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RESPIRATORY MODULATION OF MUSCLE SYMPATHETIC AND VAGAL CARDIAC OUTFLOW IN MAN

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SUMMARY

1. We studied the influence of respiration on muscle sympathetic and cardiac vagal activities in twenty conscious, healthy young adult subjects. Efferent post-ganglionic muscle sympathetic activity was measured directly with electrodes inserted percutaneously into a peroneal nerve, and vagal cardiac activity was measured indirectly from electrocardiographic changes of heart period.

2. Muscle sympathetic activity waxed and waned with respiration; maximum activity occurred at end-expiration and minimum activity occurred at end-inspiration. Voluntary control of breathing did not alter the time course or magnitude of muscle sympathetic outflow.

3. Spectral analyses showed that respiratory periodicities were present in sympathetic and vagal records. Average power at frequencies below respiratory frequencies exceeded or equalled that at respiratory frequencies in both muscle sympathetic and vagal cardiac records. A cardiac periodicity was present and conspicuous in muscle sympathetic recordings in all but one subject.

4. Diastolic arterial pressure increased during inspiration and decreased during expiration. Heart period and muscle sympathetic activity paralleled each other and were related reciprocally to changes of diastolic pressure.

5. Brief reductions of carotid baroreceptor afferent traffic provoked by neck pressure were more effective in increasing sympathetic activity in expiration than inspiration.

6. We conclude that quiet respiration is associated with parallel phasic changes in activity of medullary vagal cardiac and spinal muscle sympathetic motonuclei in man; spontaneous activity and susceptibility to excitation or inhibition by autonomic inputs are greater in expiration than inspiration. Substantial power is present in both muscle sympathetic and cardiac vagal recordings at frequencies below respiratory frequencies.

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INTRODUCTION

Because of the great complexity of central autonomic neural organization, many studies of autonomic mechanisms focus on net rhythms of neural outflow rather than on activities of individual central neurones. One such rhythm, respiratory modulation of sympathetic outflow, has been studied extensively; however, mechanisms responsible for this rhythm are understood imperfectly and there is even disagreement over what temporal relationship exists between respiratory and sympathetic rhythms. For example, most investigators (Cohen & Gootman, 1970; Koizumi, Seller, Kaufman & Brooks, 1971; Gootman & Cohen, 1974; Preiss & Polosa, 1974; Preiss, Kirchner & Polosa, 1975; Barman & Gebber, 1976) report that sympathetic activity is greater in inspiration than expiration. However, a minority of workers (Bronk, Ferguson, Margaria & Solandt, 1936; Tang, Maire & Amassian, 1957; Okada & Fox, 1967) indicate that sympathetic activity is greater in expiration than inspiration.

Many studies suggest that sympathetic activity is tied to the activity of 'phase' or 'phase spanning' respiratory neurones (Cohen & Gootman, 1970; Koizumi *et al.* 1971; Gootman & Cohen, 1974; Preiss & Polosa, 1974; Preiss *et al.* 1975); however, Barman & Gebber (1976) report that in some vagotomized, paralysed, open-chest laboratory animals, timing of sympathetic activity in relation to respiration varies with respiratory rate. Similarly, the early study of human muscle sympathetic rhythms of Hagbarth & Vallbo (1968) suggests that although bursts of muscle sympathetic activity tend to occur in expiration, they may occur at any time during the respiratory cycle.

It is likely that much of the disagreement over temporal relationships between respiratory and sympathetic rhythms arises from methodological differences among studies. Almost all studies of respiratory modulation of sympathetic neural outflow have been conducted in experimental animals. These studies necessarily have employed a variety of methods which may have influenced the results obtained, including general anaesthesia, neuromuscular paralysis, artificial ventilation, and decerebration. Although these interventions may have facilitated investigations of mechanisms, each successive intervention also may have removed the experimental preparation farther from its physiological state.

We undertook the present study for two reasons. First, we wanted to document and quantitate the relationships that exist between respiration and muscle sympathetic and vagal cardiac outflows in conscious, co-operative, resting human subjects whose autonomic activity has been altered by neither surgery nor drugs. Secondly, we wanted to determine how brief reductions of arterial baroreceptor afferent input or spontaneous changes of blood pressure alter respiratory modulation of muscle sympathetic outflow. Our principal conclusion is that respiration is associated with parallel (not reciprocal) changes of spontaneous activity and of responsiveness of muscle sympathetic and vagal cardiac motonuclei to autonomic inputs.

METHODS

This study comprises retrospective and prospective analyses of temporal relationships between respiration and muscle sympathetic efferent activity, blood pressure and vagally mediated heart period in healthy young adult men and women.

Subjects. Measurements were obtained for these approved studies from twenty adult volunteers after they gave written consent to participate. Retrospective analyses were performed on data obtained from twelve volunteers whose average age was 29 (range 21–39) years. Prospective studies were conducted with eight volunteers whose average age was 27 (range 18–32) years. All subjects were healthy and none were taking medications.

Measurements. Subjects were studied supine in a quiet room. The following measurements were recorded with an ink-writing oscillograph and an FM tape recorder: electrocardiogram, heart period (derived from electrocardiographic R wave threshold crossings), neck chamber pressure (strain gauge pressure transducer) and peroneal nerve muscle sympathetic efferent activity (see below). In the retrospective study, respiration was measured with an uncalibrated pneumograph which encircled the chest, and blood pressure was measured with a strain gauge pressure transducer connected to a brachial arterial catheter. In the prospective study, respiration was measured with a calibrated Respitrace Respiration Monitor (Ambulatory Monitoring, Inc., Ardsley, NY) and blood pressure was measured with a sphygmomanometer.

