J. Physiol. (1979), **297**, *pp.* 61–71
With 7 text-figures
Printed in Great Britain

ARTERIAL PRESSURE AND PULSE INTERVAL RESPONSES TO REPETITIVE CAROTID BARORECEPTOR STIMULI IN MAN

BY ARCHER L. BASKERVILLE, DWAIN L. ECKBERG*, AND MELISH A. THOMPSON†

From the Departments of Medicine and Biophysics, Veterans Administration Medical Center and Medical College of Virginia, Richmond, Virginia 23298, U.S.A.

(*Received 6 March 1979*)

SUMMARY

1. Carotid baroreceptors of eight healthy young men were stimulated with brief (0·6 sec), moderate (30 mmHg), single or repetitive (2, 3 or 5), R wave coupled neck suction during held expiration, and brachial arterial pressure and pulse interval changes were measured for 10 sec.

2. Mean systolic arterial pressure declined significantly from control levels after single or multiple baroreceptor stimuli. The reduction of systolic pressure was significant within the first sec after the onset of trains of baroreceptor stimuli; its duration was proportional to the number of stimuli.

3. The sinus node response to a single baroreceptor stimulus was biphasic: inhibition was followed by less intense, but more prolonged facilitation (cardio-acceleration). A single baroreflex stimulus modulated sinus node function for about 7 sec. The integral of sinus node inhibition was linearly related to the number of baroreceptor stimuli. Inhibition with five repetitive stimuli peaked at about 1·5 sec after the onset of stimulation and declined to a new steady-state level during the period of baroreceptor stimulation.

4. Human baroreflex adjustments of arterial pressure and sinus node function occur very early after a step increase of phasic baroreceptor afferent activity. The perturbation of sinus node function is complex and probably reflects changing temporal relationships between the arterial pulse and sinus node activity, and interactions between oscillating levels of acetylcholine and sinus node responsiveness to acetylcholine.

INTRODUCTION

The natural arterial baroreflex stimulus, the arterial pulse, occurs as a continuous train. The principal haemodynamic consequences of a *single* arterial baroreceptor stimulus, arterial pressure reduction and sinus node inhibition, develop after a finite latency, and decay in a predictable and reproducible manner (Brown & Eccles, 1934; Eckberg, 1976). We undertook the present study to characterize the haemo-

* Clinical Investigator, Veterans Administration.
† Present address: Milwaukee Medical Clinic, 3003 West Good Hope Road, Milwaukee, Wisconsin 53209.

0022-3751/79/6170-0078 $01.50

dynamic consequences of *trains* of baroreceptor stimuli. If changes mediated by a single baroreflex stimulus persist for more than one cardiac cycle, arterial pressure and pulse interval at any instant will be influenced not only by the most recent arterial pulse, but also by pulses which preceded it. Thus, the pattern of haemodynamic changes provoked by natural trains of baroreceptor stimuli may be more complex than that caused by a single stimulus.

We studied the early transients of arterial pressure and pulse interval provoked by a step increase of the level of phasic afferent carotid baroreceptor activity in healthy young men. Our results suggest that arterial pressure and pulse interval responses to trains of baroreceptor stimuli occur very early, and are complex.

METHODS

Carotid baroreceptors of eight young men were stimulated with moderate, brief, single or multiple (2, 3 or 5) applications of R wave coupled neck suction, and changes of brachial arterial pressure and sinus node function were measured for 10 sec.

Subjects. We studied eight healthy young men whose average age was 24 ± 0·5 (S.E. of mean) yr. All subjects gave their written, informed consent to participate in the study.

Measurements. An ink writing recorder was used to transcribe the electrocardiogram, beat-by-beat pulse interval, respiratory activity (measured with a pneumograph), and arterial and neck chamber pressures (measured with strain gauge pressure transducers). The arterial pressure transducer was positioned at the level of the right atrium and was connected to an indwelling, plastic, 21 gauge left brachial artery catheter via a short, saline filled connector. The pressure recording system used produces a flat response to 10 Hz. Volunteers were studied in the supine position.

