The Effect of Changing Interpulse Intervals on the Negative Chronotropic Response to Repetitive Bursts of Vagal Stimuli in the Dog

MATTHEW N. LEVY, STEVEN WEXBERG, CHRISTOPHER ECKEL, AND HARRISON ZIESKE

SUMMARY The chronotropic responses to repetitive bursts of vagal stimulation were determined in open-chest, anesthetized dogs. Either 5 or 10 electrical pulses were included in each stimulus burst, and the interpulse interval (Δt) was varied over the range of 5 to 150 msec. As the frequency of the stimulus bursts was progressively changed, the sinoatrial (SA) nodal pacemaker cells became synchronized with the repetitive bursts of stimuli over a certain range of burst frequencies. The magnitude of this frequency range varied with Δt. For 5 and 10 pulses/burst, the values of Δt that produced the greatest magnitude of this frequency range were 30.2 and 24.3 msec, respectively. Also, over the range of values of Δt from 5 to 50 msec, the magnitude of the negative chronotropic effect of the vagal stimulus burst varied directly with Δt. It is likely that, as the interpulse interval is increased within this range of values, either more acetylcholine is released from the vagal nerve endings per pulse or there is less saturation of the receptors on the pacemaker cell membranes during each burst.

ELECTROPHYSIOLOGICAL studies have shown that action potentials in efferent cardiac vagal fibers tend to be more clustered at certain portions of the cardiac cycle.1-4 The peak activity tends to occur at about 60-100 msec after the beginning of the systolic pressure rise in the aortic arch.2,3 However, the precise temporal distribution of such action potentials varies with changes in heart rate, arterial blood pressure, and blood volume. Under certain conditions, most of the action potentials are grouped within a relatively small portion of the cardiac cycle, whereas, under other conditions, they tend to be more evenly distributed in time. As many as 26 spikes have been observed in a given pulse-synchronous volley, with a maximum frequency of 120 Hz.1

Several studies have shown that the negative chronotropic effect of repetitive vagal stimuli depends on their timing relative to the cardiac cycle.5-8 Periodic vagal stimuli may evoke certain striking chronotropic responses, including (1) entrainment of SA nodal pacemaker cells, (2) a paradoxical, direct relationship between heart rate and vagal stimulation frequency, instead of the classical, inverse relationship, and (3) a pronounced sinus arrhythmia when the stimuli fall at certain critical points in the cardiac cycle.6-8 These responses are much more pronounced when the vagal stimuli consist of pulse-synchronous bursts, instead of equally spaced, individual impulses.4-6 Such pulse-synchronous bursts evoke patterns of efferent vagal action potentials which resemble the naturally occurring patterns. Because changing conditions alter the extent of clustering of the spontaneously occurring efferent vagal action potentials,1-4 the present study was designed to test the effect of the duration of trains of vagal stimuli and of the spacing of the individual pulses within each train on the chronotropic responses of the heart.

Methods

All experiments were conducted on mongrel dogs that were anesthetized with sodium pentobarbital, 30 mg/kg, iv. A tracheal cannula was inserted through a midline cervical incision. Both cervical vagi were transected, and a bipolar shielded iridium electrode was applied to the cardiac end of the right nerve.

Intermittent positive-pressure ventilation was started, and the chest was opened transversely through the 4th intercostal space. A bipolar electrode catheter was introduced through a midline cervical incision. Both cervical vagi were transected, and a bipolar shielded iridium electrode was applied to the cardiac end of the right nerve. The pole closer to the catheter tip lay in the atrial cavity, and the other pole was fixed at the auricular tip by a tight ligature. The atrial electrogram, the signal from the electronic stimulator (Grass, model S-4), and the arterial blood pressure (Statham, P23AA transducer) were recorded on an eight-channel oscillograph (Brush, Mark 200) and on an analog tape recorder (Honeywell, LAR 7400). The atrial electrogram and the stimulator signal served as inputs to an analog computer (EAI 580). The fol-
Vagal Effects on Heart Rate

Levy et al.

The following outputs were computed beat-by-beat and were recorded on the oscillograph: (1) the P-P interval (the time between the onsets of successive P waves), (2) the P-St interval (the time from the beginning of a P wave to the beginning of a stimulus burst), and (3) the St-St interval (the time between the onsets of successive stimulus bursts).