Neck pressure. In the prospective study, carotid baroreceptor afferent activity was reduced briefly by 30 mmHg pressure applied to a neck chamber (Eckberg, Cavanaugh, Mark & Abboud, 1975). Pressure pulses were initiated by rotation of a solenoid actuated pneumatic valve connected in series with the pressure port of a commercial vacuum cleaner. Stimuli were triggered by the upstroke of an R wave of the electrocardiogram and were terminated after the next R wave. In practice, stimuli began 0·08 s after the onset of the first R wave and ended $0{\cdot}19 \pm 0{\cdot}10$ (S.D. of difference) s after the onset of the next R wave. Thus, each neck pressure pulse was applied for slightly more than one cardiac cycle.

Neck pressure pulses were positioned at different times in the respiratory cycle as follows: a threshold was set at about the first quarter of inspiration. Inspiratory threshold crossings activated an electronic delay. After this delay (set at 0, 1, 2, 3 or 4 s), the next R wave initiated data collection sweeps. Neck pressure was applied in half of the sweeps; control trials comprised the other half.

Control of breathing. Retrospective measurements were made with subjects at rest, during periods of uncontrolled breathing. Prospective measurements were made during three different modes of breathing. First, subjects breathed spontaneously. Secondly, subjects breathed with an auditory tone delivered at about 5 s intervals (respiratory rate: 12 breaths/min), and tidal volume was measured. Thirdly, subjects breathed with the tone at 5 s intervals and attempted to produce tidal volume excursions (registered by the needle of an analogue voltmeter) similar to the average excursion established during the second period of breathing. Thus, in the prospective study, during three sequential periods of observation, subjects breathed freely, at a constant rate, and at a constant rate to a constant tidal volume. During the remainder of data collection periods in the prospective experiment, subjects breathed with the auditory tone to the tidal volume they established, and they attempted to maintain this fixed breathing pattern despite the occurrence of neck pressure pulses. Respiratory carbon dioxide concentrations were not measured.

Nerve recordings. Multiunit, post-ganglionic sympathetic efferent activity was led off from peroneal nerve muscle fascicles with tungsten micro-electrodes with uninsulated tip diameters of about 1–5 μm. Similar reference electrodes (but with larger uninsulated tips) were inserted subcutaneously 1–2 cm from recording electrodes. Electrodes were connected to a differential pre-amplifier with a gain of 1000 and to an amplifier with a gain of 50. Nerve traffic was monitored with a storage oscilloscope and a loudspeaker. The raw nerve signal was fed through a band-pass filter with a band width of 700–2000 Hz and through an amplitude discriminator to reduce remaining noise. A resistance–capacitance integrating network with a time constant of 0·1 s was used to derive mean voltages of nerve activity. These methods have been described earlier (Sundlöf & Wallin, 1977).

Data analyses. Data were analysed manually and with the aid of digital computers and a processing digital oscilloscope (Norland 3001, Norland Corporation, Fort Atkinson, WI). Both time and frequency domain analyses were performed.

Time domain analyses. Mean voltage neurograms were digitized at 100 Hz. Sympathetic bursts were identified by inspection from their appearances in the mean voltage neurograms and from their characteristic (high frequency, crescendo–decrescendo) sounds during FM tape play-back recordings. The computer determined the beginning and ending of designated bursts and established the base line between bursts as zero activity to reduce contamination of records by spontaneous shifts of base line electrical activity. Following this, the computer normalized the heights of bursts to

compensate for possible changes of voltage due to unanticipated shifts of electrode position. The largest burst occurring during periods of control observation was assigned a value of 1000 and all other bursts were normalized against this standard.

Two methods were used to quantify sympathetic activity during periods of uncontrolled or controlled breathing. First, during periods of uncontrolled breathing, sympathetic bursts were identified as described above. The computer measured all diastolic pressures and their times of occurrence during the respiratory cycle. Respiration signals were displayed on the computer console and the beginning, peak and ending of each breath were marked with a cursor. The computer determined mean durations and amplitudes for all breaths and excluded those with amplitudes or durations which deviated more than 20% from mean values. Mean voltage neurograms of muscle sympathetic activity were advanced 1·2–1·5 s, according to the height of the subject (Fagius & Wallin, 1980), to compensate for reflex delays between cardiovascular events and reflex peripheral sympathetic nerve responses. After this, sympathetic nerve activity, heart periods and diastolic arterial pressures during the remaining breaths were divided into deciles and average values for each decile were computed.

Secondly, during periods of controlled breathing, mean voltage neural activity was averaged (at 0·5 s intervals) for 10 s after early inspiration threshold crossings. Average mean voltage neurograms of muscle sympathetic activity generated in this and other analyses were advanced 1·5 s to account for peripheral sympathetic nerve conduction delays (Fagius & Wallin, 1980).

Frequency domain analyses. In retrospective studies, power spectral densities were obtained from 102·4 s sweeps (100 ms bins) of arterial pressure, muscle sympathetic activity, respiration and heart period. (Analyses of 51·2 s epochs were performed also, and yielded similar results.) Power spectral densities were analysed as follows: First, frequencies at peaks of power for each signal were measured. Secondly, frequencies at the beginning and ending of the primary arterial pressure (cardiac band) and respiration (respiration band) power densities were determined by visual inspection. Next, the integrals of muscle sympathetic activity and heart period power between 0 and 4 Hz were measured. Finally, percentages of heart period power falling below and within the respiration band and percentages of muscle sympathetic power falling below and within the respiration band and within the cardiac band were measured. Plots of power spectral density were made from 80 ms averages.