Baroreceptor stimulation. Carotid baroreceptors were stimulated by suction applied to a neck chamber (Eckberg, Cavanaugh, Mark & Abboud, 1975). Neck suction was applied for 0·6 sec by rotation of a solenoid pneumatic valve which established continuity between the neck chamber and a continuous vacuum source. Rotation of the valve occurred about 50 msec after the downslope of the R wave; thus, the external carotid baroreflex stimulus was superimposed upon the natural carotid arterial pulse. This method was chosen to simulate the natural arterial pressure pulse as closely as possible. The intensity of stimulation, −30 mmHg, was chosen because it falls in the middle of the neck suction intensity–sinus node response relationship (Eckberg, 1977). One, two, three or five stimuli were applied during held expiration, and arterial pressure and sinus node responses were measured for the next 10 sec. This experimental sequence was repeated with the vacuum source turned off to measure spontaneous arterial pressure and pulse interval changes during held expiration. Each intervention was repeated fifteen times. The sequence of interventions was varied in a random fashion.

In one subject, the recorder was run at 100 mm/sec and the area above each stimulus was measured with a planimeter. The areas of the first, second, third and fourth stimuli, expressed as percentages of the area of the fifth stimulus, were 91, 98, 98 and 100. The variance (S.D. of an observation) of the areas of the five stimuli averaged 1·8%. Thus, the stimuli were highly reproducible, but the first stimulus in each train was smaller than succeeding stimuli. This disparity resulted from unavoidable technical problems and occurred throughout all experiments. The actual stimuli delivered to one subject are shown in Fig. 1.

Data reduction. Arterial pressure measurements were taken directly from the recorder paper. The gain of the recorder amplifier was set so that a pressure change of 2 mmHg would produce a recorder pen deflection of 1 mm. Thus, arterial pressure measurements were accurate to at least 0·5 mmHg.

Pulse interval changes were measured on-line, in real time by a digital computer. There were two square wave input pulses to the computer generated by neck chamber pressure and R wave threshold crossings. The PR interval did not vary importantly during these studies; therefore, RR intervals were equal to PP intervals, and are referred to as such in this manuscript. The interval between the onset of the P wave and the R threshold crossing was measured during

each study and was subtracted from the stimulus to R wave interval to obtain the stimulus to P wave interval.

The following measurements and calculations were made for 10 sec after the beginning of the first neck suction (or valve rotation with the vacuum source turned off): the PP interval immediately preceding the stimulus (control interval); prolongation of successive PP intervals, from the control interval, after the onset of the first stimulus; and intervals between the onset of the first stimulus and successive P waves.

