J. Physiol. (1980), **304**, *pp.* 489–502
With 8 *text-figures*
Printed in Great Britain

PHASE RELATIONSHIP BETWEEN NORMAL HUMAN RESPIRATION AND BAROREFLEX RESPONSIVENESS

BY DWAIN L. ECKBERG*, YESHIAREG T. KIFLE AND VANESSA L. ROBERTS

From the Departments of Medicine and Biophysics, Veterans Administration Medical Center and Medical College of Virginia, Richmond, Virginia 23249, U.S.A.

(*Received 11 June 1979*)

SUMMARY

1. We studied the influences of phase of respiration and breathing frequency upon human sinus node responses to arterial baroreceptor stimulation.

2. Carotid baroreceptors were stimulated with brief (0·6 sec), moderate (30 mmHg) neck suction during early, mid, and late inspiration or expiration at usual breathing rates, or, during early inspiration and expiration at breathing rates of 3, 6, 12, and 24 breaths/min.

3. Baroreceptor stimuli applied during early and mid inspiration and late expiration provoked only minor sinus node inhibition; stimuli begun during late inspiration and early expiration provoked maximum sinus node inhibition.

4. At breathing rates of 3, 6 and 12 breaths/min, expiratory baroreflex responses were significantly greater than inspiratory responses; at 24 breaths/min, however, inspiratory and expiratory baroreceptor stimuli produced comparable degrees of sinus node inhibition.

5. Our results delineate an important central biological rhythm in normal man: human baroreflex responsiveness oscillates continuously during normal, quiet respiration. The phase shift of baroreflex responsiveness on respiration suggests that this interaction cannot be ascribed simply to gating synchronous with central inspiratory neurone activity. Regularization of heart rate during rapid breathing is associated with loss of the differential inspiratory–expiratory baroreflex responsiveness which is present at usual breathing rates.

INTRODUCTION

There is a well studied, but still incompletely understood interrelationship between respiratory activity and arterial baroreflex responsiveness. One manifestation of a respiratory–baroreflex interaction is sinus arrhythmia, the rhythmic speeding and slowing of heart rate which occurs during quiet respiration.

Several lines of evidence suggest that sinus arrhythmia results from a central reflex interaction. Arterial baroreceptor, or electrical carotid sinus nerve stimuli are less likely to augment efferent cardiac vagal activity or to slow heart rate when they are applied in inspiration than in expiration (Koepchen, Wagner & Lux, 1961; Iriuchijima

* Clinical Investigator, Veterans Administration.

0022-3751/80/1070-0274 $07.50

& Kumada, 1964; Jewett, 1964; Katona, Poitras, Barnett & Terry, 1970; Haymet & McCloskey, 1975; Eckberg & Orshan, 1977). Efferent activity in cardiac vagal branches is interrupted or greatly diminished during inspiration (Iriuchijima & Kumada, 1964; Jewett, 1964; Katona *et al.* 1970; Kunze, 1972); and sinus arrhythmia is nearly abolished by cholinergic blockade with atropine (Katona & Jih, 1975), or by reduction of afferent baroreceptor nerve traffic by arterial hypotension (Anrep, Pascual & Rössler, 1936*a*), bilateral common carotid artery occlusion (Schweitzer, 1935) or transection of the carotid and aortic nerves (Hering, 1933).

The phase relationship between respiration and baroreflex responsiveness has not been characterized fully. Since it is clear that baroreflex responses are smaller during inspiration than expiration, some authors have regarded this interaction as an all-or-none phenomenon. For example, Lopes & Palmer (1976) suggested that baroreflex responses are determined by the position of a central 'gate' which is closed during inspiration and open during expiration. Other authors, however, suggest that this relationship may not be straightforward. Seller, Langhorst, Richter & Koepchen (1968) found that baroreflex responsiveness *increases* during inspiration and *diminishes* during expiration. Thus, baroreflex responsiveness during respiration may vary as a continuous, rather than as a discrete, two-state (on–off) function. Moreover, putative respiratory baroreflex 'gating' is not always obvious: at rapid breathing rates, heart rate tends to become constant (Angelone & Coulter, 1964). The mechanisms underlying regularization of heart rate during rapid breathing have not been delineated.

We undertook this study to characterize quantitatively the rhythmic fluctuations of baroreflex responsiveness which occur during quiet breathing, and to determine if reduction of sinus arrhythmia during rapid breathing is due to an altered respiration–baroreflex interaction. We stimulated carotid arterial baroreceptors of unsedated human volunteers with brief suction applied to a neck chamber at six times in the respiratory cycle, at usual breathing rates or at four predetermined breathing rates. We found that the quality of central baroreflex modulation varies continuously during normal respiration, and that at rapid breathing rates, regularization of heart rate is associated with reduction of the usual differential responsiveness to inspiratory and expiratory baroreceptor stimuli.

METHODS

Carotid baroreceptors of six young adults were stimulated with brief, moderate neck suction applied during early, mid, and late inspiration or early, mid, and late expiration, at several breathing rates, and sinus node responses were measured.

Subjects. Volunteers comprised five men and one woman whose average age was 25 (range: 20–41) years. All subjects were healthy with normal blood pressures (average blood pressure: 118/78 mmHg) and none were taking medications. All subjects gave their written informed consent prior to the experiment. Each subject was studied twice.

Measurements. An ink writing recorder was used to transcribe the electrocardiogram, beat-by-beat pulse interval, end-tidal CO_2 concentration (infrared analyser), tidal volume (Fleisch pneumotachograph), and neck chamber pressure.