Experimental sequence. In retrospective studies, periods of measurement were obtained during uncontrolled breathing before other experimental interventions were made. In prospective studies, measurements were obtained during the three, 3 min periods of breathing; that is, when subjects were breathing (a) spontaneously, (b) at a constant rate and (c) at a constant rate and to a constant tidal volume. Following this, neck pressure interventions were made. Three alternating blocks of five control and five neck pressure measurements were obtained for each delay. Delays were chosen in random sequence.

Statistical analyses. Results are expressed as the mean and range, or as the mean ± S.E. of mean. Parametric (paired t test) and non-parametric statistical comparisons were made; the Wilcoxon signed rank test (Snedecor & Cochran, 1967) was used for some analyses because of the small numbers of observations and the non-Gaussian distribution of responses. Differences were considered significant when P was less than 0·05.

RESULTS

Muscle sympathetic efferent activity during uncontrolled breathing

Records showing arterial pressure, muscle sympathetic activity, respiration and heart period for two subjects are depicted in Figs. 1 and 2. In subject No. 3 (Fig. 1) muscle sympathetic bursts, arterial pressure and heart period fluctuated rhythmically with a periodicity which was about half that of respiration. In subject No. 7 (Fig. 2), muscle sympathetic activity, arterial pressure and heart period fluctuated with a periodicity which was about equal to that of respiration. Muscle sympathetic activity displayed cardiac rhythmicity in all subjects. This was difficult to appreciate from inspection of the mean voltage neurogram in subject No. 3 (Fig. 1), since sympathetic bursts occurred infrequently; however, R-wave-triggered

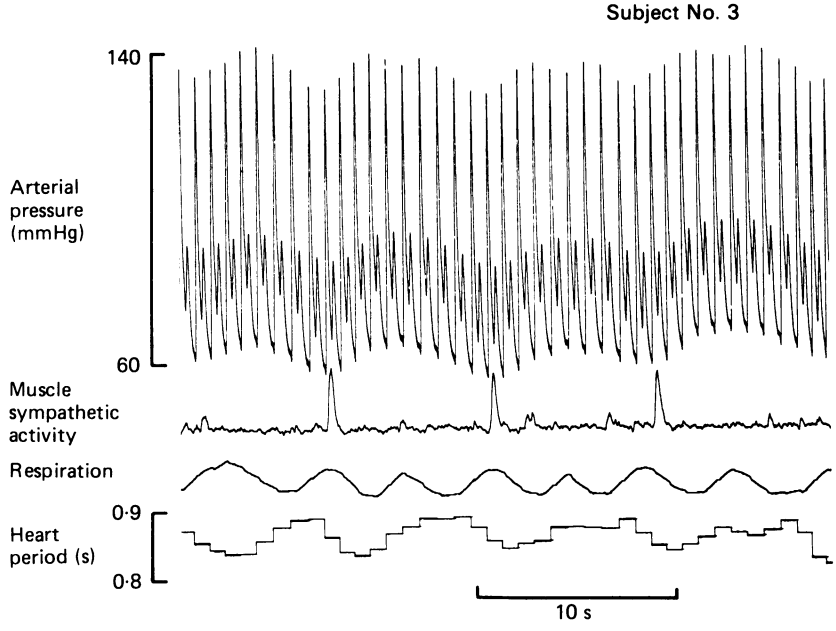

Fig. 1. Original record from one volunteer. Gain of the arterial pressure recording was increased to exaggerate small changes of pressure. Inspiration is represented by increasing signal intensity. The record of muscle sympathetic activity should be advanced 1·3–1·5 s to account for peripheral conduction delays.

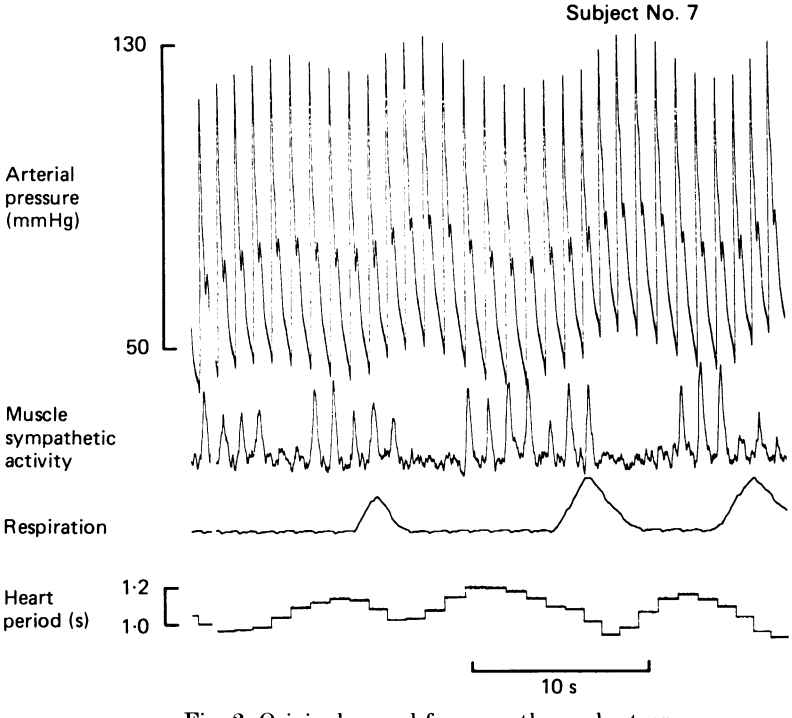

Fig. 2. Original record from another volunteer.

averages of sympathetic activity showed that the occurrence of bursts in this subject was time-locked to cardiac activity.

