Effects of the Spatial Dispersion of Acetylcholine Release on the Chronotropic Responses to Vagal Stimulation in Dogs

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We determined the effects of changing the spatial dispersion of acetylcholine release on the phase-dependent chronotropic responses to vagal stimulation in anesthetized dogs. We stimulated the vagus nerves with one brief burst of electrical pulses each cardiac cycle, and we changed the timing of the stimulus by a small, constant amount each cardiac cycle to scan the entire cycle. To vary the heterogeneity of acetylcholine release, we changed the voltage of the stimulus pulses over a range of submaximal values. To achieve the maximum homogeneity of acetylcholine release, we used supramaximal voltages, and we varied the level of acetylcholine release from each excited fiber by changing the number of pulses per burst. We used the average cardiac cycle length of the phase-response curve to assess the overall vagal effect, independent of its timing within the cardiac cycle. We found that the amplitude of the phase-response curve varied directly and the minimum-to-maximum phase difference varied inversely with the overall efficacy of vagal activity. However, for any given alteration in the overall efficacy, the specific changes in the characteristics of the phase-response curve did not depend on whether the alteration was achieved by varying the number of pulses per burst or by varying the stimulus voltage. Therefore, we conclude that although the cardiac chronotropic response is very sensitive to changes in the timing of vagal stimulation, it is not influenced appreciably by the spatial dispersion of acetylcholine release from the vagal nerve endings over a wide range of stimulation strengths. (Circulation Research 1990;67:844–851)

When the vagus nerves of an anesthetized animal are stimulated by one burst of electrical pulses each cardiac cycle, the timing of those stimuli within the cardiac cycle affects the chronotropic responses. A stimulus burst delivered at one specific phase of the cycle will elicit the maximum response, whereas a stimulus burst delivered at a different specific phase of the cycle will elicit the minimum response. If the vagal stimuli are relatively weak, an appreciable phase difference (ΔΦ) exists between the phases that elicit the minimum and maximum chronotropic responses. Thus, if a weak stimulus burst applied during a given cardiac cycle is delivered at the phase that elicits the minimum response, and if the stimuli are delivered slightly earlier in each successive cycle, the response will change very gradually until it becomes maximal. However, if the stimuli are strong, a change in phase (ΔΦ) of only a few milliseconds can alter the chronotropic response abruptly from its maximum to its minimum value.

This characteristic response of an intact animal to changes in the timing of strong vagal stimulus bursts is remarkably similar to the time-dependent chronotropic response of a single automatic cell in the sinus node. In the single cell, as the timing of the vagal stimulus is gradually shifted on successive cycles from just after to just before a critical time in its activity cycle, the chronotropic response abruptly changes from its minimum to its maximum value. The critical time precedes the beginning of the upstroke of the pacemaker action potential by an interval equal to the latent period for the released acetylcholine (ACh) to increase the potassium conductance of the cell membrane. A vagal stimulus delivered just after the critical time will be too late to delay the next expected action potential, and the chronotropic response to that stimulus will be minimal. Conversely, a vagal stimulus delivered just before the critical time will delay the next expected action potential, and the chronotropic response will be

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maximal. Thus, $\Delta \Phi$ between the times that elicit the minimum and maximum responses is very small.\textsuperscript{10,11}

The present experiments were designed to test the hypothesis that the shape of the phase-response curve (PRC) depends on the spatial homogeneity of the distribution of neuronally released ACh within the sinoatrial (S-A) node. The rationale for this hypothesis is the likelihood that the phase-dependent response of the S-A node as a whole to changes in the timing of vagal stimuli would more closely resemble the response of a single cell if the ACh were uniformly distributed than if the ACh were distributed heterogeneously.

To test our hypothesis, we altered the spatial dispersion of ACh release from efferent vagal fibers by varying the stimulus voltage. When the voltage of the stimulus pulses is supramaximal, the maximum number of fibers in the nerve trunk will be excited. For voltages less than supramaximal, the number of nerve fibers effectively excited by a given stimulus will vary directly with the stimulus voltage. It seems likely that the greater the fraction of nerve fibers that are excited in the nerve trunk, the more homogeneous will be the distribution of neurotransmitter in the innervated tissue. Conversely, the smaller the fraction of nerve fibers that are excited, the less homogeneous will be the spatial distribution of transmitter. We varied the amount of ACh being released per cardiac cycle from each excited vagal fiber by adjusting the number of stimulus pulses per burst.