Bursts of 5 and 10 rectangular pulses were used to stimulate the right vagus nerve. The duration of each pulse was 2 msec, and the voltage was supramaximal (usually 10–15 V). The principal experimental variable was the interpulse interval (Δt); i.e., the time interval between successive pulses within a burst. For each dog, several values of Δt were used, over a range from 5 to 150 msec. A series of observations then was made at a given value of Δt, and then a new value of Δt was selected. The order of employment of the various values of Δt was selected randomly.

Bursts of pulses were given in a ramp configuration of constantly changing stimulation frequencies, over a range of burst frequencies from 0 to 2.0 Hz. Ramps of both increasing and decreasing frequencies were used, at a constant rate of change of about 1.3 Hz/min. Two pairs of ascending and descending ramps were used for each value of Δt, and the responses were averaged. The data were analyzed by means of nonlinear regression techniques.

Results

The changes in cardiac cycle length (P-P interval) in response to a progressive change in vagal stimulation frequency are shown in Figure 1 for a representative experiment. Each stimulus burst contained 10 pulses, and the interpulse interval was 10 msec. When the burst frequency was below 1 Hz (near the left edge of the figure), vagal stimulation evoked large, abrupt changes in the P-P interval. Concomitantly, the timing of each burst relative to the cardiac cycle (denoted by the P-St interval) appeared to vary in a random fashion. At the arrows marked a, the cardiac activity became synchronized with the vagal stimulation; i.e., the cardiac frequency and stimulation frequency were equal. The P-P interval was 0.94 sec, which corresponds to a heart rate of 1.06 Hz (i.e., 64 beats/min), and this rate was virtually identical to the stimulation frequency.

As the stimulation frequency was increased progressively (to the right of arrows a), there was a progressive reduction in the P-P interval. This decrease in cardiac cycle length produced by an increase in vagal activity has been referred to as a "paradoxical effect." As the P-P interval progressively diminished (from arrows a to b), there was a concomitant reduction in the P-St interval; that is, the repetitive bursts of vagal stimuli occurred earlier and earlier in successive cardiac cycles. At b, the P-St interval was very close to zero; i.e., the stimulus started just after the beginning of the P wave. The P-P interval at b was 0.79 sec; i.e., the heart rate was 1.26 Hz (76 beats/min), which was virtually identical to the frequency of vagal stimulation.

A slight additional increment in stimulation frequency resulted in a shift in the P-St interval from

![Figure 1](http://circres.ahajournals.org/)

**Figure 1** The effect of a progressive increase in the frequency of vagal stimulation on the chronotropic response of the heart in a representative experiment. The cardiac cycle length is denoted by the P-P interval (top channel). The P-St interval (middle channel) is the time from the beginning of atrial activation (P wave) till the beginning of a vagal stimulus burst (denoted by the event marks along the bottom of the record). Arrows indicate the maximum P-P interval during 1:1 synchronization with the vagal stimulus burst; arrows c, the minimum P-P interval during 1:1 synchronization; and arrows b and b', the time at which the stimulus shifted from a point just after the beginning of a P wave to a point just before the beginning of the next P wave. The time marker (along top of figure) indicates 1-sec intervals.
a point (b) in the cardiac cycle just after the beginning of a P wave to a point (b') in that cycle just before the next P wave. As the vagal stimulation frequency continued to increase (from b to c), the P-P interval progressively diminished, and there was a concomitant reduction in the P-St interval (from b' to c). At c, the P-P interval was 0.74 sec, which corresponded to a heart rate of 1.35 Hz (81 beats/min); again, the heart rate equaled the stimulation frequency. Thus, between a and c, a progressive increase in vagal stimulation frequency from 1.06 to 1.35 Hz produced a corresponding increase in the heart rate; i.e., the cardiac pacemaker was synchronized in a 1:1 ratio with the periodic bursts of vagal activity. At any point between a and c, if the slope of the stimulation frequency ramp was suddenly set equal to zero and the stimulus was maintained at the prevailing frequency, the heart continued to beat at precisely that same frequency.

The changes in P-P interval over the range of 1:1 synchronization may be plotted as a function of the P-St interval; this relationship has been termed a "pacemaker response curve." A family of such curves is shown in Figure 2. All curves originated from the same dog, and 10 pulses were included in each burst. The numbers to the right of each curve indicate the interpulse interval, in milliseconds. The curve with an interpulse interval of 10 msec (second curve from the bottom) was derived from the experiment shown in Figure 1. The labels a, b, b', and c denote the points of correspondence between Figures 1 and 2.