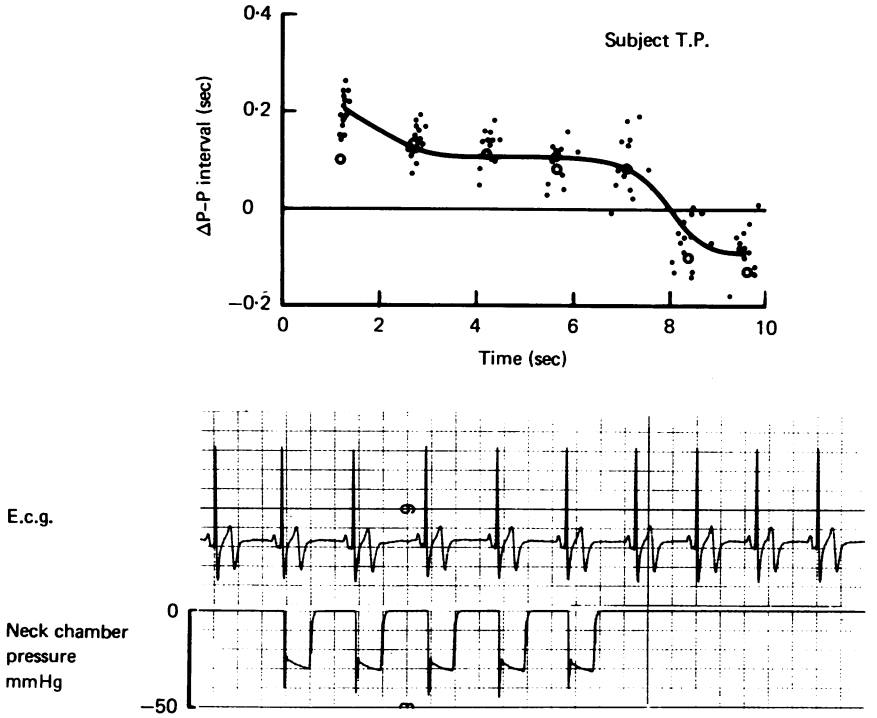

Fig. 1. All responses of one volunteer to fifteen baroreflex trains of five stimuli. Pulse interval responses to the train included in the lower portion of the Figure are indicated by large circles. The time scale of the graph is the same as that of the recorder. In this, and subsequent Figures, the reference point for the time scale (time = 0) was the leading edge of the first stimulus. The spikes in the neck chamber pressure tracing represent induced electromotive force caused by solenoid actuation. E.c.g. = electrocardiogram.

Statistical analyses. Statistical comparisons were made with the paired t test, least-squares linear regression and analysis of variance with orthogonal contrasts (Winer, 1962). Differences were considered significant when P was less than or equal to 0·05.

We also used a statistical technique (Eckberg, 1979*b*) to estimate objectively the time when the baroreflex mediated arterial pressure reduction began to recede. Briefly, we performed a least-squares linear regression analysis of the differences between systolic arterial pressure during held expiration, with and without neck suction. An arbitrary bending point (indicating the end of the fall of pressure and the beginning of the return of pressure to control levels) was chosen, and a computer program calculated the residual sum of squares for portions of the curve lying to the left, and to the right of this point. An iterative program shifted the bending point by 0·1 sec increments or decrements, and these calculations were repeated. The interval between the leading edge of the first stimulus and the time at which the residual sum of squares was least was considered to represent the duration of the hypotensive effect of baroreceptor stimulation.

RESULTS

Arterial pressure changes. The mean interval between the end of the expiratory chest movement and the first solenoid valve rotation (without neck suction) was 6·3 ± 0·4 sec. During the ensuing 10 sec of data collection, mean systolic pressure rose