**Materials and Methods**

**Surgical Procedure**

Ten mongrel dogs (18–39 kg) of either sex were anesthetized with sodium pentobarbital (30 mg/kg i.v.). A femoral vein was cannulated to permit the administration of drugs and fluids. The chest was opened transversely at the fourth intercostal space, and intermittent positive-pressure ventilation was instituted via a tracheal cannula. The pericardium then was opened. The atrial electrogram (A wave) was recorded from a bipolar electrode catheter introduced into the right atrial appendage. Arterial blood pressure was recorded from a femoral artery by means of a Statham transducer (P23BB, Gould Instruments, Inc., Cleveland).

The $\beta$-adrenergic receptors were blocked by an initial intravenous injection of propranolol (1 mg/kg), and supplemental doses (0.5 mg/kg) were given hourly. Both cervical vagi were tightly tied to remove the tonic vagal influence on the heart. A pair of stainless steel stimulating electrodes (0.2 mm, insulated to within 1 mm of the tip) was inserted into the right vagus nerve caudal to the ligature.\textsuperscript{12} The electrodes were connected to an electronic stimulator (model S-4, with isolation unit, Grass Instrument Co., Quincy, Mass.).

**Experimental Protocol**

The instrumentation and recording techniques were similar to those used in our previous studies.\textsuperscript{1,3,7} The atrial electrogram served as the input to a parallel-logic analog computer (EAI-580, Electronics Associates, Inc., West Long Beach, N.J.). The cardiac cycle length (AA interval) was computed beat by beat.

During each cardiac cycle, we delivered one burst of stimuli to the right vagus nerve at a specific time in the cardiac cycle; we will refer to this stimulation mode as “phase-coupled stimulation.” Each burst consisted of several tightly packed square-wave stimulus pulses; each pulse was 1 msec in duration and supramaximal in voltage (12–15 V), and the interpulse interval was 5 msec. The time from the beginning of an atrial depolarization (A wave) to the beginning of the next vagal stimulus (St) is denoted as the A-St interval. The analog computer was programmed to trigger the electronic stimulator (Grass S-9). The computer increased the A-St interval by a small, constant amount each beat until the entire cardiac cycle had been scanned. The computer then decreased the A-St interval by the same absolute amount each beat until the entire cardiac cycle had been scanned in the opposite direction. The AA and A-St intervals and the arterial blood pressure were recorded on an eight-channel oscillograph (Gould ES 1000) and on magnetic tape (LAR 7400, Honeywell, Denver).

Each experiment was divided into two observation periods. During the first period, we used a supramaximal voltage to stimulate all the nerve fibers in the preparation. To vary the quantity of ACh released per cardiac cycle, we included four different numbers of stimulus pulses in each burst of vagal stimulation; we call this stimulation mode the “$\Delta P$ regimen.” For any given number of pulses per burst, we scanned the cardiac cycle at least once in each direction by gradually changing the A-St intervals before we changed the number of pulses per burst. We randomized the application sequence of the various numbers of pulses per burst.

During the second observation period, we held the number of pulses per burst constant at the same maximum value that we had used in the first observation period, and we varied the stimulation voltage; we call this stimulation mode the “$\Delta V$ regimen.” The rationale for this regimen was to vary the number of efferent vagal fibers excited by the stimulus bursts but to hold constant the amount of ACh released per beat from each excited fiber. The maximum voltage we used was supramaximal; we also used three different submaximal voltages. We randomized the application order of the various voltages. The combination of supramaximal voltage and maximum number of pulses per burst was identical for the $\Delta P$ and $\Delta V$ stimulation modes.

We included one, three, five, and either seven or nine pulses in each burst of vagal stimulation during the first observation period. The pulse voltage was supramaximal (12–15 V). During the second observation period, we used four voltage levels (mean
values, 2.5, 3.5, 5.2, and 14 V) combined with the highest number of pulses per burst (seven or nine).