As shown previously, 1:1 synchronization prevails only over that portion of a pacemaker response curve at which the slope is positive. In Figure 2, the undetermined negative slope regions are represented by the dashed, straight lines. The amplitude of a given pacemaker response curve is the difference between the maximal and minimal P-P intervals; i.e., the difference between the P-P intervals at points a and c in Figures 1 and 2. The amplitude expresses the magnitude of the range of cardiac cycle lengths over which 1:1 synchronization prevails.

Figure 2 shows that the characteristics of the pacemaker response curves vary with the interpulse interval, At. As At was increased from 5 to 10 to 25 msec, there was a progressive increase in the amplitude of the pacemaker response curve, and in the mean P-P interval over the entire curve. When At was increased from 25 to 50 msec, there was no appreciable change in the mean P-P interval, but the amplitude of the pacemaker response curve was diminished.

In the dog from which Figures 1 and 2 were derived, stimulus bursts were used that contained either 5 or 10 pulses, and the following values of At were used: 5, 10, 25, 50, and 100 msec. For 5 pulses/burst, a At of 250 msec was also used. The various permutations of At and numbers of pulses per burst were applied in a random sequence. The amplitudes of the resultant pacemaker response curves are shown in Figure 3. It is apparent that for At < 100 msec, the amplitude of the pacemaker response curve was greater with 10 than with 5 pulses per burst. Also with either 5 or 10 pulses per

---

**Figure 2** The change in cardiac cycle length (P-P interval) as a function of the P-St interval, in the same representative experiment depicted in Figure 1. Vagal stimuli all consisted of 10 pulses/burst; the interpulse intervals are denoted by the numbers (in msec) at the right end of each curve. The continuous portions of each curve were derived from records similar to that shown in Figure 1; the dashed portions are interpolated.

**Figure 3** The amplitude of the pacemaker response curve as a function of interpulse interval (At) in a representative experiment. The data were derived from the same dog as in Figures 1 and 2. The open circles were obtained with vagal stimuli containing 5 pulses/burst, the closed circles, with 10 pulses/burst. The curves represent the following regression equations: for 5 pulses/burst, \[ A = 1099 \exp(-At/38.39) - 1081 \exp(-At/28.26), \] and for 10 pulses/burst, \[ A = 1762 \exp(-At/24.82) - 1779 \exp(-At/15.36), \] where A is the curve amplitude, and At, the interpulse interval.
burst, the amplitude of the pacemaker response curve became greater as Δt was raised up to 25 msec. With greater intervals, the amplitude decreased as Δt was increased.

Regression equations of the form \( A = c_1 \exp(-\Delta t/\kappa_1) - c_2 \exp(-\Delta t/\kappa_2) \) were derived for the data obtained with 5 and 10 pulses/burst, where \( A \) is the amplitude of the pacemaker response curve, \( \Delta t \) is the interpulse interval, and \( c_1, c_2, \kappa_1, \) and \( \kappa_2 \) are the regression coefficients. The continuous curves in Figure 3 represent the corresponding regression equations. The equations were differentiated, and the first derivatives were set equal to zero to determine the maxima. For the data in Figure 3, the peak amplitude with 5 and 10 pulses/burst occurred at interpulse intervals of 31.0 and 19.7 msec, respectively.

Regression equations of this form were derived for the data from each dog. The equations then were solved for amplitudes at interpulse intervals of 5, 10, 25, 40, 50, 100, and 150 msec, and from these fitted values were derived the composite data shown in Figure 4. For values of \( \Delta t < 100 \) msec, the curve amplitudes were greater with 10 than with 5 pulses/burst. With either 5 or 10 pulses/burst, the curve amplitudes increased progressively as \( \Delta t \) was increased from 5 msec to some optimal value. For 5 pulses/burst, the optimal value of \( \Delta t \) was 30.2 msec, and the peak amplitude was 216 msec; for 10 pulses/burst, the corresponding values were 24.3 and 345 msec, respectively. The differences in peak amplitude at 5 and 10 pulses/burst were calculated for each experiment. The mean difference for all experiments was significantly different from zero.

\[ P < 0.005. \]

Also, the difference in the values of \( \Delta t \) that produced the peak amplitude was determined for each experiment. The mean difference for all experiments was not statistically significant.