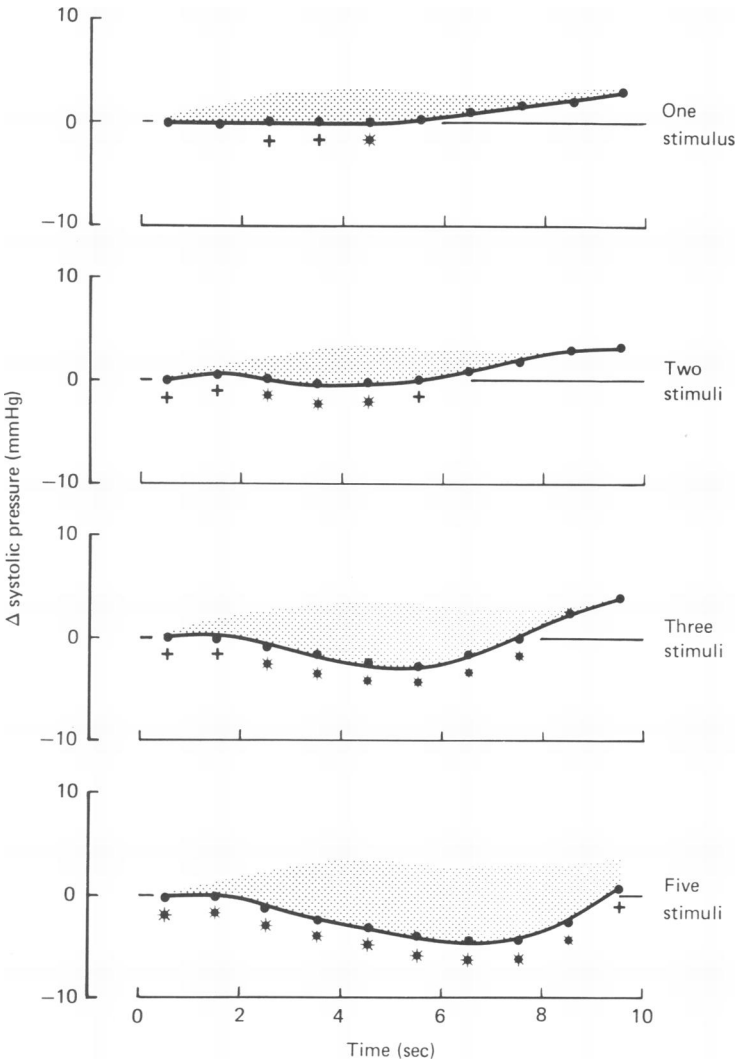

Fig. 2. Mean systolic pressure changes during held expiration with (continuous line, circles) and without (upper margin of each stippled area) neck suction for all volunteers. The S.E. of an observation was not depicted because it was small (average: 0·7 mmHg) and consistent (85 % lay between 0·5 and 1·0 mmHg). Symbols indicate paired (pressure change with or without neck suction) statistical comparisons (+ = $P < 0.05$; * = $P < 0.01$).

steadily (from 128 ± 4 mmHg) by 3·6 ± 1·1 mmHg ($P < 0.001$, compared with the control pressure); mean diastolic pressure rose (from 74 ± 2 mmHg) by 4·8 ± 1·0 mmHg ($P < 0.001$). The mean changes of systolic pressures, per sec, were 0·6 ± 0·1, 1·6 ± 0·4,

2·5 ± 0·5, 3·1 ± 0·7, 3·5 ± 0·9, 3·0 ± 0·9, 2·9 ± 0·9, 2·9 ± 0·9, 3·3 ± 1·1, and 3·6 ± 1·1 mmHg. The spontaneous rise of systolic pressure during held expiration is depicted in Fig. 2 (upper margin of each stippled area).

The time courses of systolic arterial pressure changes after the onset of single or repetitive baroreceptor stimuli are summarized in Fig. 2. Single stimuli and trains of two stimuli did not lead to significant reduction of systolic arterial pressure below the

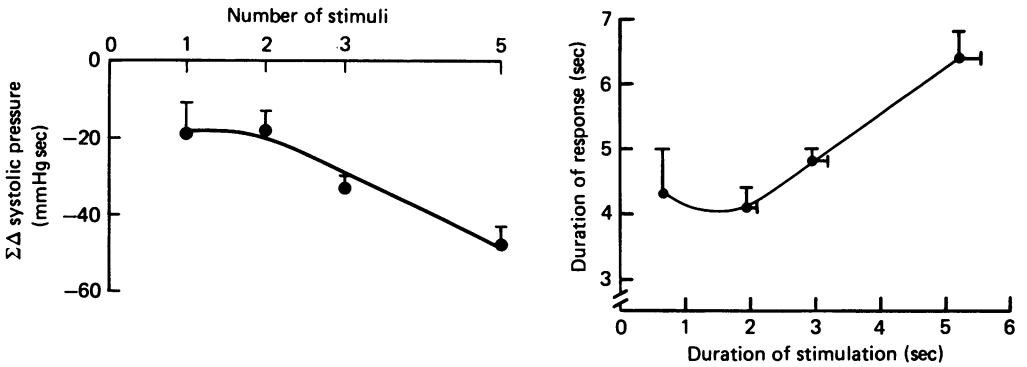

Fig. 3. Mean integrals (stippled areas, Fig. 2) of the changes of systolic pressure. Brackets encompass 1 S.E. of an observation.

Fig. 4. Mean duration of the hypotensive response. The duration of the response was considered to be the time from the onset of the first stimulus until the pressure reduction began to lessen (see Methods).

last pressure recorded before the onset of stimulation (indicated by the 0 base line); however, systolic pressures after these interventions were significantly lower than pressures at the same intervals after the onset of held expiration without neck suction (the disparities are shown by the stippled areas). Fig. 2 indicates that significant reductions of systolic arterial pressure during trains of baroreceptor stimuli occurred within the first second, and that the duration and magnitude of pressure reduction were proportional to the number of stimuli in the train.