Data Analysis

We used linear regression analysis and a mixed model analysis of variance to assess 1) the chronotropic response in each animal as a function of the stimulus voltage and number of pulses per burst, and 2) certain critical features of the PRC as functions of the mean chronotropic response. The fixed factors in the analysis of variance were the two modes (ΔP and ΔV) and the four intensity levels of vagal stimulation. The random factor comprised the individual dogs.

Results

Representative Experiments

Figure 1 demonstrates the chronotropic responses to vagal stimulation in a representative animal. One burst of seven supramaximal pulses was delivered at a preset time (A-St interval) in each cardiac cycle. The AA interval varied periodically as we progressively increased and decreased the A-St intervals of those stimulus bursts in successive cardiac cycles. At an A-St interval of 630 msec (Figure 1, arrow c), a small change in that interval evoked a large, abrupt change in cardiac cycle length (from arrow a to b).

The phase dependency of the chronotropic response to vagal stimulation may be depicted by a
PRC, in which the changes in cardiac cycle length are plotted as a function of the A-St interval. Figure 2 displays the curves derived from the data we obtained when we included one, three, and seven pulses in each burst of vagal stimuli in the same animal from which Figure 1 had been recorded. The curve for seven pulses per burst (7P) was derived from the tracings shown in Figure 1. Data also were obtained for five pulses per burst, but we did not include the corresponding PRC in Figure 2 to avoid cluttering the figure.

We measured the following distinguishing features of each PRC: the minimum and maximum AA intervals, the mean AA interval (\( \overline{AA} \)), the curve amplitude, and the minimum-to-maximum phase difference (\( \Delta \Phi \)). The ordinate values \( (Y_a \text{ and } Y_b) \) of points \( a \text{ and } b \) on a given curve are the minimum and the maximum AA intervals, respectively, for that curve. The \( \overline{AA} \) of a given PRC is the average value over the entire range of A-St intervals for that curve. To determine \( \overline{AA} \) for a given PRC, we integrated the curve and divided the integral by the maximum A-St interval for that curve \( (X_c \text{ for curve 7P}) \). The amplitude of a given PRC is the difference between the maximum and minimum AA intervals; that is, it equals \( Y_c - Y_a \). The abscissas \( (X_a \text{ and } X_b) \) of points \( a \text{ and } b \) are the A-St intervals, respectively, that are associated with the minimum and maximum points on the PRC. The minimum-to-maximum \( \Delta \Phi \) of a PRC is the decrement in the A-St interval necessary to change the cardiac cycle length from its minimum to its maximum value. For example, \( \Delta \Phi \) for curve 7P (Figure 2) is \( X_c - X_b \), which is 13 msec.

Figure 3 compares the effects of changing the number of pulses per burst with the effects of changing the voltage of vagal stimulation on \( \overline{AA} \), \( \Delta \Phi \), and the curve amplitude in this same animal. As we increased the number of pulses per burst (\( \Delta P \) regimen) from one to seven while holding the voltage constant (12 V), \( \overline{AA} \) progressively increased from 1,010 to 1,222 msec, the curve amplitude increased from 180 to 595 msec, and \( \Delta \Phi \) decreased from 310 to 13 msec. These changes in curve characteristics evoked by the \( \Delta P \) regimen also are readily apparent from inspection of the curves in Figure 2.

Similarly, as we increased the strength of the vagal stimuli (\( \Delta V \) regimen) from 3.2 to 12 V (Figure 3) while maintaining a constant number (seven) of stimulus pulses per burst, \( \overline{AA} \) progressively increased from 1,028 to 1,244 msec, the curve amplitude increased from 140 to 570 msec, and \( \Delta \Phi \) decreased from 290 to 20 msec.

We arbitrarily selected \( \overline{AA} \) as our index of the overall efficacy of vagal stimulation. This index is the mean response to vagal stimuli over the entire range of A-St intervals, and hence is independent of the timing of those stimuli. To compare the effects of the \( \Delta V \) and \( \Delta P \) regimens on the characteristics of the PRC at comparable levels of vagal efficacy, we plotted \( \Delta \Phi \) and the curve amplitude as functions of \( \overline{AA} \).