The arithmetic average of the maximal and minimal values for each pacemaker response curve was determined as an approximation of the mean P-P interval for that curve. For each dog, third-degree polynomial regression equations were derived. The following composite regression equations were derived: for 5 pulses/burst, \( Y = 720.9 + 4.907 \Delta t + 0.0228 (\Delta t)^2 - 0.00104 (\Delta t)^3 \); and for 10 pulses/burst, \( Y = 700.4 + 16.43 \Delta t - 0.1355 (\Delta t)^2 - 0.0002 (\Delta t)^3 \). The lowest value of the nonlinear correlation coefficient (\( r \)) was 0.76, and \( r > 0.90 \) for 16 of the 20 regression equations. From the regression equations for the individual experiments, fitted values of the averages were determined over the \( \Delta t \) range from 5 to 50 msec, at intervals of 5 msec. From these fitted values, regression equations were computed for the composite data from the entire series of experiments. The curves derived from these regression equations are shown in Figure 5. It is apparent that, for any given value of \( \Delta t \), the average P-P interval was greater with 10 pulses/burst than with 5 pulses/burst. Also, an increase in \( \Delta t \) was accompanied by an increase in the average P-P interval, regardless of the number of pulses/burst. The rate of change of the average P-P interval with \( \Delta t \) decreased as \( \Delta t \) increased. At values of \( \Delta t \) close to 50 msec, the slope approached zero; i.e., there was virtually no further increase in the average P-P interval as \( \Delta t \) approached 50 msec.
Discussion

The data from this study and from previous experiments have shown that the time in the cardiac cycle at which a vagal stimulus is delivered is an important determinant of the chronotropic response. Thus, at some point in the cardiac cycle, a vagal stimulus will be maximally effective; at some other point in the cycle, it will be minimally effective. Such maximally and minimally effective times are denoted by the letters a and c in Figure 6, to correspond with the notations in Figures 1 and 2. If the vagal stimulus consists of a burst of 5 pulses, and if the third pulse occurs at the time of maximum efficacy (a), it might be anticipated that more closely spaced bursts of impulses would have a greater negative chronotropic effect than would more widely spaced impulses. In Figure 6, for example, 5-pulse bursts are shown with interpulse intervals (Δt) of 5 and 25 msec. For either value of Δt, the third pulse in the burst is shown to occur at time a. It is evident from the figure that the negative chronotropic effects of pulses 1, 2, 4, and 5 are greater for Δt = 5 msec than for Δt = 25. Other factors being equal, therefore, the maximal negative chronotropic effect of an entire burst of 5 pulses should be greater when Δt = 5 msec than when Δt = 25 msec.

Similarly, if the third pulse in the burst falls at the time of minimal efficacy (c), the negative chronotropic effect of a tightly packed burst of pulses (Δt = 5 msec) should be less than that of a more loosely packed burst of pulses (Δt = 25 msec). In Figure 6, for example, the negative chronotropic effects of pulses 1, 2, 4, and 5 are less for Δt = 5 msec than for Δt = 25 msec. Hence, the ability of a burst of several pulses to resolve the maximal and minimal negative chronotropic effects of vagal stimulation should be greatest at some small value of Δt, and should become more blunted as the value of Δt is progressively increased. This ability of a burst of vagal stimuli with a given value of Δt to define the maximal and minimal chronotropic effects will be referred to as the "resolution power" of the burst.

The amplitude of the pacemaker response curve was defined above as the difference between the maximal and minimal ordinate values. On the basis of the resolution power alone, therefore, the amplitude of the pacemaker response curves should be maximum at some small value of Δt, and it should diminish as Δt is progressively increased. However, as shown in Figures 3 and 4, the amplitude of the pacemaker response curves was not maximum at the lowest value of Δt (5 msec) used in our experiments, but the amplitude increased considerably as Δt was increased from this least value up to about 25 to 30 msec. Beyond the optimal value of Δt, the amplitude of the pacemaker response curve did diminish progressively with further increases in Δt. It is likely, therefore, that at least two opposing mechanisms come into play to determine the effect of the interpulse interval on the amplitude of the pacemaker response curve. One factor is the resolution power of the burst of impulses; this power diminishes as Δt increases. An opposing factor probably involves a change in either the quantity of acetylcholine released or the saturation of the response with a change in Δt. It is apparent from Figure 2 that, as the interpulse interval was increased from 5 to 25 msec, there was a concomitant increase in the mean P-P interval. For any given P-St interval, the P-P interval was greater with Δt = 25 msec than with Δt = 5 msec. For any given curve, regardless of the interpulse interval, 1:1 synchronization prevailed; i.e., there was one burst of stimuli during each cardiac cycle. Because the P-P interval was greater at a given P-St interval when Δt = 25 msec than when Δt = 5 msec, there were actually fewer vagal stimulus bursts given per unit of time at the greater than at the lesser value of Δt. It is apparent, therefore, that the stimulus bursts with the greater interpulse intervals exerted a more potent negative chronotropic effect than did those with the lesser interpulse intervals.