Control of respiration. Subjects were studied supine, in a quiet, darkened room. The pneumotachograph and CO_2 sample withdrawal lines were connected to a comfortable, but airtight anaesthesia face mask. Respiratory frequency and tidal volume were measured over a 5 min period after the subjects had become accustomed to the research environment. Respiratory frequency was controlled by a timed auditory signal delivered to headphones worn by the

volunteers. Respiratory rates were set at the average rate established by the volunteers during the initial five minute rest period, or at 3, 6, 12, and 24 breaths/min. Thus, we obtained measurements at the subjects' usual breathing frequencies (which averaged 10·3 breaths/min), at rates slightly slower (6 breaths/min) and slightly faster (12 breaths/min) than usual, and at rates which represented frank hypoventilation (3 breaths/min) and hyperventilation (24 breaths/min). Tidal volume was maintained at the level established during the rest periods, and was controlled by the volunteers who were guided by the excursions of an integrated pneumotachograph signal which they viewed upon a calibrated oscilloscope.

In the Tables and Figures, breathing rates are expressed as the interval between breaths. Breathing rates between data collection periods (which lasted 1 min or less) were not controlled; subjects tended to hyperventilate after very slow breathing and to hypoventilate after rapid breathing. The short periods of data collection, and the voluntary breathing patterns between periods of data collection prevented the large changes of end-tidal CO_2 concentration which would have occurred during sustained hypoventilation or hyperventilation.

Baroreceptor stimulation. Carotid baroreceptors were stimulated by suction applied to a neck chamber (Eckberg, Cavanaugh, Mark & Abboud, 1975). Neck suction was initiated by rotation of a solenoid pneumatic valve which established continuity between the neck chamber and a vacuum source. Rotation of the pneumatic valve was triggered by respiratory threshold crossings set at early, mid, and late inspiration, and early, mid, and late expiration (expiration was defined as the period of expiratory airflow). During studies in which breathing rate was varied systematically, pneumatic valve rotation was triggered by early inspiration or early expiration threshold crossings.

Stimuli of -30 mmHg for 0·6 sec were applied fifteen times at each respiratory threshold crossing, at each respiratory rate, and changes of P–P intervals (from the last P–P interval completed prior to the threshold crossing) were measured for the ensuing 3·6 sec. This experimental sequence was repeated with the vacuum source turned off to measure spontaneous fluctuations of P–P interval provoked by breathing. The different phases of the respiratory cycle and the different respiratory rates were studied in random sequence.

All measurements and calculations were made in real time by a dedicated on line digital computer. A threshold detector was set to time the upstroke of either the P wave or the R wave of the subject's electrocardiogram. The time interval from the actual onset of the P wave until this threshold crossing was subtracted from the stimulus-to-electrocardiogram threshold interval to obtain the stimulus-to-P wave interval for each cardiac cycle which occurred during the 3·6 sec following the stimulus onset, as described earlier (Eckberg, 1977*a*). Changes of successive P–P intervals (from the P–P interval immediately preceding the stimulus) were plotted as a function of the time elapsed between the stimulus and the P wave concluding each cardiac cycle (Eckberg, 1977*b*). P–P interval changes were averaged at 0·6 sec intervals.

Statistical analyses. Statistical significance was determined with the paired *t*-test (Winer, 1962). Differences were considered significant when P was less than 0·05.

RESULTS

Measurements were obtained from nine subjects, but data from three were discarded because their studies were technically unsatisfactory. One subject was unable to regulate his breathing according to the auditory and visual signals supplied. Two other subjects altered their tidal volumes when neck suction was applied. The remaining six subjects adequately controlled their breathing frequencies and tidal volumes throughout the experiment. In these subjects, tidal volumes and end-tidal carbon dioxide concentrations were comparable with and without neck suction.

Influence of respiratory phase. Fig. 1 shows P-P (or 'pulse') interval responses of one subject during one breath without neck suction (left panel), one in which neck suction was applied in mid inspiration (middle panel), and one in which neck suction was applied during mid expiration (right panel). The mid inspiratory stimulus did not provoke a major change of the usual pulse interval response to a breath, but the mid

expiratory stimulus provoked abrupt and profound pulse interval prolongation. The neck suction stimulus altered the pattern of respiratory airflow in a minor way.

Fig. 2 shows *all* pulse interval changes measured from a different volunteer after early inspiratory and mid expiratory threshold crossings, with and without neck suction. The spontaneous pulse interval response to inspiration (upper panel, circles) was biphasic: minor pulse interval shortening (cardioacceleration) was followed by

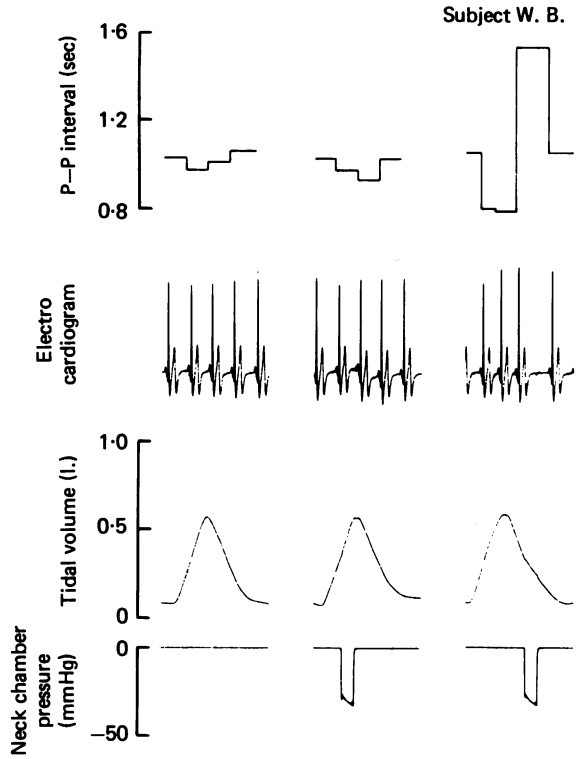

Fig. 1. Pulse interval changes of one subject during respiration with (centre and right panels) and without neck suction (left panel). The baroreflex stimulus applied during mid expiration (right panel) provoked a much greater sinus-node response than the stimulus applied during mid inspiration. Neck suction altered the usual breathing pattern in a minor way. Beat-by-beat pulse intervals were drawn after the experiment.