Figure 4 demonstrates how \( \Delta \Phi \) and the curve amplitude vary with \( \overline{AA} \) for the data shown in Figure 3. The curve amplitude increased, but \( \Delta \Phi \) decreased as \( \overline{AA} \) was increased (Figure 4); the relations were approximately linear (0.93 < \( r^2 \) < 1). The relation of \( \Delta \Phi \) to \( \overline{AA} \) derived from the \( \Delta P \) regimen did not differ significantly from that derived from the \( \Delta V \) regimen. Similarly, the relation of the curve amplitude to \( \overline{AA} \) derived from the \( \Delta P \) regimen did not differ significantly from that derived from the \( \Delta V \) regimen.

**Composite Data**

The composite effects of the \( \Delta P \) and \( \Delta V \) regimens resembled the changes that were evoked in the representative experiment (Figures 1–3). The \( \overline{AA} \) and the curve amplitude increased and \( \Delta \Phi \) decreased as we raised the level of vagal stimulation by either the \( \Delta P \) or the \( \Delta V \) regimen.
To determine whether the effects of the ΔV regimen on the PRC characteristics differed significantly from the corresponding effects of the ΔP regimen, we derived linear regression equations of the amplitude and the ΔΦ of the PRC as functions of AA for each experiment. We found that linear equations provided satisfactory fits to the data from the individual experiments; the mean value (±SEM) of r² for all equations was 0.91±0.01 (Table 1).

To analyze the composite data derived from the individual linear regression equations, we determined the predicted effects of the changes in voltage (ΔV) and of the changes in pulses per burst (ΔP) at four arbitrary levels of AA. This regression procedure allowed us to compare the responses to the ΔV and ΔP stimulation modes at equivalent levels of the independent variable (AA). The arbitrary levels selected for any given experiment were within the

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<th>Table 1. Mean Values of r² (±SEM) for the Linear Regression Equations That Represent the Amplitude and Phase Difference as Functions of the AA Interval</th>
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Amp, amplitude; ΔΦ, phase difference; ΔP, changes in the number of stimulus pulses per burst; ΔV, changes in the stimulus voltage.

range of AA values that prevailed in that experiment; that is, we did not extrapolate.

The composite regression lines derived from the data from all 10 animals are shown in Figure 5. The mean values of the four arbitrary levels of AA are indicated by the X coordinates of the data points in this figure. Because all data points on each curve in Figure 5 represent the mean values derived from the individual linear regression equations, each composite regression equation fits the corresponding points perfectly; that is, r²=1. Figure 5 shows that ΔΦ varied inversely with AA and that the curve amplitude varied directly with AA. These directional effects of AA on ΔΦ and on the amplitude prevailed regardless of whether the changes in AA were achieved by the ΔP or ΔV regimen.

The relations of ΔΦ and curve amplitude to AA for the two stimulation modes (Figure 5) were assessed by analyses of variance; these relations were derived from the regression equations from each experiment. The changes in ΔΦ and in amplitude associated with the changes in AA both were highly significant (p<0.001). However, the effects evoked by the ΔP regimen on either ΔΦ or amplitude were not significantly different from the corresponding effects evoked by the ΔV regimen; that is, the stimulation mode was not a significant factor. Similarly, the interactions between the stimulation mode and the AA level were not significant.

Discussion

Our results demonstrate that when one burst of stimuli is delivered to the vagus nerves each cardiac
cycle, a rise in the stimulation level (voltage or number of pulses) increases $\Delta A$ and the amplitude of the PRC and decreases the minimum-to-maximum $\Delta \Phi$. When $\Delta \Phi$ and curve amplitude are expressed as functions of $\Delta A$, the effect of a given change in $\Delta A$ on the amplitude or on $\Delta \Phi$ does not depend on whether that change in $\Delta A$ is achieved by altering the number of pulses per burst ($\Delta P$) or the voltage ($\Delta V$) of those pulses. These two different stimulation modes probably generate different spatial patterns of ACh release in the cardiac tissues, as explained below. Hence, the spatial pattern of ACh release, within limits, does not appear to influence appreciably the phase-response characteristics of the chronotropic response to vagal stimulation.