The relationship between the stippled areas (integrals of the differences of systolic pressure) and the number of stimuli is shown in Fig. 3. One and two stimuli led to comparable reductions of systolic pressure; two, three and five stimuli provoked integrated pressure reductions which were linearly ($r = 0{\cdot}68$, $P < 0{\cdot}001$) related to the number of stimuli. The estimated duration of the baroreflex mediated hypotensive effect is shown in Fig. 4. (This Figure also indicates the mean duration of the total period of stimulation, for each stimulus pattern.) One and two stimuli (stimulation lasting 0·6 and 1·9 sec) provoked pressure reduction which began to recede at 4·3 ± 0·7 and 4·1 ± 0·3 sec. With trains of two, three and five stimuli, pressure reduction began to recede about 2 sec after the end of each train.

Changes of diastolic pressures (Fig. 5) tended to parallel changes of systolic pressure; for this reason, we focused our attention primarily upon systolic pressures. In the fifty pairs of data (one measurement/sec for 10 sec; four patterns of stimuli and one control), mean changes were comparable ($P > 0{\cdot}05$) in 32, systolic changes

were greater than diastolic in eleven, and diastolic changes were greater than systolic in seven.

Sinus node responses. All responses of one subject to fifteen trains of five baroreceptor stimuli are shown in Fig. 1. To obtain this plot, prolongation of successive PP intervals was plotted as a function of the interval between the onset of the first

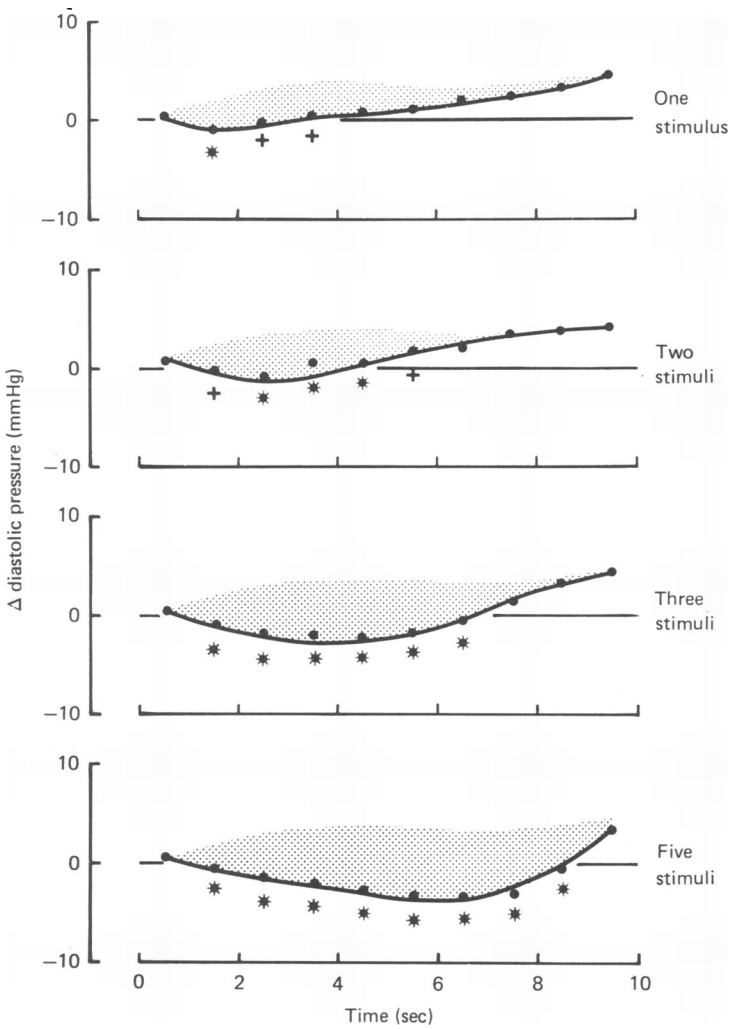

Fig. 5. Mean diastolic pressure changes during held expiration with (continuous line, circles) and without (upper margin of each stippled area) neck suction.

stimulus and P waves concluding each cycle. The aggregation of points at regular intervals occurred because of the coupling of stimuli to the R waves of successive beats. In this volunteer (who had the slowest base line heart rate of all those studied) there were no P waves during the first sec after the onset of baroreceptor stimulation. The level of inhibition peaked at about 1·3 sec and declined to a new steady-state level during the period of stimulation. After the cessation of stimulation, inhibition

declined and was followed by facilitation (heart rate slowing was succeeded by cardioacceleration).

