval between activations distal to the site of block or potential block (ΔNN). The block probably occurred in the atrial-junctional or high nodal regions, since this is where ACh has a maximal effect. Panel B of Figure 8 is thus comparable to the ΔAV response in an “unpaced” heart, but now where the un paced effect (i.e., lengthened ΔNN) occurs over only a portion of the AV pathway (distal to the block); that is, the interval between midnodal activation in panel B (N2N2) is suddenly lengthened over that of panel A (N2N2). The effect on AV due solely to this ΔNN is approximated by the response of panel C to N2N2. However, the actual change in ΔAV (i.e., ΔNNV) would be somewhat less, since -11.3 msec represents the effects of traversal of the entire AV pathway, whereas ΔNN represents the effects of traversal of only part of the pathway. The difference between the ΔAV responses of panels A and B (73.6 - (-7.1) = 80.7 msec is considerably greater than the -11.3 response of panel C. This is indeed a paradoxical response, but now it can be said that the mechanisms of this paradoxical effect are located at sites distal to the block, since all other factors up to the block site presumably remained constant in panels A and B except the absence or presence of block. A similar argument holds for the comparison of the responses of panels D and E of Figure 8 with the appropriate playback response (presumed to be about 13-15 msec less than control to a ΔNN in excess of 1,200 msec). The magnitude of the paradoxical response of panels D and E is considerably less than that of panels A and B.

Panel F of Figure 8 depicts an idealized pure (i.e., at constant AA) vagal effect curve for AV conduction over the same time scale and with the same time origin (time of stimulus) as all the panels above it (A-E) in Figure 8. This curve is based on the postulated time course of ACh concentration in the vicinity of AV nodal cells, as derived from a functionally isomorphic mathematical model of ACh release, diffusion, and cholinesterase inactivation as previously worked out in our laboratory. The points on the curve labeled AB and DE are at those times at which the paradoxical effect occurs for panels A, B and D, E, respectively. Thus the reduction in the magnitude of the paradoxical effect with time after the stimulus can simply be ascribable to the decreased amplitude of the vagal effect at point DE as opposed to point AB in panel F.

The mechanism of the paradoxical effect at AV nodal sites remains to be clarified, but is probably quite complex. Although it might logically be considered, a detailed argument (beyond the scope of this paper) can be developed to postulate that increased action potential widths and refractory periods just distal to the site of the block are not likely to play a part in the AV nodal component of the paradoxical response.

In some rabbits it was found that when normal AV conduction was blocked by ACh, the ventricles were activated via bypass pathways at much shorter than normal conduction times. If also present in the dog, such bypass connections could directly account for part of the paradoxical response. If so, it should also be possible to observe the paradoxical response with a paced heart. This was seen in only two of 55 dogs here, therefore this mechanism is probably rare under these experimental conditions.

**ATRIAL MECHANISMS**

The vagal stimulation experiments in which the high (A1) and low (A2) atrial potentials were recorded shed considerable light on the origin of the paradoxical response. From these it is seen that, on the average, mechanisms operating between the A1 and A2 sites account for about one-third, and those between A2 and the ventricle (V) for about two-thirds, of the paradoxical response amplitude (Table 1). However, in some experimental runs either ΔAA or ΔAV accounted for almost all of this amplitude. Hence, no general rule about a relative distribution between the two regions of the conduction system can be made, except that both atrial and AV junctional mechanisms play a significant role.

Some shift in atrial excitation-conduction patterns was seen in all seven dogs studied, there being an extensive shift in six of the seven. The atrial pacemaker may shift away from the SA node with vagal stimulation (e.g., Fig. 9), as has been reported by others. Most of these studies concluded that the richly innervated SA nodal area was more severely depressed by vagal stimulation than was surrounding atrial tissue, thus allowing emergence of non-nodal foci. Comparison of the present work with these studies is difficult because in all but one of them steady state levels of stimulation were used. However, transient pacemaker wander was seen by Spear and Moore with single vagal bursts. They also found that a given vagal stimulus had a greater effect on SA than AV nodal function, a conclusion confirmed here (compare the amplitudes of the ΔAA and ΔAV-P curves of Figs. 4-6).

It has been found that atrial activation normally pro-
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ceeds along multiple wavefronts, and that this variability is a major determinant of AV nodal conduction time. Also pacing the heart near the coronary sinus significantly reduces AV conduction time, possibly because of a change in site and/or mode of AV nodal impulse entry. Such a mechanism per se (i.e., independent of Ach) could also be playing some role in the paradoxical response. That is, some shifts of atrial activation patterns with the playback experiments and using the A₁ and A₂ electrodes were occasionally seen (not illustrated). In these, the coronary sinus region was activated sooner than control on the beat subsequent to the long beat, and the pacemaker site may have shifted near to this coronary sinus area. Extensive shifts without Ach were not a common finding, however, and if present they usually occurred only with maximal AA prolongation, so that this mechanism is probably not a major component of the paradoxical response. Thus, from the present evidence and that of others, one part of a purely atrial component of the paradoxical response may be attributed to shifts of atrial pacemaking site or of activation patterns due to vagal activity (major role) or due to AA per se (minor role).

A second part of an atrial component can be due to the effect of Ach on atrial conduction velocity and refractoriness. A primary effect of Ach is to reduce atrial action potential duration, but it also increases atrial conduction velocity, thus contributing another atrial component to the paradoxical response. Such an increase may be attributable to a decrease in atrial membrane resistance and/or a stimulation of atrial depolarization via action on the sodium-carrying system. Additionally, atrial refractory periods can be shortened by vagal stimulation in dogs, an effect probably related to increased potassium permeability. An increase in potassium concentration in isolated rabbit atria with Ach has also been implicated in a shift of atrial pacemaker sites.

Finally, one note of caution should be expressed concerning the results of the present work. This is that playback vagal effect curves were obtained using a fixed pacing site, and presumably resultant similar atrial conduction patterns, for each playback cardiac cycle. However, the effects of the lengthened AA interval due to Ach in the unpaced heart preparation included a component due to altered atrial conduction patterns and/or pacemaking site on sequential cardiac cycles (Figs. 9 and 10). Thus, it may not be strictly correct in a mathematical context to compare the difference between the paced and un paced heart curves with the playback curve, since this comparison may be statistically confounded. However, the alternative would have been to either: (1) physically duplicate the changing atrial activation patterns and (rarely) pacemaking sites while producing the playback curves, which would have been an experimental impossibility in our laboratory, or (2) make no comparison at all, an option rejected since an imperfect comparison, with its limitations understood, is clearly of greater benefit. The extent to which the present results are suspect is therefore difficult to ascertain. Some comfort is gained, however, from the observation that in only one of seven dogs there was a detectable shift of pacemaker site, and this would be the major source of error in the comparison. Thus, although this comparison may not furnish a quantitative measure, the data do provide qualitative estimates of the paradoxical effect. I believe that this, plus the additional data on the mechanisms of its origin, are sufficient to justify the conclusions presented.

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References

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