lengthening. In this subject, neck suction (triangles) provoked very minor pulse-interval prolongation when delivered in early inspiration, but major pulse interval prolongation when delivered in mid expiration (lower panel).

Average responses of all six subjects are shown in Fig. 3. Stimuli delivered in early and mid inspiration provoked minor pulse interval prolongation. There was considerable overlap between P – P interval changes which occurred spontaneously and those which followed neck suction. Baroreceptor stimuli applied during mid inspiration did not provoke significant pulse interval prolongation. In contrast, stimuli begun during other phases of respiration led to significant sinus node inhibition. The temporal pattern of responses to inspiratory stimuli appeared to be different from that of responses to expiratory stimuli: in each instance, maximum average inspiratory

responses occurred at 1·5 sec, whereas maximum average expiratory responses occurred at 0·9 sec, after the onset of the stimulus. Paired statistical comparisons between peak responses (between 0·6 and 1·8 sec) to stimuli begun at all phases of the respiratory cycle are given in Table 1.

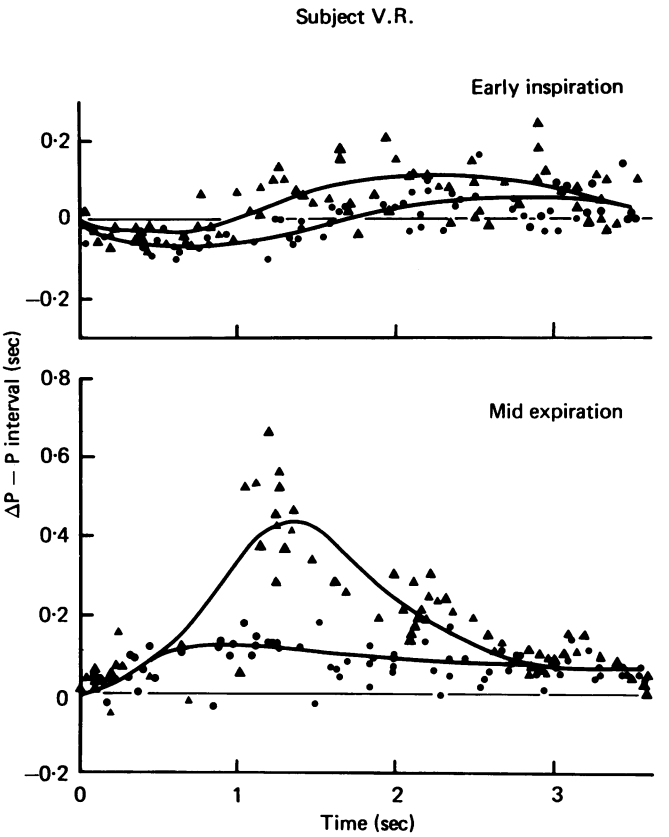

Fig. 2. All P–P interval responses from a different subject than the one shown in Fig. 1 to stimuli applied in early inspiration or mid expiration. Spontaneous P–P interval changes after the respiration threshold crossings are shown as circles, and changes after neck suction are shown as triangles. Responses were averaged at 0·6 sec intervals to obtain average curves.

The average tidal volume, times of baroreceptor stimulation, and maximum pulse interval responses to neck suction for all subjects are depicted in Fig. 4. There was an oscillation of baroreflex responsiveness during the respiratory cycle: responses were minimal when stimuli were applied in early and mid inspiration, maximal when stimuli were applied in late inspiration and early expiration, and intermediate when stimuli were applied in mid and late expiration.

Influence of respiratory rate. Average pulse interval changes of all volunteers during respiratory rates of 3, 6, 12, and 24 breaths/min are shown in Fig. 5. Neck suction during early inspiration (left panel) provoked significant pulse interval prolongation only at the slowest and most rapid breathing rates studied. Baroreceptor stimuli delivered during early expiration (right panel) led to significant pulse-interval pro-