These conclusions are verified by the composite data shown in Figure 5. As Δt was increased from 5 to 50 msec, there was a progressive increase in the average P-P interval. These data strongly suggest either a saturation phenomenon at the cardiac receptors, a change in the quantity of acetylcholine (ACh) released at the nerve endings per pulse, or a combination of the two phenomena. The intensities of the individual pulses used in these experiments were supramaximal. Therefore, the ACh in the region of the muscarinic receptors on pacemaker cells may have achieved supramaximal concentrations when the individual pulses were tightly packed. This tendency toward saturation would be less pronounced the greater the interval between successive pulses.

Alternatively, the quantity of ACh released per

![Diagram](http://circres.ahajournals.org/)
pulse might increase with greater spacing between the individual pulses. At the lower values of Δt, it is conceivable that the stimulus repetition rate may be such that the efferent cardiac vagal fibers are not able to conduct impulses at such high frequencies. The smallest value of Δt used in the present study was 5 msec, which corresponds to a stimulus repetition rate of 200 Hz. In a recent study by McAllen and Spyer,10 five of 15 cardiac vagal preganglionic neurons tested in the cat had an absolute refractory period of 5 msec or greater. Such fibers would not be able to conduct impulses at the smallest value of Δt used in our experiments. In a previous study10 on dogs that was conducted in our laboratory, the value of Δt used in all experiments was 3 msec. There was a clear gradation in the magnitudes of the responses with changes in the number of stimuli per burst. For example, the chronotropic response to two stimuli per burst (Δt = 3 msec) was considerably greater than that obtained with only one stimulus per burst (e.g., Fig. 1, Ref. 8). It is likely, therefore, that most of the efferent vagal fibers were able to conduct impulses at the minimal value of Δt (5 msec) used in the present series of experiments.

Therefore, the change in ACh release may be ascribable to processes taking place at the synapse between the pre- and postganglionic parasympathetic neurons or at the junction between the postganglionic nerve terminals and the cardiac effector cells. Studies on various types of synapses have shown that when the period between presynaptic action potentials is too small, there may be inadequate time for some neurosecretory vesicles to move close enough to the presynaptic terminal membrane to be released into the synaptic cleft at the arrival of the next action potential.11,12 The experiments of Dennis et al.13 have demonstrated that synaptic transmission at parasympathetic ganglia in the frog heart resembles the processes that take place at most other synapses.

It is also likely that a negative feedback mechanism operates at parasympathetic postganglionic nerve terminals, whereby ACh released at the terminals tends to inhibit subsequent release from the same nerve endings.14-16 The more tightly packed the individual pulses in a burst, the greater will be the ACh concentration at the postganglionic nerve terminals during the burst. This in turn may tend to diminish the quantity of ACh released from these same terminals. Such a negative feedback mechanism has been demonstrated at cerebral synapses44 and at parasympathetic terminals in the intestine,15,16 but it has not yet been shown to operate in the heart.

Thus, we propose that two opposing mechanisms are activated as the interpulse interval is changed. As Δt is increased, the tendency for less saturation of the postsynaptic receptors or more neurotransmitter release serves to augment the amplitude of the pacemaker response curve. Conversely, the resolution of power of the stimulus bursts will diminish as Δt is increased, and therefore the curve amplitude will be reduced. The result of these two opposing effects probably accounts for the overall results observed in Figures 3 and 4. As Δt is increased up to its optimal value of 25 to 30 msec, the enhancing factors evidently predominate; at Δt exceeds the optimal value, the curtailing factors are preponderant.

Efferent cardiac vagal impulses tend to occur at preferential times in the cardiac cycle,14 as noted in the introduction. The fraction of the cycle over which the vagal impulses are distributed varies with the prevailing conditions, but the groups of impulses may occupy a substantial fraction of the cardiac cycle. The data presented in this study show that, even when the grouped efferent impulses occupy a large fraction of the cardiac cycle, they may still exert a potent synchronizing effect on the SA nodal pacemaker cells. For example, in the pacemaker response curves shown in Figure 2, there were 10 pulses/burst, and four different interpulse intervals. The total duration of a given burst is (n - 1) Δt, where n is the number of pulses per burst, and Δt is the interpulse interval. For Δt = 50 msec, therefore, the burst duration was 450 msec, and the average P-P interval was 970 msec (Fig. 2). Thus, the vagal burst occupied almost half of the duration of the cardiac cycle, and yet 1:1 synchronization prevailed over an appreciable range of P-P intervals (180 msec). Over such a range, heart rate bears a direct rather than an inverse relationship to the frequency of the bursts of vagal activity. In the intact animal, therefore, the characteristics of the grouping of efferent vagal activity may be an important determinant of the magnitude and even the direction of an evoked change in heart rate. It is also evident that considerably more information is required before the precise relationship between heart rate and vagal activity is known.