**Automatic Cell Entrainment**

The shape of the PRC reflects certain characteristic features of the vagal control of the heart.\textsuperscript{1-11,14} The $\Delta A$ of the PRC for the chronotropic response denotes the overall responsiveness of the automatic cells to vagal stimulation, regardless of the timing of those stimuli within the cardiac cycle. The amplitude of the PRC defines the range of AA intervals over which the automatic cells can be entrained in a 1:1 ratio by free-running, repetitive bursts of vagal stimuli;\textsuperscript{1-2} free-running stimuli are those that are not intentionally delivered at preset times in the cardiac cycle.

Free-running, repetitive bursts of vagal stimuli entrain the firing of pacemaker cells in the S-A node by negative feedback.\textsuperscript{1} The mechanism is entirely ascribable to the time-dependent nature of the chronotropic response of the heart to vagal stimulation.\textsuperscript{1-3,6} The PRC defines this time dependency. At any point on the PRC, the slope denotes the change in responsiveness of the S-A node cells to an alteration in timing of the vagal stimuli. The entrainment tendency is related to the slope of the PRC over that portion of the cardiac cycle during which the slope is positive. The greater the positive slope of the PRC, the stronger the negative feedback mechanism; that is, the more effectively the automatic cells will be entrained.

The above assertions can be explained with the aid of Figure 6. Consider segments of two PRCs, one segment (panel A) with a slope of 0.8 and the other (panel B) with a slope of 0.2. Assume that for each example, the stimulator fires a stimulus burst pre-
cisey once each second. Assume also that these stimulus bursts temporarily entrain the heart effectively, such that it beats once per second. The cardiac pacemaker cells adjust their firing times such that the vagal stimulus bursts will fall at that phase of the cardiac cycle at which those stimuli will elicit cardiac cycles precisely 1 second long. In Figures 6A and 6B, that phase will constitute an A-St interval of 250 msec (point S). Assume also that the electronic stimulator is a perfect oscillator, but that the cardiac pacemaker occasionally responds imperfectly to the vagal stimulation, and it may fire at a period not equal to 1 second.

Let the beginnings of two consecutive cardiac cycles represent the ideal condition under which the heart is perfectly entrained by the vagal stimulus bursts delivered once per second (Figures 6C and 6D). Then, \( A_t A'_t = A_t A'_t = S_t S_t = S_t S_t = 1,000 \) msec. However, let the fourth atrial depolarization occur prematurely by 250 msec; that is, \( A_4 A'_4 = 750 \) msec. Therefore, \( A_4 S_t \) will be increased by 250 msec to a value of 500 msec (C in Figures 6A and 6B).

If the PRC slope were equal to 0.8 (Figure 6A), the greater A-St interval (\( A'_4 S_t \)) would have a strong negative chronotropic effect and would lengthen the next cardiac cycle by 200 msec (0.8 \( \Delta S_t \)); that is, \( A_4 A'_4 \) would equal 1,200 msec. It is evident from Figure 6C that the next atrial depolarization (\( A'_4 \)) would occur at almost the same time that it would have (at \( A_4 \)) if the atrial depolarization \( A'_4 \) had not occurred prematurely. Within one cardiac cycle, the timing of atrial depolarization (at \( C_4 \)) is almost identical to that (at \( S \)) which prevails during stable entrainment (Figure 6A).

By contrast, if the PRC slope were only 0.2 (Figure 6B), the tendency to maintain a constant temporal relation between pacemaker and stimulator firing would be more tenuous. An equivalent shortening of the \( A'_4 A'_4 \) and consequent prolongation of the A-St interval by 250 msec (\( A'_4 S_t \)) would now have a relatively weak negative chronotropic effect. It would prolong the next cardiac cycle by only 50 msec (0.2 \( \times 250 \)); the length of cycle \( A'_4 A'_4 \) would be 1,050 msec (Figure 6D). This small increase in cardiac cycle length would represent only a small correction for the previous short cardiac cycle (\( A'_4 A'_4 \)). The timing of atrial depolarization (at \( C_4 \), Figure 6B) is far from that (at \( S \)) which prevails during stable entrainment. It is evident, therefore, that entrainment would be achieved much more slowly after a perturbation when the PRC slope equals 0.2 than when it equals 0.8.