Responses of all volunteers, averaged at 1 sec intervals, are depicted in Fig. 6. The mean PP interval during held expiration without neck suction (designated 0) did not differ significantly from the mean control interval, which was 1·07 ± 0·07 sec.

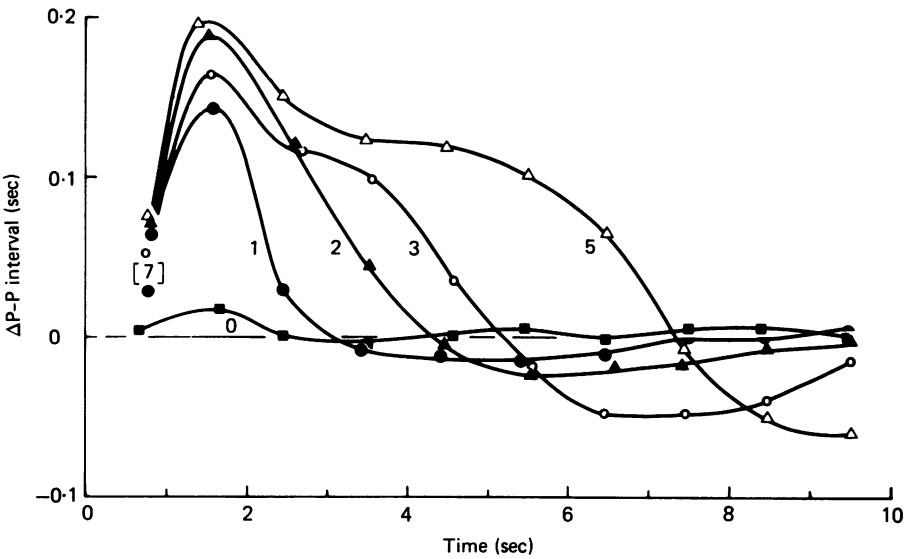

Fig. 6. Mean PP interval responses of all volunteers to all interventions. Numbers in the Figure refer to the number of baroreceptor stimuli for each curve. Changes of pulse interval during held expiration without neck suction are designated 0. In one subject, P waves did not occur during the first second after the onset of baroreceptor stimulation.

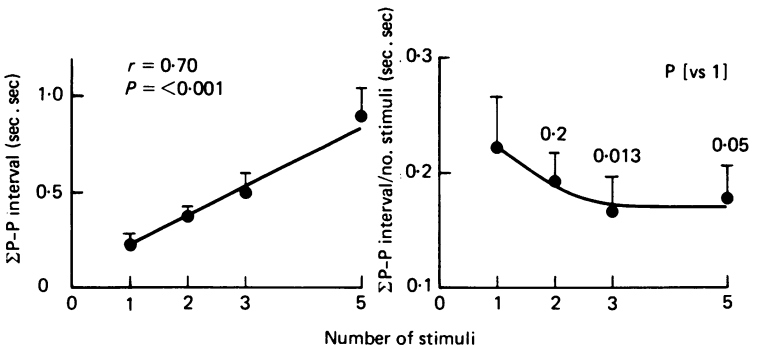

Fig. 7. Mean integrals of the sinus node inhibition (areas above the base line, Fig. 6), left panel, and mean integral of inhibition divided by the number of stimuli, right panel.

Baroreflex mediated sinus node inhibition was maximal at about 1·5 sec. The timing of the onset of the decline of inhibition varied directly with the number of stimuli; the rate of decline appeared to be independent of the number of stimuli. During trains of five stimuli, the level of sinus node inhibition reached a new, steady-state. Sinus node inhibition was followed by facilitation which appeared to be proportional to the number of stimuli.