Power spectral density analyses of records from these and six other subjects are depicted in Fig. 3. We tested for stationarity of these data as follows: we captured two successive 102·4 s samples of data from each subject, calculated integrals of each area of interest as described above and compared measurements (with the paired t test) from the first period with those from the second. Four of the five areas from earlier and later data collection periods were comparable ($P > 0{\cdot}05$); power in the respiration band of heart period was significantly ($P < 0{\cdot}03$) less during the second measurement period. We concluded that these results indicate probable stationarity of the data and thus support the validity of spectral density analyses.

Spectral analyses of arterial pressure (Fig. 3, top panel) identified several distinct frequencies. (Multiple peaks of power reflect the frequency content of the complex arterial pressure wave form; they were not present when comparable analyses were performed with a sine wave signal.) In all subjects, there was a small aggregation of power at very low frequencies (at about 0·1 Hz). The second peak of arterial pressure power reflects cardiac frequency (average: 1·12, range: 0·93–1·32 Hz); the third and fourth peaks appear to be harmonics of the second frequency (their frequencies averaged 2·0 and 2·95 times that of the first major peak).

Cardiac periodicity (corresponding with the primary peak of arterial pressure power) in muscle sympathetic power (second panel) was prominent in all subjects except No. 3. (The recording obtained from this subject (Fig. 1) showed that his sympathetic bursts occurred infrequently, with a periodicity of about half that of respiration.) Also, in most subjects there was considerable muscle sympathetic power at frequencies below the respiratory frequency. Power at these low frequencies also is striking in heart period analyses (fourth panel). In most subjects, peaks of muscle sympathetic and heart period power coinciding with those of respiration (third panel) merged with power at lower frequencies.

Mathematical analyses of the power spectral densities of muscle sympathetic activity and heart period depicted in Fig. 3 are given in Table 1. The most prominent aggregation of muscle sympathetic power occurred at the cardiac frequency (which accounted for an average of 22 (range: 12–38) % of power between 0 and 4 Hz). Muscle sympathetic power at respiratory frequencies was less (average: 12, range: 5–19 %), and muscle sympathetic and heart period power below respiratory frequencies was substantial (averages: 12 (range: 3–22) and 51 (range: 37–61) %) in all subjects.

A previous study (Sundlöf & Wallin, 1978*a*) showed that although there is no significant relationship between systolic arterial pressure and muscle sympathetic activity, there is a strong inverse correlation between diastolic arterial pressure and muscle sympathetic activity. Fig. 4 depicts the relationship between average diastolic arterial pressure and muscle sympathetic activity in nine subjects during an average respiratory cycle. This analysis shows that there is a respiration-related, phasic, inverse relationship between muscle sympathetic activity (top panel) and diastolic arterial pressure (third panel). Fig. 4 also demonstrates that when adjustments are made for reflex latency, changes of muscle sympathetic activity and heart period (which quantitatively reflects changes of vagal cardiac activity (Katona, Poitras, Barnett & Terry, 1970)) occur in parallel. These relations were described well by a