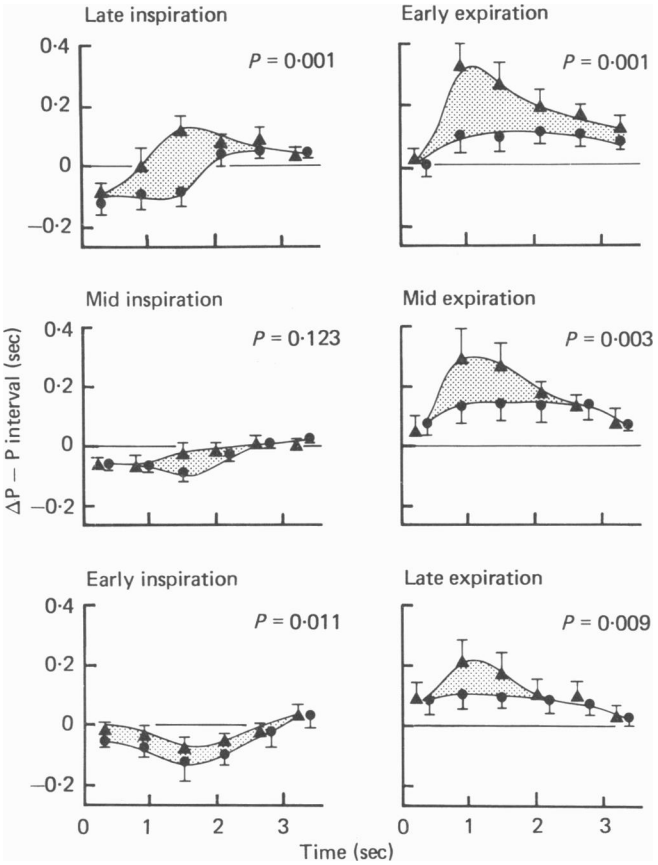

Fig. 3. Average pulse interval changes after each of six tidal volume threshold crossings, with (triangles) and without (circles) neck suction. *P* values were derived from a paired *t* analysis. Brackets encompass one S.E. of mean. The stippled areas indicate the change of pulse interval provoked by baroreceptor stimuli.

TABLE 1. Statistical analyses of maximal sinus-node responses (between 0·6 and 1·8 sec) to neck suction begun at different times in the respiratory cycle. *P* values were calculated with the paired *t* test

		Inspiration		Expiration		
		Mid	Late	Early	Mid	Late
Inspiration	Early	0·796	0·008	0·002	0·001	0·073
	Mid	—	0·002	0·015	0·009	0·041
	Late	—	—	0·292	0·992	0·275
Expiration	Early	—	—	—	0·159	0·063
	Mid	—	—	—	—	0·051

longation at all respiratory frequencies. Statistical analyses of these response patterns are given in Table 2 and Fig. 6. Responses to expiratory baroreceptor stimuli were significantly greater than responses to inspiratory stimuli at 3, 6 and 12 breaths/min. At 24 breaths/min, however, inspiratory and expiratory baroreceptor stimuli provoked comparable degrees of pulse-interval prolongation. Loss of the usual differential baroreflex responsiveness between inspiration and expiration was due primarily to reduction of expiratory baroreflex responses (Fig. 6).

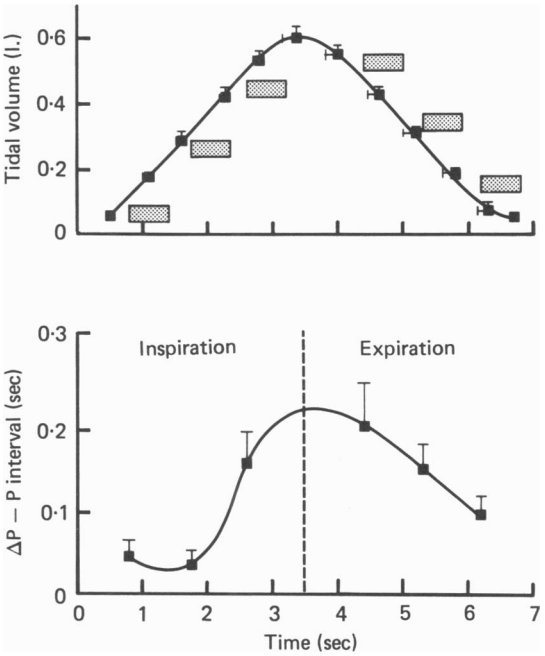

Fig. 4. The upper panel depicts the average tidal volume (integrated pneumotachograph signal) and the time of onset and duration of each baroreflex stimulus (stippled bars) for all volunteers. In the lower panel, average maximum P – P interval responses to neck suction are plotted at the time of the onset of the stimulus in the respiratory cycle. These measurements were obtained by subtracting pulse intervals occurring between 0·6 and 1·8 sec after the threshold crossing from those which followed neck suction during the same period of measurement. Similar patterns were found when differences were calculated for the entire 3·6 sec period of observation, and for the interval between 0·6 and 2·4 sec.

Tidal volume averaged 0·59 ± 0·01 l, and was maintained within very narrow limits by all volunteers (average S.D. of an observation: 15, range 11–22 ml.). The durations of inspiratory and expiratory airflow (measured at 5 and 95% of tidal volume) were comparable at 3, 6 and 12, but were reduced significantly at 24 breaths/min (Fig. 7).

Average end-tidal carbon dioxide concentrations at 3, 6, 12, and 24 breaths/min were 4·9 ± 0·3, 5·1 ± 0·3, 4·9 ± 0·4 and 4·5 ± 0·3%. Co_2 concentration at 24 breaths/min was comparable with that at 12 breaths/min ($P = 0·138$) but was significantly lower than that at 3 and 6 breaths/min ($P = 0·030$ and 0·011). The average control pulse intervals (all P–P intervals concluded during the 200 msec period before the tidal