The integrals of inhibition (area under the positive portion of each curve) were measured and are depicted in Fig. 7. The mean integral of inhibition, left panel, was linearly ($r = 0{\cdot}70$, $P < 0{\cdot}001$) related to the number of stimuli. The integral of inhibition, divided by the number of stimuli is shown in the right panel. The greatest inhibition per stimulus resulted from a single stimulus; the amount of inhibition per stimulus was less with two stimuli and was least with trains of three and five stimuli.

DISCUSSION

We studied transient changes of arterial pressure and pulse interval provoked by short trains of carotid arterial baroreceptor stimuli. We focused upon the *earliest* baroreflex responses because we felt that these would be least likely to be altered by opposing changes triggered by reflex aortic hypotension. We applied stimuli in R wave coupled *trains* because we wanted to reproduce the natural arterial baroreflex stimulus as faithfully as possible.

Arterial pressure changes. In this study, we initiated baroreceptor stimulation after about 6 sec of held expiration, and measured arterial pressure and pulse interval changes during the ensuing 10 sec. We chose this approach for two reasons. First, the average pulse interval is nearly constant during held expiration (Eckberg, 1976; this manuscript, Fig. 6). Therefore, changes of pulse interval after baroreceptor stimulation are more likely to be due to the baroreflex than to spontaneous variability. Secondly, respiratory activity appears to modulate human baroreflex responses (Eckberg & Orshan, 1977); it is likely that baroreflex responses elicited during held expiration are more uniform than those elicited without regard to the phase of respiration.

Systolic and diastolic pressures rose steadily during held expiration without baroreceptor stimulation (Figs. 2 and 5, upper margin of each stippled area). The rise of mean systolic pressure was minor (maximum: 3·6 mmHg), but highly significant ($P < 0{\cdot}001$). Although single and paired baroreceptor stimuli did not lower systolic arterial pressure below the level immediately prior to the onset of stimulation (designated 0 in each Figure) they significantly delayed the appearance of the normal rise which would have occurred.

The lowering of systolic pressure from control levels (Fig. 2, stippled areas), during the first sec after the onset of baroreceptor stimulation was small (mean: 0·7 mmHg), but significant for all trains of baroreceptor stimuli. Although baroreceptor stimulation may lead to abrupt cessation of efferent sympathetic nervous activity (Green & Heffron, 1968), reductions of systemic arterial pressure occur more slowly (Folkow, 1952). Therefore, it is likely that the small reduction of systolic pressure during the first sec of baroreceptor stimulation was due to cardiac slowing. We speculate that as early as the third sec, however, other factors, including reduction of systemic vascular resistance and possibly, left ventricular contractility may have begun to contribute. During the third sec, prolongation of the pulse interval had begun to decline (Fig. 6), but the reduction of systolic pressure continued apace (Fig. 2).

After the onset of the baroreflex train, arterial pressure declined steadily (Figs. 2 and 5). This steady decline is probably due primarily to abrupt withdrawal or

diminution of efferent sympathetic vasoconstrictor activity. Reversal of this process began about 2 sec after the end of the last baroreceptor stimulus (Fig. 4). Presumably restoration of efferent vasoconstrictor activity occurred earlier than this.

Sinus node responses. The mean pulse interval did not change significantly during held expiration (Fig. 6). During this period, a burst of efferent vagal activity probably followed each natural arterial pulse; thus, the level of sinus node inhibition was constant despite fluctuating levels of acetylcholine.

Sinus node inhibition occurred within the first sec after the onset of the first baroreceptor stimulus, and was maximal between the first and second seconds. Inhibition persisted for about 3 sec after the onset of a single baroreceptor stimulus, and was succeeded by facilitation (cardioacceleration). The duration of altered sinus node function (reflex latency and sinus node inhibition and facilitation) after a single stimulus was about 7 sec.