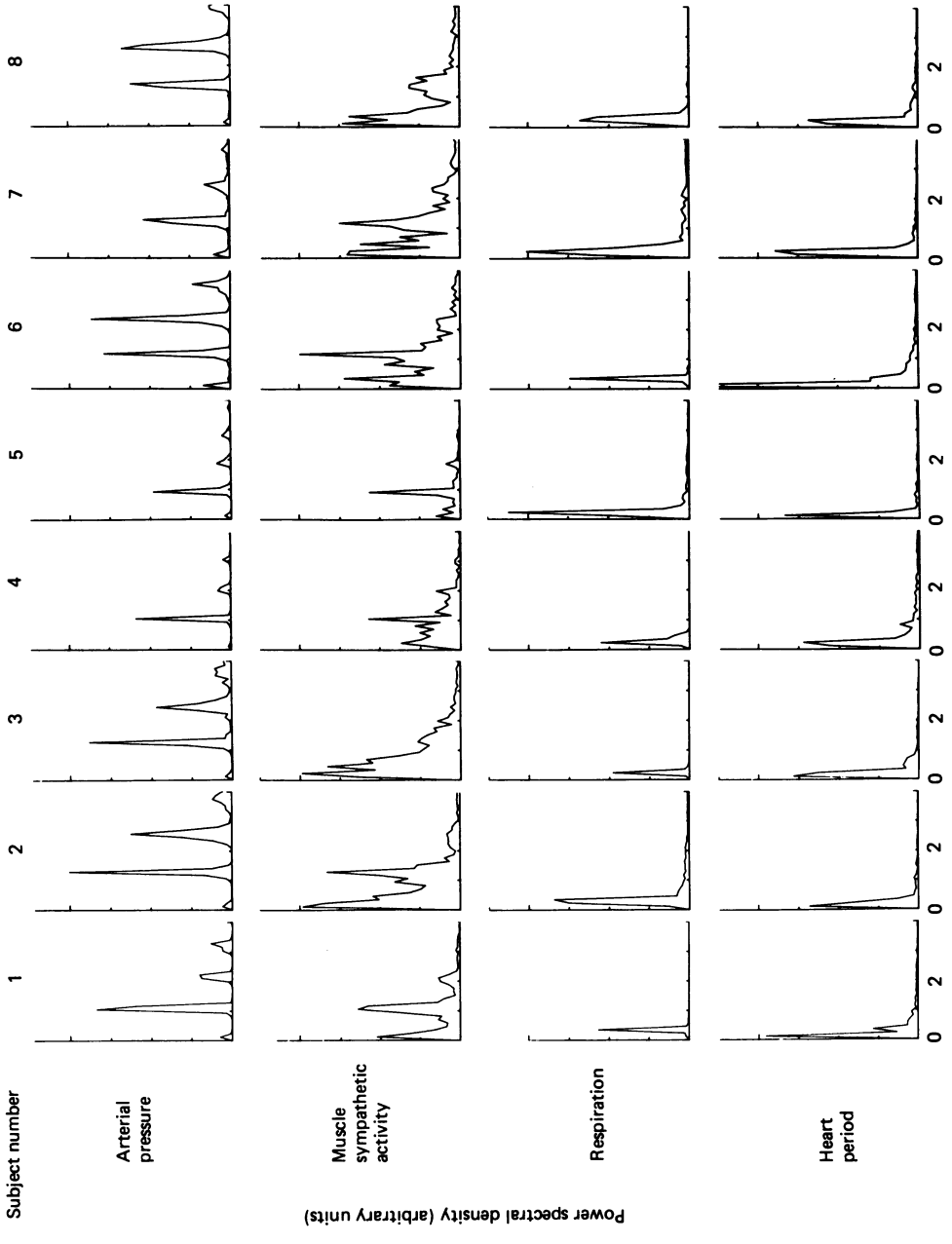

Fig. 3. Power spectral densities derived from analyses from eight subjects.

TABLE 1. Power spectral densities of muscle sympathetic activity and heart period

	Muscle sympathetic activity			Heart period	
Subject No.	% less than respiratory frequency	% at respiratory frequency	% at arterial pressure frequency	% less than respiratory frequency	% at respiratory frequency
1	15	12	34	54	21
2	13	12	19	60	10
3	18	5	17	61	25
4	3	14	16	44	26
5	12	19	26	49	34
6	9	14	17	37	29
7	6	8	38	47	22
8	22	9	12	52	14
Mean	12	12	22	51	23

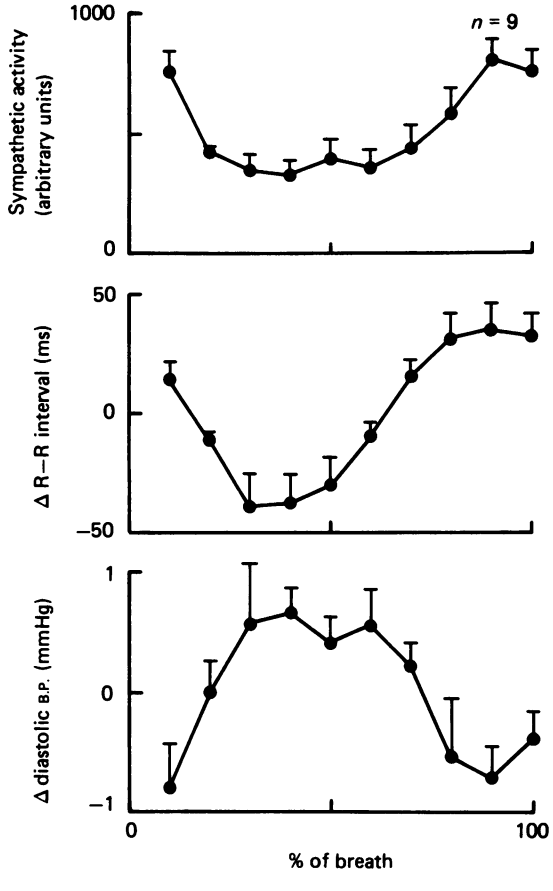

Fig. 4. Relationships among average diastolic arterial pressure (B.P.), heart period and muscle sympathetic activity in nine subjects. Sympathetic activity was advanced 1·2–1·5 s to account for baroreflex delays. Error bars indicate one S.E. of mean.

quadratic polynomial function with positive linear and quadratic coefficients (Grizzle & Allen, 1969).

Muscle sympathetic activity during controlled breathing

Average tidal volumes and muscle sympathetic activities of eight subjects during uncontrolled, frequency controlled and frequency and tidal volume controlled breathing are depicted in Fig. 5. Tidal volume (upper panel) was less, but insignificantly

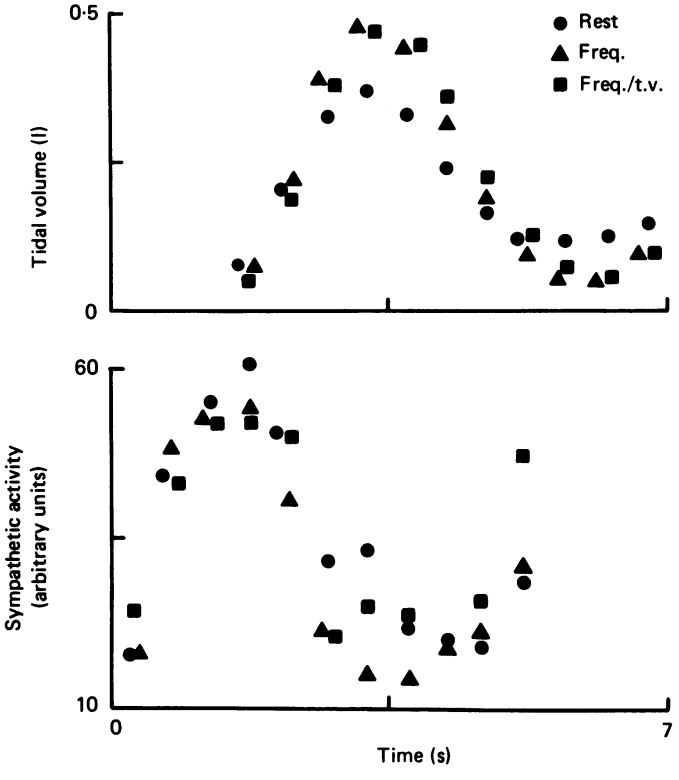

Fig. 5. Average tidal volume and muscle sympathetic efferent activity during uncontrolled breathing (rest), frequency controlled (freq.) and frequency and tidal volume controlled (freq./t.v.) breathing. Tidal volumes and sympathetic activities were comparable ($P > 0{\cdot}05$) during the three conditions.

so during uncontrolled breathing (●, 'rest') than during the two types of controlled breathing. The time course of the average breath during uncontrolled breathing was similar to that of breaths during the other two types of breathing, and the interval between breaths was shorter ($4{\cdot}9 \pm 0{\cdot}4$ *vs.* $5{\cdot}0 \pm 0{\cdot}1$ and $5{\cdot}0 \pm 0{\cdot}1$ s), but insignificantly so.