Our present results (e.g., Figure 2) and our previous investigations\(^2\)–\(^4\) have shown that when vagal stimuli of different strengths are used to generate PRCs, the positive slopes increase directly with the stimulus strength. In Figure 2, for example, the mean value of the positive slope for curve 7P equals the curve amplitude (\( Y_7 - Y_1 \)) divided by the range of A-St values \( [(X_0 - X_i) + (X_i - X_f)] \) that correspond to the positive slope region of the PRC; \( X_i \) and \( X_f \) are the X coordinates of points i and f. For curve 7P, \( Y_7 - Y_1 = 595 \) msec, and \( [(X_0 - X_i) + (X_i - X_f)] = 1,087 \) msec; therefore, the mean slope is 0.55. Similar computation shows that the mean slope of curve 1P in Figure 2 is only 0.19. Hence, the entraining tendency of the stimulus bursts that contained seven pulses (curve 7P) was about three times greater than that of the stimulus bursts that contained only one pulse (curve 1P).

**Spatial Dispersion of Vagal Activity**

Because repetitive bursts of vagal activity tend to entrain the firing of automatic cells in the S-A node, it is reasonable to postulate that the efficacy of entrainment would be influenced by the spatial distribution of the released ACh to the individual automatic cells that constitute the node. When the ACh release is more homogeneous, the effects of the vagal activity on the individual automatic cells would be more uniform. Conversely, a more heterogeneous release of ACh would exert disparate effects on the individual cells. Therefore, uniformly distributed innervation would be expected to entrain the automatic cells more tightly than would a heterogeneous distributed innervation.

To alter the spatial dispersion of ACh release, we varied the vagal stimulus voltage. When we used high levels of voltage and of pulses per burst to stimulate the vagus nerve, the maximum number of fibers in the nerve trunk would be excited and a large amount of ACh would be released from each excited vagal fiber. The released ACh, therefore, would produce the maximum chronotropic response.

When we used the same high voltage level but relatively few pulses per burst, the maximum number of nerve fibers would still be excited but less ACh would be released from each fiber. The chronotropic response would be smaller, but the spatial distribution of ACh release still would be relatively homogeneous. Conversely, when we used low voltage levels but a greater number of pulses per burst, relatively few vagal fibers would be excited, but a large amount of ACh would be released from each of the excited fibers.

Certain combinations of voltage and pulses per burst during the \( \Delta V \) stimulation regimen would release the same amount of ACh into the S-A node region, as would certain other combinations of voltage and pulses per burst during the \( \Delta P \) stimulation regimen. However, even when two different stimulation combinations release equal quantities of ACh, the spatial distribution of that release would tend to be more uniform the higher the voltage, and it would tend to be more heterogeneous the lower the voltage.

Our experimental results (Figures 1–3) indicate that as we increased the intensity of vagal stimulation, whether by the \( \Delta V \) or the \( \Delta P \) regimens, the amplitude of the PRC increased and the value of \( \Delta \Phi \) decreased. These characteristics of the PRC are associated with an increased entrainment of the automatic cells by the periodic vagal activity; that is,
the range over which the pacemaker cells would fire at a frequency equal to that of the frequency of the vagal bursts would increase. For any given level of AA, however, the ΔΦ and amplitude of the PRC were not influenced appreciably by whether the change in vagal stimulation intensity was achieved by the ΔV or the ΔP regimen (Figures 4 and 5). Hence, the uniformity of ACh release did not appear to be an important determinant of the ability of periodic vagal stimuli to entrain the pacemaker firing.

The explanation of these unanticipated results may be related to the nature of the population of pacemaker cells responsible for generating the cardiac rhythm under a given set of vagal stimulation conditions. It is well established that as vagal activity changes, the site of the dominant pacemaker cells in the S-A node may shift.15–17 Some automatic cells are more richly innervated than others or are more sensitive to ACh.17,18 As the level of vagal activity increases, the firing frequency of those cells will be diminished more than will the firing frequency of less richly innervated or less responsive cells. Hence, in the presence of vagal activity, the automatic cells that are less richly innervated or are less sensitive to ACh will tend to fire at a higher frequency and thus are more likely to be the dominant pacemakers. Although these dominant pacemaker cells would be influenced by the overall level of vagal activity (AA), they might not be influenced appreciably by the spatial distribution of that activity. That is, the neural effects on these less richly innervated dominant pacemaker cells might not depend appreciably on whether the efferent vagal fibers release ACh in a homogeneous or heterogeneous pattern.

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References


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