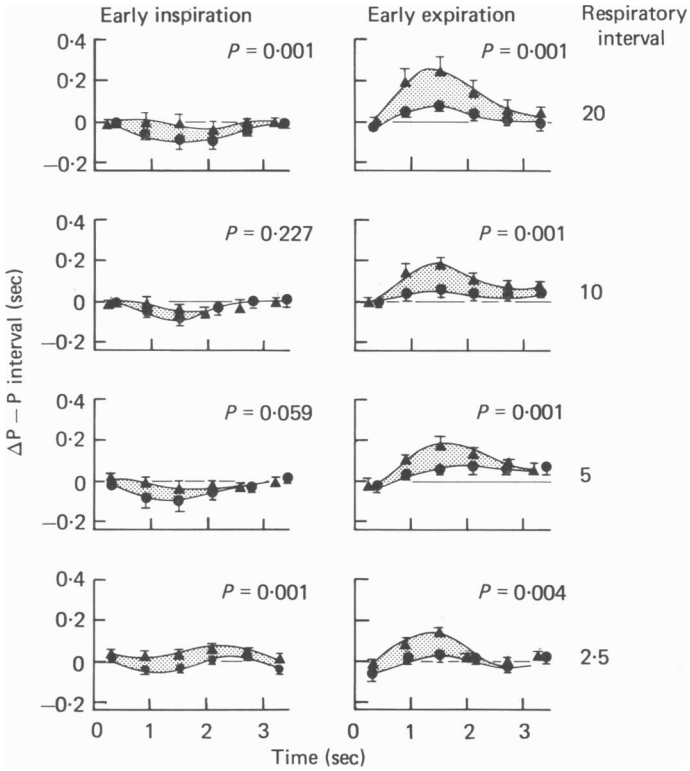

Fig. 5. Average P – P interval changes after early inspiratory or early expiratory tidal volume threshold crossings, with (triangles) or without (circles) neck suction, for all volunteers.

TABLE 2. *P* values (paired *t* test) for comparisons between maximal sinus-node responses (between 0·6 and 1·8 sec) to neck suction begun in early inspiration or early expiration at different respiratory rates. Respiration rate is expressed as the interval between breaths (20 sec = respiratory rate of 3 breaths/min)

	Inspiration			Expiration			
Inspiration	10	5	2·5	20	10	5	2·5
20	0·094	0·679	0·374	0·021	0·029	0·082	0·320
10	—	0·447	0·018	0·005	0·004	0·001	0·010
5	—	—	0·495	0·010	0·043	0·008	0·022
2·5	—	—	—	0·028	0·047	0·177	0·470
Expiration							
10	—	—	—	0·030	—	0·546	0·275
5	—	—	—	0·096	—	—	0·301
2·5	—	—	—	0·320	—	—	—

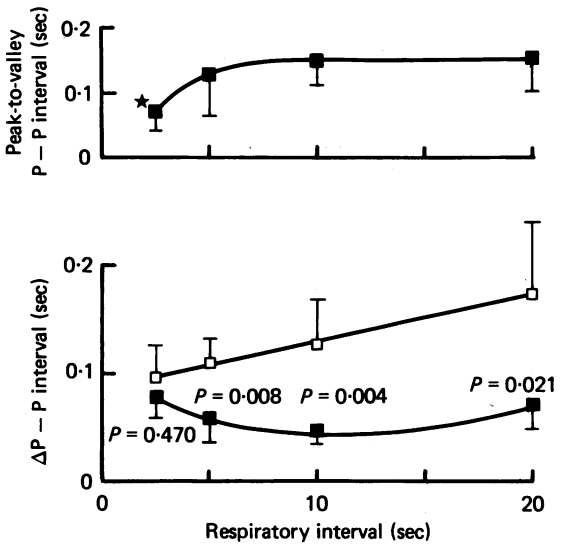

Fig. 6. Average differences between peak-to-valley P–P intervals at each breathing frequency (upper panel) and average maximum (between 0·6 and 1·8 sec after the tidal volume threshold crossing) responses to inspiratory (filled squares) and expiratory (open squares) baroreceptor stimuli at each breathing frequency (lower panel). The average peak-to-valley pulse interval change at 24 breaths/min (star) was significantly less than that at six (P = 0·006) and three breaths/min (P = 0·030). P values in the lower panel refer to paired observations at each breathing frequency.

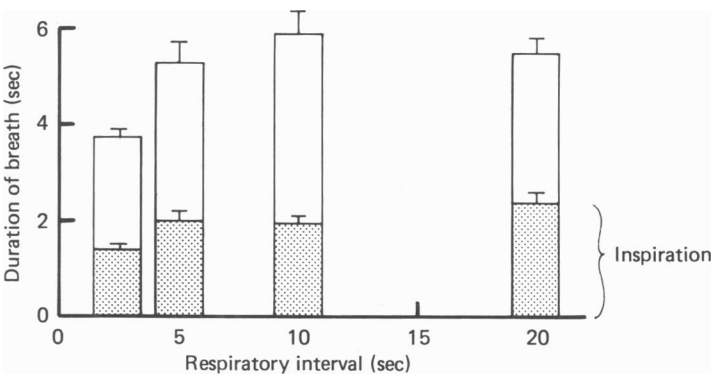

Fig. 7. Average duration of inspiratory (stippled area) and expiratory airflow (clear area) for all volunteers. The inspiratory duration at 24 breaths/min (interval of 2·5 sec) was significantly shorter than that at 12 (P = 0·025) and 3 breaths/min (P = 0·005). The average expiratory duration at 24 breaths/min was significantly shorter than that at 12 (P = 0·017), 6 (P = 0·003), and 3 breaths/min (P = 0·001). The percentage of each breath accounted for by inspiration was comparable at each breathing frequency.

volume threshold crossing) were 1·00 ± 0·08, 0·99 ± 0·07, 1·00 ± 0·08 and 0·92 ± 0·07 at 3, 6, 12, and 24 breaths/min (P, n.s.). Peak-to-valley changes of pulse interval with breathing, used as a measure of the magnitude of sinus arrhythmia, declined significantly at the most rapid breathing rate (Fig. 6, upper panel).