Average muscle sympathetic outflow (Fig. 5, lower panel) exhibited a prominent respiratory periodicity, such that its onset occurred at about the beginning, and its peak occurred at about the end of expiratory air flow. Importantly, sympathetic outflow was comparable ($P = 0{\cdot}178$) during uncontrolled and controlled breathing, according to the function described by Grizzle & Allen (1969) (see previous paragraph).

This suggests that the constraint imposed for this study, that subjects control their breathing frequency and tidal volume, did not alter muscle sympathetic outflow importantly. These results support the conclusion of Tang *et al.* (1957) that higher centres provoke respiration-related changes of sympathetic outflow indirectly through their influences upon breathing rather than directly through their influences upon autonomic motonuclei. Hirsch & Bishop (1981) have shown already that voluntary control of breathing does not alter vagal cardiac outflow as reflected in Bode plots of respiratory frequency and heart rate.

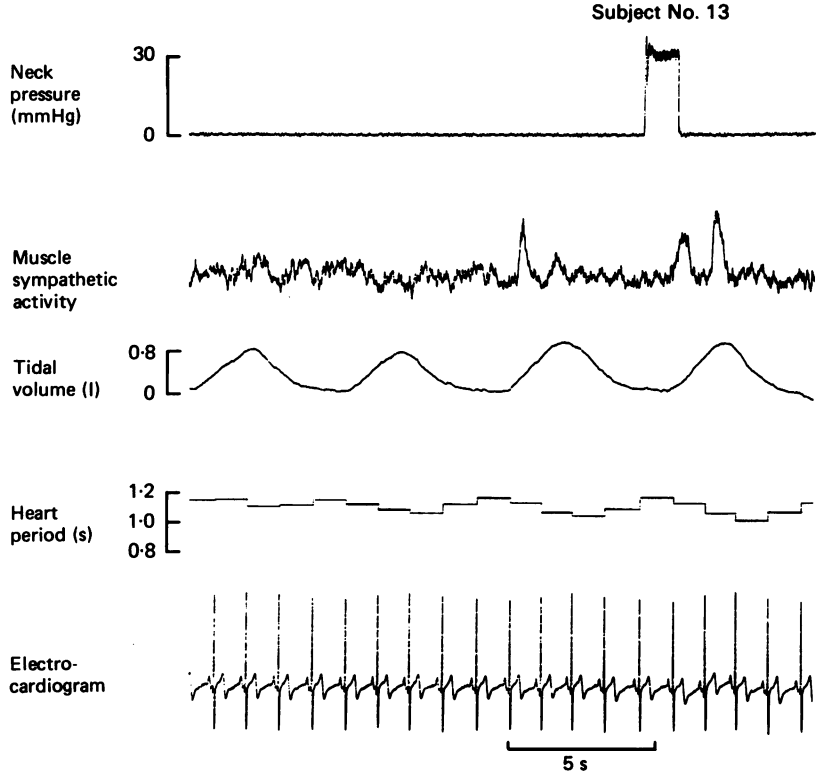

Fig. 6. Original record of one subject showing responses to brief neck pressure. In this subject, applications of neck pressure usually elicited two bursts of sympathetic activity.

Muscle sympathetic responses to brief reductions of carotid afferent baroreceptor traffic

Fig. 6 depicts an original record showing the response of one subject (No. 13) to brief neck pressure applied in late expiration. In this subject, neck pressure was followed by two pulse-synchronous bursts of muscle sympathetic activity. In most applications of neck pressure in other subjects, increases of muscle sympathetic activity were limited to only one cardiac cycle.

Average tidal volume (control, without neck pressure) and average sympathetic responses of all eight subjects to neck pressure applied at five different times in the respiratory cycle are shown in Fig. 7. (Muscle sympathetic responses were calculated by subtracting normalized control muscle sympathetic activity during one R–R interval from post-neck pressure activity during the same interval after the respiratory

threshold crossing (see Methods).) The largest increases of sympathetic activity (lower panel) followed stimuli delivered in mid and late expiration (stimulus delays of 3 and 4 s). This period of maximum responsiveness coincided approximately with the times of maximum spontaneous sympathetic activity (Fig. 5, lower panel). Responses to neck pressure applied during late expiration (delays of 3 and 4 s) were greater ($P = 0{\cdot}03$ and $0{\cdot}055$) than those to pressure pulses applied during early inspiration (delays of zero). Differences between these responses and those following neck pressure applied 1 and 2 s after the beginning of inspiration were not significant.