References
5. Reid JVO: The cardiac pacemaker: effects of regularly spaced nervous input. Am Heart J 78: 56-64, 1969
10. McAllen RM, Spyer KM: The location of cardiac vagal...
Beneficial Action of a New Angiotensin-Converting Enzyme Inhibitor (SQ 14,225) in Hemorrhagic Shock in Cats

GEORGE J. TRACHTE AND ALLAN M. LEFER

SUMMARY A new angiotensin-converting enzyme inhibitor (CEI), SQ 14,225, was infused at 0.5 mg/kg per hr, iv, into cats to determine its effect in hemorrhagic shock. Cats were bled to a mean arterial blood pressure (MABP) of 40 mm Hg for 150 minutes; this was followed by reinfusion and a 120-minute postoligemic observation period. Hemorrhagic shock and sham shock controls were given an infusion of the CEI or its vehicle (0.9% NaCl). The degree of converting enzyme inhibition was assessed by measuring pressor responses to angiotensin I and II and by radioimmunoassay determination of plasma angiotensin II concentrations. In vitro studies on cat papillary muscles and vascular smooth muscle strips revealed no direct isotropic or vasoactive effect of SQ 14,225. Nevertheless, hemorrhaged cats given the CEI demonstrated a significantly higher final arterial pressure than hemorrhaged cats given 0.9% NaCl (96 vs. 51 mm Hg) (P < 0.01), indicating a significant prolongation of circulatory stability which is closely related to survival. Circulating lysosomal hydrolase (i.e., cathepsin D) activity (3.5 vs. 11-fold increases) and total plasma proteolysis (25% vs. 100% increases) were significantly reduced in the shocked cats given the CEI compared to the untreated shocked animals. Formation of a myocardial depressant factor (MDF) also was significantly diminished by CEI treatment (26 vs. 62 U). These results indicate that CEI improved the hemodynamic and biochemical status of cats in hemorrhagic shock and suggest that blockade of angiotensin II formation may be beneficial in hemorrhagic shock. Abolition of other actions of converting enzymes (e.g., potentiation of bradykinin action or inhibition of proteolysis) may also be involved in the protective mechanisms.

This is particularly relevant in hemorrhagic shock, since early hypoperfusion of the splanchic organs and later myocardial impairment are processes in which angiotensin II may play an important contributory role.

The development of a more efficient CEI, SQ 14,225, provided a pharmacological method with which to attempt to characterize the role of angiotensin II in hemorrhagic shock, as well as to assess the effectiveness of converting enzyme inhibitors as therapeutic agents in shock. These possibilities were tested in cats subjected to a standardized hemorrhagic shock protocol with particular attention given to the consequences of lysosomal integrity and proteolysis as well as to hemodynamic status. Angiotensin II concentrations were monitored to test the completeness of the converting enzyme blockade and to evaluate the time course of changes in circulating angiotensin II concentra-

From the Department of Physiology, Jefferson Medical College, Thomas Jefferson University, Philadelphia, Pennsylvania.

Supported in part by Research Grant No. HL14777 from the National Heart, Lung, and Blood Institute of the National Institutes of Health.

Dr. Trachte is a Fellow of the Ischemia-Shock Research Institute of Thomas Jefferson University.

Address for reprints: Dr. Allan M. Lefer, Department of Physiology, Jefferson Medical College, Thomas Jefferson University, Philadelphia, Pennsylvania 19107.

Received February 27, 1978, accepted for publication May 17, 1978.
The effect of changing interpulse intervals on the negative chronotropic response to repetitive bursts of vagal stimuli in the dog.
M N Levy, S Wexberg, C Eckel and H Zieske

Circ Res. 1978;43:570-576
doi: 10.1161/01.RES.43.4.570

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1978 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/43/4/570

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation Research can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation Research is online at:
http://circres.ahajournals.org/subscriptions/