DISCUSSION

There are two major new findings in this study. First, human baroreflex responsiveness oscillates continuously during normal quiet respiration; the phase shift of baroreflex responsiveness on respiration is such that this interaction cannot be ascribed simply to gating synchronous with central inspiratory or expiratory neurone activity. Secondly, regularization of heart rate during rapid breathing is associated with loss of the differential responsiveness to inspiratory and expiratory baroreceptor stimuli which is found at usual breathing rates. This effect appears to be an expression of the linear relationship which exists between expiratory baroreflex responsiveness and respiratory interval.

Influence of respiratory phase. Baroreceptor stimuli delivered in early and mid inspiration provoked only minimal sinus-node inhibition, but stimuli begun during late inspiration provoked major sinus-node inhibition. Thus, inspiratory baroreflex refractoriness is not absolute, but depends upon the phase of inspiration. An earlier study (Eckberg & Orshan, 1977) demonstrated that even during early inspiration, substantial sinus-node inhibition can be provoked if the intensity of baroreceptor stimulation is sufficiently large. Related observations were made in anaesthetized dogs by Anrep *et al.* (1936*a*) and Iriuchijima & Kumada (1964). Our findings also are qualitatively similar to those of Koepchen *et al.* (1961) who found that baroreflex responsiveness of anaesthetized dogs increases progressively during *inspiration.*

These findings do not resolve the dispute (Anrep, Pascual & Rössler, 1936*b*) regarding the nature of central modulation of baroreflex responsiveness during inspiration. We cannot determine whether 'irradiation' from central inspiratory motoneurones, or afferent input from pulmonary and thoracic stretch receptors predominates; both types of activity would be expected to be maximal in late inspiration (Adrian, 1933; Cohen, 1968), when we found near peak baroreflex responsiveness. However, our observations do not exclude the possibility that efferent inspiratory motoneurone activity or afferent pulmonary and thoracic stretch receptor activity modulates baroreflex responsiveness; they merely indicate that this relationship cannot be one of simple inverse proportionality.

We found a progressive decline of baroreflex responsiveness during expiratory airflow. Thus, phasic reduction of baroreflex responses during normal respiration is not strictly an inspiratory phenomenon. Katona *et al.* (1970) found that efferent cardiac vagal activity ceases before the *onset* of inspiratory motoneurone activity and resumes before the *cessation* of inspiratory activity. The pattern of vagally mediated (Eckberg, 1980) sinus-node responses to baroreceptor stimulation appears to mirror the pattern of efferent sympathetic activity which predominates in inspiration and late expiration in experimental animals (Joels & Samueloff, 1956; Cohen & Gootman, 1970).

In a recent study from this laboratory (Eckberg, 1980), we found that resting systolic arterial pressure lies only about 10 mmHg above the threshold for activation of carotid baroreceptor–cardiac reflex responses. Large, phasic reductions of systolic pressure during quiet breathing could shift this relationship into the threshold region and lower baroreflex responses, independent of any respiratory–baroreflex interaction. This possibility seems remote because, under the conditions of this study, fluctuations

of systolic pressure are small and are out of phase with fluctuations of baroreflex responsiveness: in seven healthy young men studied earlier (D. L. Eckberg, unpublished), systolic pressure during early, mid, and late inspiration and early, mid, and late expiration averaged 134 ± 5, 132 ± 5, 131 ± 4, 133 ± 4, 134 ± 5 and 135 ± 5 mmHg.

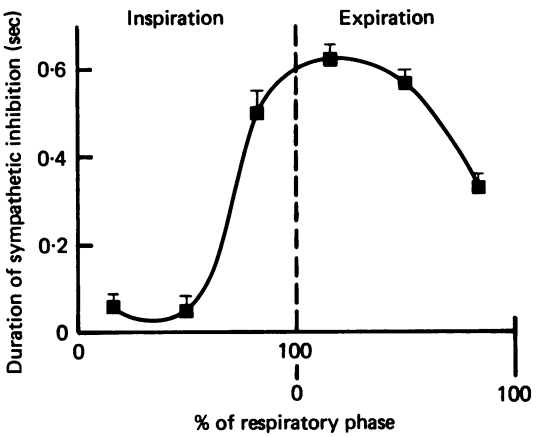

Fig. 8. These data are replotted from Fig. 2, Seller *et al.* (1968). They depict the average duration of inhibition of efferent lumbar sympathetic activity provoked by multiple electrical carotid sinus nerve stimuli (7 *V*, 0·02 msec/stimulus, 50 stimuli/sec for 2 sec) begun at different times in the respiratory cycle of one anaesthetized, paralysed, artificially ventilated dog.

The phase relationship we observed is probably representative of the physiology which obtains during normal quiet respiration; our findings conform with what has been learned previously from experimental animals (Koepchen *et al.* 1961; Haymet & McCloskey, 1975) and man (Eckberg & Orshan, 1977). The similarity between our results and those of Seller *et al.* (1968) is particularly striking (data from one of their experiments are replotted in Fig. 8); it suggests that the pattern of respiration-related oscillation of baroreflex responsiveness (cholinergic augmentation *or sympathetic inhibition*) is independent of species and unrelated to use of anaesthesia. However, we have not excluded the possibility that under different experimental circumstances phase relationships between baroreflex responsiveness and respiratory activity may be different.