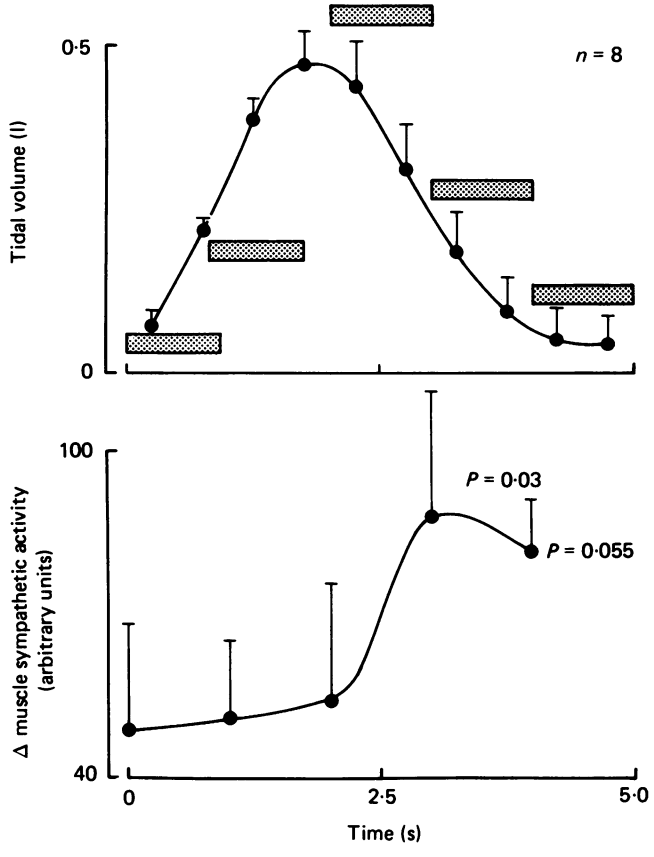

Fig. 7. Average integrated sympathetic responses of eight subjects to neck pressure applied at different times in the respiratory cycle (the times that stimuli began and their durations are indicated by stippled rectangles). Tidal volume was derived from 0·5 s averages of respiratory signals. Changes of muscle sympathetic activity during one R–R interval were calculated by subtracting control activity from activity after neck pressure stimuli. *P* values refer to comparisons with responses at zero delay.

DISCUSSION

There are two principal new findings in this study of autonomic cardiovascular control in conscious man. First, quiet breathing is associated with a generalized process in which medullary vagal cardiac and spinal muscle sympathetic motonuclei

fluctuate in similar ways. Inspiration is associated with suppression of sympathetic firing and sympathetic responsiveness to brief reductions of arterial baroreceptor input, and expiration is associated with facilitation of sympathetic firing and responsiveness to reduced baroreceptor activity. Similar temporal response patterns of vagal fluctuations of heart period (Katona *et al.* 1970) and of vagal responses to brief increases of arterial baroreceptor traffic during quiet respiration (Eckberg & Orshan, 1977; Eckberg, Kifle & Roberts, 1980) were reported earlier. These findings, and related observations of Seller, Langhorst, Richter & Koepchen (1968) that the duration of sympathetic inhibition after electrical carotid sinus nerve stimulation fluctuates similarly during the respiratory cycle, support the conclusion that respiration is associated with modulation of responsiveness of muscle sympathetic and vagal cardiac motonuclei to autonomic afferent inputs, and that the expiratory phase of respiration is associated with heightened responsiveness of both groups of motonuclei to both inhibitory and facilitatory inputs.

Secondly, although respiratory rhythms are unmistakable in vagal cardiac and muscle sympathetic recordings, low frequency periodicity is prominent in both records and is dominant in vagal cardiac recordings. Low frequency blood pressure waves have been identified in anaesthetized animals, but usually are apparent only after experimental interventions, such as haemorrhage (Okada & Fox, 1967).

Temporal relationships between breathing and muscle sympathetic activity

The first goal of this study was to describe temporal relationships between breathing and sympathetic activity during quiet, spontaneous breathing. We found, as others before us (see Introduction), that sympathetic neural outflow waxes and wanes during the respiratory cycle. However, contrary to most earlier findings that increases of sympathetic activity occur primarily during inspiration (Cohen & Gootman, 1970; Koizumi *et al.* 1971; Gootman & Cohen, 1974; Preiss & Polosa, 1974; Preiss *et al.* 1975; Barman & Gebber, 1976), we found that increases of sympathetic outflow begin at the beginning of expiration, reach their peak at the end of expiration, decline during inspiration and reach their nadir in late inspiration, when phrenic nerve outflow is greatest (Eldridge, 1971).

This temporal relationship was found with both prospective (Fig. 5) and retrospective analyses (Fig. 4) and during controlled and uncontrolled breathing (Fig. 5). In our study, we advanced muscle sympathetic activity 1·3–1·5 s, to account for the baroreflex latency (which comprises primarily peripheral conduction delays over slow-conducting, unmyelinated sympathetic C fibres (Fagius & Wallin, 1980)). It is conceivable that this delay may have been slightly shorter, since we did not measure nerve conduction latencies in our subjects. However, it is likely that choice of an inappropriately long nerve conduction latency would force minor quantitative, rather than major qualitative changes of our conclusions. For example, an error as large as 0·5 s would not modify the conclusion that muscle sympathetic activity declines as inspiration progresses and phrenic nerve activity increases.

Our findings contradict those of Gregor, Jänig & Wiprich (1977) who also measured post-ganglionic muscle sympathetic efferent activity (in anaesthetized cats) and found that sympathetic activity paralleled phrenic nerve (that is, inspiratory) activity. Our findings are similar to those of others (Bronk *et al.* 1936; Tang *et al.*

1957; Okada & Fox, 1967; Hagbarth & Vallbo, 1968), who also found expiratory predominance of sympathetic outflows (splanchnic and cardiac). However, we doubt that the pattern we observed is fixed, since Barman & Gebber (1976), Cohen & Gootman (1970) and Preiss & Polosa (1974) found that the timing of sympathetic activity within the respiratory cycle may change with changes of breathing pattern.