An earlier study (Eckberg, 1979*a*) showed that cardioacceleration after a brief baroreceptor stimulus is cholinergically mediated: this response was not altered by β-adrenergic blockade with propranolol, but was abolished by cholinergic blockade with atropine. We cannot determine what contribution the early, minor fall of arterial pressure after the onset of baroreceptor stimulation made to this cardioacceleration. We speculate (but cannot prove) that cardioacceleration after a *single* baroreflex stimulus was not influenced importantly by this factor. Neither systolic nor diastolic pressure fell significantly below the level immediately prior to the onset of the stimulus, and the mean difference between systolic pressures during held expiration with and without baroreceptor stimulation was only $1{\cdot}9 \pm 0{\cdot}3$ mmHg. Also, in one subject, cardioacceleration occurred after a single baroreflex stimulus despite a small *elevation* of arterial pressure above control levels. Cardioacceleration also follows a single electrical vagus nerve stimulus to the *isolated* heart (Spear, Kronhaus, Moore & Kline, 1979) and is believed to result from a complex membrane effect of acetylcholine. In this *in vitro* experiment, cardioacceleration cannot be attributed to reflex hypotension. Our results suggest that this phenomenon occurs in man and is an integral part of the sinus node response to a burst of efferent vagal traffic.

During a train of five baroreceptor stimuli, the pulse interval reached a new, steady-state level (Figs. 1 and 6). It is likely that this plateau was due to the attainment of a new equilibrium between augmented, oscillating levels of acetylcholine and sinus node membrane responsiveness to acetylcholine. A similar situation may have obtained during held expiration without baroreceptor stimulation (Fig. 6) when pulse interval was constant despite putative, continuous fluctuations of sinus node acetylcholine concentration.

We speculate that the level of the new plateau was lower than the maximum level of inhibition primarily because initial cardiac slowing shifted the natural arterial pulse to a position within the cardiac cycle where it provoked less sinus node inhibition (Eckberg, 1976). This mechanism probably occurs physiologically: any abrupt change of heart rate will reorder the temporal relationship between the inhibitory arterial pulse and sinus node susceptibility to cholinergic inhibition. This reasoning may also explain why single baroreflex stimuli provoked more sinus node inhibition per stimulus than repetitive stimuli (Fig. 7, right panel). An alternative, and not

mutually exclusive explanation for the new plateau is that the new level reflected, in part, the algebraic sum of inhibitory and facilitatory influences. Cardioacceleration provoked by the earliest stimuli in the train would have occurred by the time the new plateau was established.

The linear relationship between the integral of sinus node inhibition and the number of stimuli in trains of baroreflex stimuli (Fig. 7, left panel) suggests that reproducible, repetitive baroreceptor stimuli release reproducible quantities of acetylcholine. The linear relationship between the integral of systolic arterial pressure (Fig. 3) and the duration of the hypotensive effect of baroreflex trains (Fig. 4), suggests that each baroreceptor stimulus in a train provokes similar withdrawal of vasoconstrictor activity.

Synthesis. The human arterial baroreceptor reflex is an exquisite, finely tuned, rapidly responding homeostatic mechanism. Reduction of systolic arterial pressure and heart rate begin within 1 sec after an increase of the level of phasic afferent baroreceptor traffic. If the new level of baroreceptor activity persists for several heart beats, a new hemodynamic equilibrium is established. If the level of baroreceptor activity returns to normal, arterial pressure and pulse interval are restored to previous levels within a few seconds.

The arterial pressure response occurring during the *first* second after the onset of a train of baroreceptor stimuli appears to constitute a special case; rules which apply later, do not apply in the first second (Figs. 3 and 4). This earliest arterial pressure response is probably mediated exclusively by heart rate slowing.

The sinus node response to baroreceptor stimulation is more complex than the arterial pressure response: the level of inhibition declines during constant levels of stimulation, and sinus node facilitation as well as inhibition, occurs. Sinus node responses probably are determined by several factors, including shifting temporal relations between the natural arterial pulse and sinus node depolarization, and simultaneously oscillating levels of acetylcholine and sinus node responsiveness to acetylcholine.

We thank Dr George W. Burke, III, Constance Ann Lazzaro, Karen Jean Fister, Rebecca R. Alberti, Katherine A. Harris, Laura Giannitrapani, Harry Bastow, III, and Douglas L. Bronnenberg for their expert assistance.

This research was supported by grants from the Veterans Administration and the National Institutes of Health (HL22546 and HL22296).

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