Indeed, several lines of evidence support this possibility. Koepchen & Thurau (1959) showed that blood pressure and respiratory rhythms are not always synchronized; oscillations of blood pressure sometimes occur at one-half, or twice the respiratory rhythm. Ax & Luby (1961) found in man that sleep may unlock the usual 1:1 phase relationship between heart rate and respiration. Moreover, Davies & Neilson (1967, Fig. 2) documented the persistence of rhythmic oscillations of heart rate in man, despite the cessation of respiration. Barman & Gebber (1967) observed that spontaneous changes of the respiratory frequency of anaesthetized cats may be accompanied by dramatic alterations of phase relationships between phrenic and efferent sympathetic nerve activity. Finally, in the present study we found that rapid breath-

ing abolishes the differential baroreflex responsiveness which usually exists between the inspiratory and expiratory phases of respiration.

Influence of respiratory rate. In the course of this investigation, we confirmed an observation made much earlier (Fredericq, 1882) that the degree of sinus arrhythmia is reduced during rapid breathing (Fig. 6). We expected, but did not find a similar reduction of sinus arrhythmia with very slow respiratory rates, as reported by others (Angelone & Coulter, 1964; Womack, 1971). The evidence cited in the Introduction suggests that respiration-related central modulation of baroreflex sinus-node inhibition is responsible, in large measure, for the phenomenon of sinus arrhythmia. Our finding of an association between reduction of sinus arrhythmia at rapid breathing rates and loss of the normal differential baroreflex responsiveness during inspiration and expiration is consonant with this view. Although this association is sufficient to explain regularization of heart rate during rapid breathing we have not proven a definite cause and effect relationship.

Several mechanisms may be invoked to explain these results. Reduction of expiratory baroreflex responsiveness during rapid breathing may have been secondary to hypocapnia. This seems unlikely for several reasons. The degree of hypocapnia which occurred during rapid breathing (24 breaths/min) was minor (CO_2 concentration, $4{\cdot}5 \pm 0{\cdot}3\%$ calculated end-tidal p_{CO_2} 34·2 mmHg). *Inspiratory* baroreflex responses at 24 breaths/min were significantly *greater* than those at 6 breaths/min (Table 2) even though end-tidal CO_2 concentration was significantly lower. Finally, we are not aware that an association between mild hypocapnia and reduced baroreflex responsiveness has been demonstrated in man. Therefore, although we cannot exclude the possibility that the minimal hypocapnia which developed at 24 breaths/min exerted some influence upon our results, we doubt that this influence was major. However, we cannot predict from our study what influence *severe* hypocapnia might have upon human baroreflex responsiveness.

A second explanation for our findings is that expiratory baroreflex responses during rapid breathing were reduced non-specifically by the physical effort required (Eckberg, Fletcher & Braunwald, 1972). This seems unlikely because *inspiratory* responses at 24 breaths/min were significantly *greater* than inspiratory responses at 6 breaths/min (Table 2). Also, inspiratory baroreceptor stimuli provoked significant sinus-node inhibition at 24 breaths/min but failed to do so at 6 and 12 breaths/min (Fig. 5).

The phase relationship between respiration and baroreflex responsiveness (Fig. 4) may help to explain the effects of respiratory rate. First, the duration of inspiration was shortest at 24 breaths/min (Fig. 7). The augmentation of inspiratory baroreflex responses at this respiratory rate (Fig. 6, Table 2) may have resulted because the 0·6 sec baroreflex stimulus begun in early inspiration extended farther into inspiration at this breathing rate than at less rapid rates. A second, not mutually exclusive possibility, is that the phase relationship between breathing and baroreflex responsiveness may be different at different breathing rates. Rapid breathing may shift the cyclical variation of baroreflex responsiveness to the left so that responses during inspiration increase and responses during expiration decrease.

Our findings complement results from earlier studies conducted in experimental animals. Katona *et al.* 1970, found that when anaesthetized dogs were artificially ventilated to suppress spontaneous respiratory activity, respiratory variability of

efferent cardiac vagal activity was reduced greatly. Haymet & McCloskey (1975) found that in anaesthetized dogs during artificial hyperventilation, baroreceptor or chemoreceptor stimuli failed to provoke cardiac slowing, even when they were applied in expiration.

In this study, we regarded the central nervous system as a 'black box'; we applied a highly reproducible and controllable input, carotid stimulation with neck suction, and we measured with great accuracy an output, the P – P interval of the electrocardiogram. Our subjects voluntarily maintained normal tidal volumes and breathing rates within very narrow limits of tolerance. We cannot determine to what extent *voluntary* breathing influenced central oscillations. Nevertheless, our observations and interpretations complement and extend those made earlier in more direct, but also more invasive studies conducted by others with experimental animals.

We acknowledge our appreciation to Professor H. P. Koepchen for his critical review of this manuscript, to Mr Harry Bastow, III and Mr Joseph A. Rich for their skilled technical assistance, and to Ms Constance Ann Lazzaro for her expert secretarial help. This research was supported by grants from the Veterans Administration and the National Institutes of Health (HL 22546 and HL 22296). Ms Vanessa L. Roberts was a Minority Hypertension Research Development Trainee and was supported by a grant (5T 32HL07309) from the National Institutes of Health.

REFERENCES

ADRIAN E. D. (1933). Afferent impulses in the vagus and their effect on respiration. *J. Physiol.* **79**, 332–358.

ANGELONE, A. & COULTER, N. A., JR. (1964). Respiratory sinus arrhythmia: a frequency dependent phenomenon. *J. appl. Physiol.* **19**, 479–482.

ANREP, G. V., PASCUAL, W. & RÖSSLER, R. (1936*a*). Respiratory variations of the heart rate. I – The reflex mechanism of the respiratory arrhythmia. *Proc. R. Soc.* B **119**, 191–217.