A major issue raised by our study is: does the respiratory periodicity we observed in sympathetic recordings represent a direct influence of breathing upon sympathetic motoneurones or is this periodicity secondary to some other respiration-related rhythm? Although our data provide new information on this issue, they probably do not resolve it definitively.

If respiration influences sympathetic activity directly, our data are inconsistent with the suggestion (Cohen & Gootman, 1970; Gootman & Cohen, 1974) that respiratory periodicity of sympathetic outflow results primarily from facilitation of sympathetic activity by inspiratory motoneurones. Rather, our results favour the opposite conclusion, that if sympathetic motonuclei are influenced directly by respiratory activity, they are inhibited by inspiratory motoneurone activity. An alternative interpretation is that respiratory modulation of sympathetic outflow results primarily from inhibition of sympathetic activity by afferent pulmonary and thoracic stretch receptor activity (Gootman & Cohen, 1974), which increases during inspiration.

If the influence of breathing on sympathetic activity is indirect, it may be secondary to respiration-related fluctuations of arterial or cardiopulmonary baroreceptor activity. Earlier reports from human studies have documented a close inverse correlation between changes of diastolic arterial pressure and muscle sympathetic activity (Sundlöf & Wallin, 1978*a*; Wallin & Sundlöf, 1979), and in the present study spontaneous changes of muscle sympathetic activity during the respiratory cycle were related inversely to changes of diastolic blood pressure (Fig. 4). Moreover, our finding of expiratory facilitation of sympathetic responses to reductions of carotid afferent traffic also may be secondary to blood pressure fluctuations. Blood pressure fell during expiration and rose during inspiration, and it is known that at a given diastolic arterial pressure level, sympathetic outflow is greater when blood pressure is falling than when it is rising (Sundlöf & Wallin, 1978*a*).

Thus, our data are explicable in terms of blood pressure fluctuations. However, studies published by others suggest that changes of autonomic outflow which are temporally related to changes of blood pressure may not be caused by those blood pressure changes. Gregor *et al.* (1977) identified two respiration-related components of muscle vasoconstrictor activity in anaesthetized cats; one of these was independent of blood pressure fluctuations. Also, Koepchen & Thurau (1959) reported that respiratory periodicity of vagal outflow is preserved when blood pressure is varied artificially, out of phase with respiration. Moreover, Preiss & Polosa (1974) showed that low frequency changes of sympathetic activity which are associated with changes of arterial pressure under control conditions, persist after those changes of blood pressure are prevented from occurring by mechanical buffering, or administration of α-adrenergic blocking drugs.

Muscle sympathetic activity is known to be influenced by cardiopulmonary receptors (Sundlöf & Wallin, 1978*b*); therefore, an indirect influence of breathing on

muscle sympathetic activity may be mediated by changes of cardiopulmonary receptor activity, associated with respiration-related fluctuations of venous return to the heart. No systematic study has been made of the influence of changes of cardiopulmonary pressures on sympathetic activity, but occasional recordings have suggested that sympathetic activity correlates much more closely with arterial than central venous pressure (Fig. 5 in Burke, Sundlöf & Wallin, 1977). These limited data suggest that cardiopulmonary receptors are less likely to be mediators for respiratory rhythmicity of sympathetic outflow to muscle than are arterial baroreceptors.

Respiratory variability of baroreflex influences on sympathetic nuclei

Others have recognized that susceptibility of sympathetic nuclei to baroreceptor influences varies phasically with respiration. Seller *et al.* (1968) found that in dogs, inhibition of lumbar sympathetic outflow is more profound and lasts longer when electrical carotid sinus nerve stimuli are applied in expiration than inspiration. We found that brief reductions of carotid baroreceptor afferent traffic are more likely to increase sympathetic outflow to muscle when they are applied in expiration than inspiration (Fig. 7). This finding differs from those of Cohen & Gootman (1970), and Davis, McCloskey & Potter (1977), who found that sympathetically mediated sinus node responses are greater when carotid artery occlusions are made in inspiration than expiration, but it is compatible with the conclusion of these authors that the period of greatest responsiveness of sympathetic motonuclei to changes of autonomic input tends to coincide with the phase of respiration in which spontaneous activity is greatest.

Spectral density analyses

Power spectral densities of two inputs (arterial pressure and respiration (see Results)) were measured to gain additional insights into complex central autonomic control. These analyses (Fig. 3 and Table 1) confirm conclusions reached by other means that sympathetic outflow reflects cardiac and respiratory rhythms. However, they suggest that in most conscious humans, neither influence is prepossessing; rather, dominant periodicities in both vagal (R–R interval fluctuations) and sympathetic recordings are of very low frequencies (with periods of between 7 and 15 s) and are associated with similar, low frequency blood pressure changes. Our data do not identify the cause of low frequency components in these spectral analyses, but one possibility is that they represent 'third order' or 'Mayer' waves (Mayer, 1876; Schweitzer, 1945), which have periods of about 10 s. This slow periodicity was illustrated most clearly by subject No. 3 (Figs. 1 and 3), but it was also apparent in spectral analyses of blood pressure and sympathetic activity in other subjects.

In conclusion, we have measured respiration-related changes of post-ganglionic sympathetic neural traffic to skeletal muscle directly, and vagal traffic to the heart indirectly from changes of heart period, in conscious, co-operative human volunteers. Our results suggest that respiration is associated with changes of medullary and spinal neural efferent activity which are manifested in vagal and sympathetic motonuclei by parallel, not reciprocal changes of spontaneous activity and responsiveness to autonomic influences. Our data indicate also that, although respiratory influences are

unmistakable, there is substantial power in both muscle sympathetic and vagal cardiac activity at frequencies below respiratory frequencies.

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