ANREP, G. V., PASCUAL, W. & RÖSSLER, R. (1936*b*). Respiratory variations of the heart rate. II – The central mechanism of the respiratory arrhythmia and the inter-relations between the central and the reflex mechanisms. *Proc. R. Soc.* B **119**, 218–230.

AX, A. & LUBY, E. D. (1961). Autonomic responses to sleep deprivation. *Archs gen. Psychiat.* **4**, 55–59.

BARMAN, S. M. & GEBBER, G. L. (1976). Basis for synchronization of sympathetic and phrenic nerve discharges. *Am. J. Physiol.* **231**, 1601–1607.

COHEN, M. I. (1968). Discharge patterns of brain-stem respiratory neurons in relation to carbon dioxide tension. *J. Neurophysiol.* **31**, 142–165.

COHEN, M. I. & GOOTMAN, P. M. (1970). Periodicities in efferent discharge of splanchnic nerve of the cat. *Am. J. Physiol.* **218**, 1092–1101.

DAVIES, C. T. M. & NEILSON, J. M. M. (1967). Disturbance of heart rhythm during recovery from exercise in man. *J. appl. Physiol.* **22**, 943–946.

ECKBERG, D. L. (1977*a*). Baroreflex inhibition of the human sinus node: importance of stimulus intensity, duration, and rate of pressure change. *J. Physiol.* **269**, 561–577.

ECKBERG, D. L. (1977*b*). Adaptation of the human carotid baroreceptor–cardiac reflex. *J. Physiol.* **269**, 579–589.

ECKBERG, D. L. (1980). Nonlinearities of the human carotid baroreceptor–cardiac reflex. *Circulation Res.* (in the Press).

ECKBERG, D. L., CAVANAUGH, M. S., MARK, A. L. & ABBOUD, F. M. (1975). A simplified neck suction device for activation of carotid baroreceptors. *J. Lab. clin. Med.* **85**, 167–173.

ECKBERG, D. L., FLETCHER, G. F. & BRAUNWALD, E. (1972). Mechanism of prolongation of the R – R interval with electrical stimulation of the carotid sinus nerves in man. *Circulation Res.* **30**, 131–138.

ECKBERG, D. L. & ORSHAN, C. R. (1977). Respiratory and baroreceptor reflex interactions in man. *J. clin. Invest.* **59**, 780–785.

FREDERICQ, L. (1882). De l'influence de la respiration sur la circulation. *Archs Biol., Paris* **3**, 55–100.

HAYMET, B. T. & MCCLOSKEY, D. I. (1975). Baroreceptor and chemoreceptor influences on heart rate during the respiratory cycle in the dog. *J. Physiol.* **245**, 699–712.

HERING, H. E. (1933). Kreislauf und Nervensystem. *Verh. dt. Ges. KreislForsch.* **6**, 13–50.

IRIUCHIJIMA, J. & KUMADA, M. (1964). Activity of single vagal fibers efferent to the heart. *Jap. J. Physiol.* **14**, 479–487.

JEWETT, D. L. (1964). Activity of single efferent fibres in the cervical vagus nerve of the dog, with special reference to possible cardio-inhibitory fibres. *J. Physiol.* **175**, 321–357.

JOELS, N. & SAMUELOFF, M. (1956). The activity of the medullary centres in diffusion respiration. *J. Physiol.* **133**, 360–372.

KATONA, P. G. & JIH, F. (1975). Respiratory sinus arrhythmia: noninvasive measure of parasympathetic cardiac control. *J. appl. Physiol.* **39**, 801–805.

KATONA, P. G., POITRAS, J. W., BARNETT, G. O. & TERRY, B. S. (1970). Cardiac vagal efferent activity and heart period in the carotid sinus reflex. *Am. J. Physiol.* **218**, 1030–1037.

KOEPCHEN, H. P. & THURAU, K. (1959). Über die Entstehungsbedingungen der atemsynchronen Schwankungen des Vagustonus (Respiratorische Arrhythmie). *Pflügers Arch. ges. Physiol.* **269**, 10–30.

KOEPCHEN, H. P., WAGNER, P.-H. & LUX, H. D. (1961). Über die Zusammenhängezwischenzentraler Erregbarkeit, reflektorischem Tonus und Atemrhythmus bei der nervösen Steuerung der Herzfrequenz. *Pflügers Arch. ges. Physiol.* **273**, 443–465.

KUNZE, D. L. (1972). Reflex discharge patterns of cardiac vagal efferent fibres. *J. Physiol.* **222**, 1–15.

LOPES, O. U. & PALMER, J. F. (1976). Proposed respiratory 'gating' mechanism for cardiac slowing. *Nature, Lond.* **264**, 454–456.

SCHWEITZER, A. (1935). Zur Frage der respiratorischen Arrhythmie. *Verh. dt. ges. KreislForsch.* **8**, 148–154.

SELLER, H., LANGHORST, P., RICHTER, D. & KOEPCHEN, H. P. (1968). Über die Abhängigkeit der pressoreceptorischen Hemmung des Sympathicus von der Atemphase und ihre Auswirkung in der Vasomotorik. *Pflügers Arch.* **302**, 300–314.

WINER, B. J. (1962). *Statistical Principles in Experimental Design*, second ed., pp. 35–37. New York: McGraw-Hill.

WOMACK, B. F. (1971). The analysis of respiratory sinus arrhythmia using spectral analysis and digital filtering. *IEEE Trans. bio-med. Engng* **18**, 399–409.